Official title: Therapeutic Equivalence Study of Generic Brinzolamide 1% Ophthalmic suspension Compared to Reference Listed Drug Azopt® (Brinzolamide) Ophthalmic Suspension 1% in Subjects With Primary Open Angle Glaucoma or Ocular Hypertension.

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Statistical Analysis Plan

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Sponsor Identification:	Sun Pharmaceutical Industries Ltd
Phase:	Phase 3
Sponsor Study Number:	BRIN-20-01
[redacted]	[redacted]

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STATISTICAL ANALYSIS PLAN	
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[redacted]	[redacted]
[redacted]	[redacted]
Date of SAP:	20/Sep/2023
[redacted]	[redacted]
Scope:	Final

2 Signatures

Sponsor:	Sun Pharmaceutical Industries Ltd
Protocol [redacted]	BRIN-20-01 [redacted]
[redacted]	[redacted]
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4 Abbreviations

ABBREVIATION	DEFINITION
AE	Adverse Event
BSCVA	Best-Spectacle Corrected Visual Acuity
CI	Confidence Interval
eCRF	Electronic Case Report Form
IOP	Intraocular Pressure
ITT	Intent-To-Treat
MedDRA	Medical Dictionary of Regulatory Affairs
MMRM	Mixed Model Of Repeated Measures
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SAP	Statistical Analysis Plan
SOC	system organ class
SPIL	Sun Pharmaceutical Industries Ltd
TOST	Two one-sided tests
TEAE	Treatment-Emergent Adverse Event
TID	Three Times Daily
w/v	Weight per Volume

5 Introduction

This statistical analysis plan (SAP) provides explicit guidance and describes the planned statistical and data handling methods to be followed during the final reporting and analyses. The intent of this document is to provide detailed information of the analysis of trial data related to safety and efficacy and to describe any applicable statistical procedures explicitly. The relevant statements are quoted directly from the protocol, within the applicable sections in this document (SAP). This SAP should be read in conjunction with the study protocol [redacted] 12 May 2021 and electronic case report form (eCRF) [redacted]

6 Study Objectives

The following are the study objectives:

6.1.1 Primary Objectives

To evaluate the therapeutic equivalence of TID dosing (will be done approximately 8.00 AM. (±60 minutes), 4.00 PM. (±60 minutes) and 10.00 PM. (±60 minutes) of SPIL's Brinzolamide ophthalmic suspension USP 1% (10mL) w/v compared with Azopt® 1% (10mL) in subjects with open-angle glaucoma or ocular hypertension.

6.1.2 Secondary Objectives

The secondary objective is to evaluate the safety of TID dosing of SPIL's Brinzolamide ophthalmic suspension USP 1% w/v compared with Azopt® 1% in subjects with open-angle glaucoma or ocular hypertension.

