SUMMITANALYTICAL	**STATISTICAL ANALYSIS PLAN** **CONFIDENTIAL**

Betaliq, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Randomized, Multicenter, Observer-Masked Study to Compare the Safety and Efficacy of BTQ-1901-A, BTQ-1901-B, and BTQ-1902 to Timolol 0.5% in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension
Protocol Number:	BTQ-1901-1902-201
Phase:	Phase 2
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SAP Date:	12APR2022
Status:	FINAL 1.0

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation/Term	Definition
AE	Adverse event
AIC	Akaike Information Criteria
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BCVA	Best-corrected visual acuity
BID	Twice daily
BP	Blood pressure
CI	Confidence interval
eCRF	Electronic case report form
EDC	Electronic data capture
HR	Heart rate
IOP	Intraocular pressure
ITT	Intent-to-treat population
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
LogMAR	Logarithm of the minimum angle of resolution
LS mean	Least squares means
MMRM	Mixed model for repeated measures
MedDRA	Medical Dictionary for Regulatory Activities
OD	Right eye
OHT	Ocular hypertension
OS	Left eye
POAG	Primary open angle glaucoma
PK	Pharmacokinetic
PT	Preferred term
ROCK	Rho-associated protein kinase
PP	Per-protocol population
SAE	Serious adverse event
SAF	Safety population

Abbreviation/Term	Definition
SAP	Statistical Analysis Plan
SE or se	Standard error
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
VF	Visual field
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

3.1. Preface

This document presents a statistical analysis plan (SAP) for Betaliq, Inc. Protocol BTQ-1901-1902-201 (*A Randomized, Multicenter, Observer-Masked Study to Compare the Safety and Efficacy of BTQ-1901-A, BTQ-1901-B, and BTQ-1902 to Timolol 0.5% in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension*).

Reference materials for this statistical plan include the protocol BTQ-1901-1902-201 (Version 1.0 Dated: 01JUN2020) and Case Report Forms (Final Version 4.0, dated 20JUL2021).

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to unmasking of any study data. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes. In such an event, arbitrary treatment group assignments must be randomly linked to subjects, effectively rendering any output of programs meaningless.

For the reasons stated here the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

3.2. Purpose of Analyses

The purposes of the planned analyses described in this SAP are to compare the safety and efficacy of BTQ-1901-A, BTQ-1901-B, and BTQ-1902 to Timolol 0.5% in subjects with primary open angle glaucoma (POAG) or ocular hypertension (OHT). Results from the analyses completed will be included in the final clinical study report for BTQ-1901-1902-201, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report, but will be fully documented in the document containing the additional analyses.

3.3. Summary of Statistical Analysis Changes to the Protocol

The analyses described in this analysis plan are consistent with the analyses described in the study protocol.

4. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints defined in the protocol include safety and efficacy endpoints. Objectives and pre-specified endpoints are as follows:

4.1. Study Objectives

4.1.1. Primary Objective

The primary objective of the study is to evaluate ocular and systemic safety and the efficacy of BTQ-1901-A, BTQ-1901-B, and BTQ-1902 ophthalmic suspensions in comparison to timolol 0.5% ophthalmic solution in subjects with POAG or OHT.

4.2. Study Endpoints

4.2.1. Efficacy Endpoints

4.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be intraocular pressure (IOP) values at each time point (8:00 AM, 2 hours after dosing of study medication [~10:00 AM], 4:00 PM) at Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84.

4.2.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will include the following:

- Change from baseline (Visit 3/Qualification/Baseline) in the average of the 3 daily IOP measurements at each post baseline visit.
- Time-matched change from baseline (Visit 3/Qualification/Baseline) in IOP measurements at all time points at Visit 4/Day 15, Visit 5/Day 42 and Visit 6/Day 84.

4.2.2. Safety Endpoints

Safety and tolerability endpoints will include the following:

- Bilateral ophthalmic examination results (LogMAR best-corrected visual acuity [BCVA], slit lamp examination, ophthalmoscopy/dilated fundus examination, visual field [VF