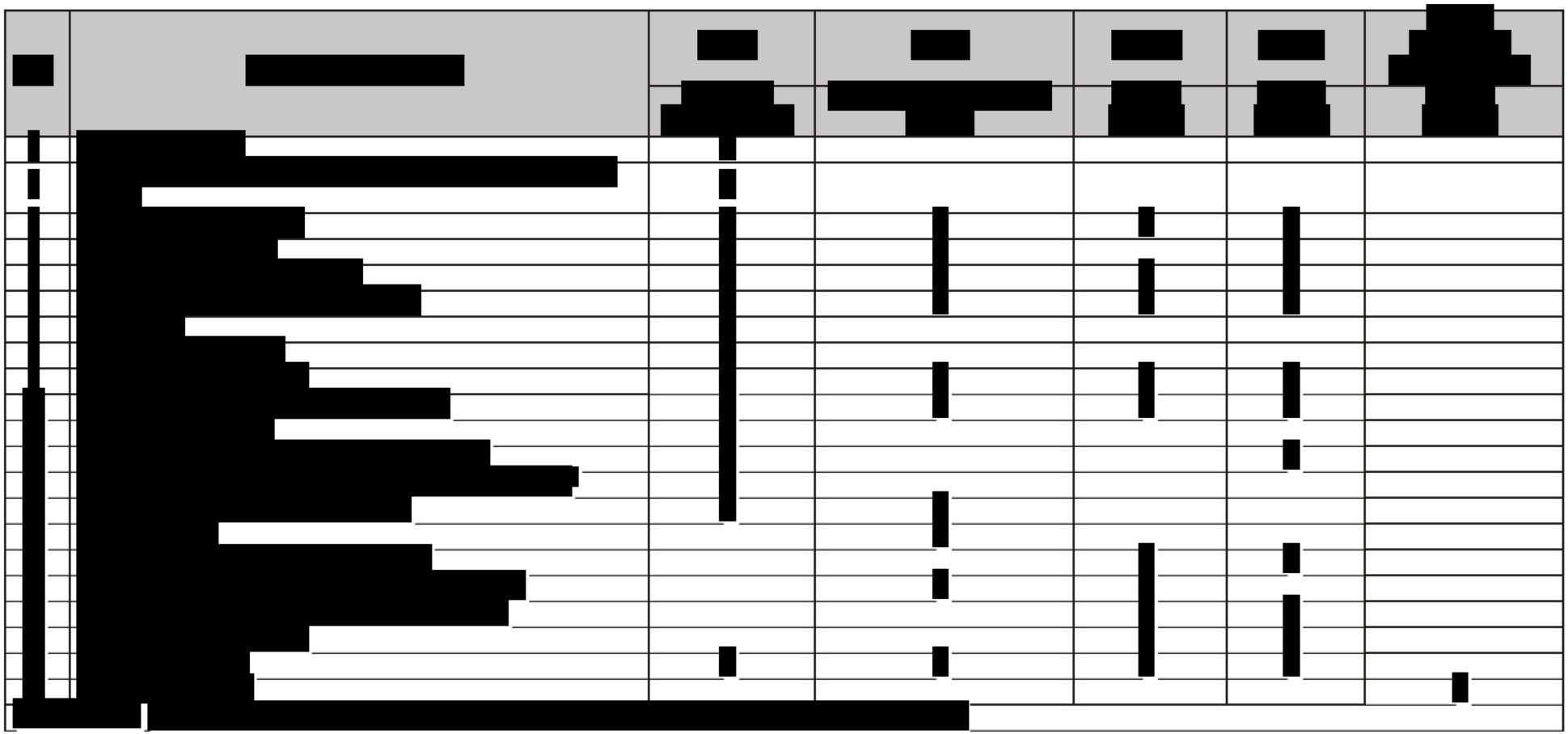
7 Study Design

7.1 Overview

7.1.1 Study Design

This is a randomized, Investigator-masked, multiple-center, parallel-group, therapeutic equivalence study with clinical endpoint (endpoint is mean difference in IOP of both eyes between the 2 treatment groups).

Treatment period will consist of TID dosing for 6 weeks. Subjects who are chronically treated with ocular hypotensive medications are required to undergo appropriate washout periods prior to study entry to minimize any residual effects of other active ocular hypotensive medications.



7.1.2 Treatment Groups

Approximately 666 subjects (333 per treatment arm) will be randomized in this study in a 1:1 treatment allocation ratio. The study will be conducted in Russia and India, out of 666 subjects466 subjects will be recruited in Russia and 200 subjects will be recruited in India.

IMP: Brinzolamide ophthalmic suspension USP 1% w/v, 10mL.

RLD: Azopt® 1% (brinzolamide ophthalmic suspension), 10mL.

7.2 Study Endpoints

7.2.1 Primary Efficacy Endpoint

Primary endpoint of this study is to assess the mean difference in IOP of both eyes between the two treatment groups dosed in each eye TID approximately at 8.00 AM. (±60 minutes), 4.00 PM. (±60 minutes) and 10.00 PM. (±60 minutes) and sample collected at four time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and 10:00 a m. (2 hours) at the Day 14 (Week 2) and Day 42 (Week 6) visits.

7.2.2 Secondary Efficacy End point

Change from baseline in IOP of both eyes between the 2 treatment groups at 4 time points, i.e., at approximately 8:00 a m. (hour 0; before the morning drop) and 10:00 a.m. (hour 2) at the Day 14 (Week 2) and Day 42 (Week 6) visits.

7.2.3 Safety Assessments

- Incidence and severity of AEs
- BSCVA
- Slit lamp Biomicroscopy
- Tonometry
- Dilated fundus exam, including Cup/Disc ratio

8 General Statistical Considerations

8.1 Descriptive Statistics

The following descriptive statistics will be calculated for continuous data and for categorical data:

Summary statistics are displayed with the following digits:

Description	Characteristic	Number of decimal places
Count	n	0
Count corresponding to the number of patients for a group	N	0
Mean	Mean	As in source + 1
Standard Deviation	SD	Mean+1
Minimum	Min	As in source
Median	Median	As in source + 1
Maximum	Max	As in source
Percentage relative to N #	%	1
Confidence Interval	CI	Respective Estimate+2
1st Quartile / 3rd Quartile	Q1/Q3	As in source + 1

Number of decimal places can be more than one, if necessary. All table percentages should be rounded to one decimal place if not stated otherwise.

All data will be presented in the subject data listings.

If either table or listing does not include any observation, then the following placeholder will be used: "NO DATA CONTRIBUTED TO THIS TABLE / LISTING".

8.2 Analysis Population

Analysis Population	Definition
All Screened Population	All patients who have signed the informed consent form
Intent-to-Treat Population	The Intent-to-Treat (ITT) population consists of all subjects who are randomized into the study. and ITT based analysis will be used as confirmatory analyses
Per Protocol Population	The PP population includes all randomized subjects who meet all inclusion/exclusion criteria, and complete evaluations at week 2, week 6 (with compliance between 75 to 125%) with no major protocol deviations that would affect the treatment evaluation (primary endpoint). The PP population will be considered the primary analysis population for the study and will summarize subjects as treated.
Safety Population	The safety population includes all subjects who receive at least 1 dose of study medication. The safety population will be used to summarize safety variables and will summarize subjects as treated.

Note: As there are multiple examples of violations to GCP and ALCOA principles, all the data reported from Site # 122 is not reliable. Hence, based on the clinical investigation report dated 13 Sep 2023, it has been agreed to remove all the 20-subject data from the efficacy analysis These 20 subjects will be included in the safety analysis of the study data. However, safety data will be presented with and without subjects from Site #122.

8.3 Definitions

In the following table, the definitions and calculation of derived variables are summarized.

Variable / Term	Definition / Way of calculation
Treatment Start Date	Date of dose administration on Day
Treatment End Date	Date of Last Study Medication Taken in EoS page in CRF
Duration of exposure	Treatment end date- treatment start date + 1
Treatment Emergent AE (TEAE)	An AE will be considered as treatment-emergent if the time of onset is on or after the time of the first study drug administration or any AE that exist prior to first dose and if it increased in severity during the study
IOP	IOP will be measured at least twice in each eye with the right eye measured first. If the difference of the first 2 measurements is ≤ 1 mm Hg, the average of these 2 measurements will be used as the IOP data for this eye. If the difference is > 1 mm Hg, a third measurement will be taken, and the median of these 3 measurements will be used as the IOP data for this eye.

Variable / Term	Definition / Way of calculation
Masking	In order to maintain the double-blind nature of the study, all study-related individuals, including the subjects, ancillary study site staff, clinical monitor(s), Investigator, Sponsor, and CRO staff, will remain blinded to the administered treatment.

8.4 Protocol Violation/Deviation

The relevant protocol violations/deviations have to be defined by a systematic data review prior to database closure. For this purpose, protocol violations that occurred during the study such as violations of inclusion/exclusion criteria or forbidden concomitant medications or patient non-compliance will be assessed as 'major' or 'minor' depending on their potential to interfere with the objectives of the study. Listings will be prepared to show the eligibility of all patients. Comprehensive justification for the classification of a protocol violation/deviation as "major" will be given in the integrated clinical study report.

A separate Protocol deviation listing will be prepared for the patients who discontinued the study or could not able to continue the study treatment or could not visit the study center or any procedure could not be performed.

8.5 Data Handling

8.5.1 Imputation of Missing data

Efficacy:

The analyses of the efficacy variable IOP) will be completed on observed data only (without imputation).

Safety:

To handle missing or partial AE and concomitant medication dates, the following rules will be applied.

For partial start dates:

The below table will illustrate how the imputation to be performed for unknown date/month/year.

DD	MM	YYYY	Imputation
Known	Known	Unknown	Do not impute the date but assign a missing value.
Known	Unknown	Known	a. If the year matches the year of the dose date, then impute the month and day of the dose date. b. Otherwise, assign "January."
Unknown	Known	Known	a. If the month and year match the month and year of the first dose date, then impute the day of the dose date. b. Otherwise, assign "01."

For partial end dates:

The below table will illustrate how the imputation to be performed for unknown date/month/year.

DD	MM	YYYY	Imputation
Known	Known	Unknown	Do not impute the date but assign a missing value.
Known	Unknown	Known	Assign month as "December."
Unknown	Known	Known	Assign last day of the month

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pretreatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken, and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration, then the most conservative approach is taken, and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

3. If the start date is missing but the stop date is not missing and is before the day of study dose and after the date of signed informed consent, then the AE (or medication) is considered to be before treatment (or prior medication).

4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken, and medication is considered to be concomitant while the AE is defined by start date.

If the Adverse Event Relationship flag is missing, the relationship for adverse event will be imputed and will be considered as related. If the Adverse Event Severity flag is missing, the severity will be imputed with the maximum severity will be considered as severity.

8.6 Sample Size Calculation

An equivalence test of means using two one-sided tests on data from a parallel-group design with sample sizes of 266 in the SPIL's Brinzolamide ophthalmic suspension 1% and 266 in Azopt® 1% achieves 90% power at an $\alpha = 0.05$ significance level when the true difference between the means is 0, the standard deviation is 3.5, and the 95% equivalence limits are -1.0 and 1.0.

Considering the possibility of 20% of subjects not being evaluable either due to dropping out of the study or having major protocol violations, approximately 333 subjects will be enrolled in each treatment group for a total of 666 subjects in the study.

8.7 Interim Analysis

There is no interim analysis planned for the study.

8.8 Statistical Software

All statistical analyses will be performed with SAS®, Version 9.4 or later.

9 Statistical Analyses

9.1 Subject Disposition

Subject disposition will be tabulated with number and percentages of patient's screened, screen failed, randomized, dosed, completed the study according to the protocol or discontinued the study prematurely. The patients who prematurely discontinued the study and the reasons for their discontinuation will be presented. The disposition table will be summarized using "Screened population" by treatment group.

9.2 Demographic Data and Baseline Characteristics

The demographic data and baseline characteristics will be summarized using descriptive statistics or by frequency and percentage for the applicable parameters using SAF Population by treatment group.

- Age
- Gender
- Race
- Ethnicity
- Iris color
- Childbearing potential
- Best Spectacle-Corrected Visual Acuity Score (Left / Right Eye)

9.3 Medical History

All general medical history conditions and concomitant diseases will be coded using MedDRA version 24.0. General medical history conditions and concomitant diseases will be summarized by system organ class, preferred term and by treatment group using SAF population. The version of the utilized dictionary will be presented as part of the provided tables and listings. Listing of medical history will be provided.

9.4 Prior and concomitant medication

Prior and concomitant medications will be assessed at screening, while concomitant medications will be assessed at each subsequent study visit. Medications will be coded using WHODG MAR 1, 2021.

Medication will be classified as prior, if the end date is known and is prior to the first use of the study medication. Medications that are ongoing or ended after the first use of the study medication will be classified as concomitant. If the end date of the medication is unknown, it will also be considered as concomitant. Handling of missing date explained in section (Imputation of missing data section 8.5).

Prior and concomitant medications will be separately summarized by ATC class (the highest available level), preferred name and treatment group for the safety population. Listings will be presented for prior and concomitant medications.

9.5 Protocol Deviation

Protocol deviations will be summarized by Number of patients with protocol deviations (Major/). Protocol deviations will also be summarized by Number of patients with Major/Minor Protocol Deviations by its category and treatment using SAF population.

Table and Listings will be presented for all the protocol deviations and separate table and listings.

9.6 Efficacy Analysis

Primary and secondary efficacy endpoint will be analysed using the PP population.

9.6.1 Primary Efficacy Endpoint

Mean difference in IOP of both eyes between the two treatment groups at four time points, i.e., at approximately 8:00 a m. (hour 0; before the morning drop) and 10:00 a.m. (2 hours) at the Day 14 (Week 2) and Day 42 (Week 6) visits

IOP measurements will be taken using a Goldmann applanation tonometer. IOP will be measured at least twice in each eye with the right eye measured first. If the difference of the first 2 measurements is ≤ 1 mm Hg, the average of these 2 measurements will be used as the IOP data for this eye. If the difference is > 1 mm Hg, a third measurement will be taken, and the median of these 3 measurements will be used as the IOP data for this eye.

Two-sample 95% CIs around the difference in the mean IOP (both eyes) at each timepoints i.e., at approximately 8:00 a m. [hour 0; before the morning drop] and 10:00 a.m. [hour 2] at the Day 14 [Week 2] and Day 42 [Week 6]) visits will be constructed using a two-sample t-distribution.

The hypotheses for a two-sample equivalence test are:

H_o: $\mu < \Theta_L$ or $\mu > \Theta_U$

H_1: $\Theta_L \leq \mu \geq \Theta_U$

Where,

μ: Difference in mean IOP between treatment groups within study period

Θ_L: -1.5mm Hg and (-1.0mm Hg)

Θ_U: 1.5mm Hg and (1.0mm Hg)

The overall p-value of the equivalence test will be reported, which is the larger of the two p-values of the tests L and U. Rejection of H_0 in favour of H_1 at significance level α occurs if and only if the 100 (1-2α) % confidence interval for μ is contained within (-1.5, 1.5) and (-1.0, 1.0). Two sample t-test also assumes equality of variances in the treatment groups, hence depending on the results from Levene's test, CI, and p-values from Equal (Pooled) or Unequal (Satterthwaite) variance will be reported.

This analysis also will be tested for ITT population to check the robustness of the result.

9.6.2 Secondary Efficacy Endpoints

Change from baseline in IOP of both eyes between the 2 treatment groups at 4 time points, i.e., at approximately 8:00 AM. (hour 0; before the morning drop) and 10:00 AM. (hour 2) at the Day 14 (Week 2) and Day 42 (Week 6) visits.

For change from baseline IOP, baseline will refer to the time-matched measure at Visit 2. Change from baseline will be calculated as visit x – baseline. The overall p-value of the equivalence test will be reported, which is the larger of the two p-values of the tests L and U. Rejection of H0 in favour of H1 at significance level α occurs if and only if the 100 (1-2α) % confidence interval for μ is contained within (-1.5, 1.5) and (-1.0, 1.0). Two sample t-test also assumes equality of variances in the treatment groups, hence depending on the results from Levene's test, CI and p-values from Equal (Pooled) or Unequal (Satterthwaite) variance will be reported. This mean IOP must be within ± 1.5 mm Hg using the PP population for all time points measured and within ± 1.0 mm Hg using the PP population for the majority of time points measured.

This analysis also will be tested for ITT population to check the robustness of the result.

In addition to these individual confidence intervals, a mixed effects repeated measures model, with random effect for subject, covariate for baseline IOP, and fixed effects for treatment and day/time (within subject repeated measures) will be fitted to the data. Appropriate covariance structure will be used to model the within subject, between time point variances with order of treatment Visit treatment*visit and baseline as covariate. Individual and simultaneous confidence intervals will then be constructed based on this MMRM model at each of the time points. The 95% simultaneous confidence intervals will use the Tukey-Kramer method to adjust for multiple comparisons across all 4 time points. Above mentioned analysis will be performed on PP and ITT population.

9.6.3 Safety Analysis

The safety population includes all randomized subjects who receive study product

9.6.3.1 Adverse Events

The primary safety analysis will summarize ocular (in both the eyes) and non-ocular AEs for all treated subjects using discrete summaries at the subject level by Medical Dictionary for Regulatory Activities (MedDRA®), SOC, and PT for each treatment group. A TEAE will be defined as occurring after the first dose of study medication for the period. Treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity. For safety summaries the unit of analyses will be both eyes for ocular measures and will be the subject for non-ocular safety measures as well as all AEs.

An AE will be considered as treatment-emergent if the time of onset is on or after the time of the first study drug administration or any AE that exist prior to first dose and if it increased in severity during the study period. Handling of missing data and date are explained in section 8.5 (Imputation of missing data).

An overall summary table, which summarizes, the number and percentages of patients with adverse events, serious adverse events, adverse events leading to death, adverse events related to study drug, Study Drug Discontinued Permanently due to adverse event and adverse events by severity categories will be provided by treatment groups.

Patients experiencing any treatment emerging adverse events will be summarized by Preferred Term (PT), SOC and treatment group. The number and percentage of patients with at least one TEAE, SAE, permanently discontinued study treatment (IP) due to AE, AE leading to Death, AE by relationship and TEAEs of severe intensity will be summarized by system organ class, preferred term and treatment group.

Furthermore, listings of SAEs and AEs that lead to study withdrawal will be provided.

AEs Tables by primary system organ class, preferred term and treatment group will be sorted in descending order of counts.

A patient experiencing the same AE multiple times will be counted only once for that preferred term. Similarly, if a patient experiences multiple AEs within the same system organ class that patient will be counted only once in that system organ class. Maximum severity will be considered if a patient has multiple severity reported for same AE. In summaries by relationship, if a subject has the same AE on multiple occasions, the closest relationship to study drug, will be used for summary.

9.6.3.2 Vital Signs

The actual and change from baseline of Heart rate and blood pressure will be summarized descriptively using SAF population and treatment group. In addition, number and percentage of patients reaching ‘Normal’, ‘Abnormal CS’ and ‘Abnormal NCS’ results for vital signs parameters will be summarized by treatment group and visit using SAF population.

Data listings will be presented for vital signs parameters.

9.6.3.3 Best spectacle-corrected visual acuity (BSCVA)

The actual and change from baseline of Base logMAR, Number of letters missed and Visual Acuity Testing for each eye will be summarized descriptively using SAF population and treatment group.

Data listings will be presented for best spectacle-corrected visual acuity (BSCVA)

9.6.3.4 Corneal pachymetry (CP)

Corneal pachymetry data will be summarized descriptively using the SAF population and treatment group.

Data listings will be presented for Corneal pachymetry (CP).

9.6.3.5 Slit-lamp biomicroscopy (SLIT)

Slit-lamp biomicroscopy (SLIT) will be summarized by frequencies and percentages using the SAF population and treatment group by each visit.

Listing will be provided for the Slit-lamp biomicroscopy (SLIT)

9.6.3.6 Gonioscopy (GONI)

Gonioscopy (GONI) will be summarized by frequencies and percentages using the SAF population and treatment group.

Listing will be provided for the Gonioscopy (GONI)

9.6.3.7 Dilated ophthalmoscopy, including C/D ratio (DO)

Dilated ophthalmoscopy, including C/D ratio (DO) will be summarized by frequencies and percentages using the SAF population and treatment group by visit.

Listing will be provided for the Dilated ophthalmoscopy, including C/D ratio (DO)

9.6.3.8 Automated Perimetry (AP)

Automated Perimetry (AP) will be summarized by frequencies and percentages using the SAF population and treatment group.

Listing will be provided for the Automated Perimetry (AP)

9.6.3.9 Discontinue current IOP-lowering Medication (DIOPM)

Discontinue current IOP-lowering Medication (DIOPM) will be summarized using frequency and percentage using the SAF population and treatment group.

9.6.3.10 Dispense study medication and compliance diary (DSMCD)

Dispense study medication and compliance diary (DSMCD) will be summarized using frequency and percentage using the SAF population and treatment group and visit.

Listing will be provided for the Dispense study medication and compliance diary (DSMCD)

9.6.3.11 Urine pregnancy test

Listing will be provided for the Urine pregnancy test.

9.7 Data Manipulation and Subgroup Analyses

Not Applicable.

10 Deviation from the Study Protocol

Not Applicable.

11 Database Lock and Unblinding

The SAP will be finalized prior to database lock. After the data cleaning process is finalized according to the data management plan (DMP) and the assignment of patients to the analysis sets is agreed and signed by the sponsor, the study database will be locked.

12 References

Not Applicable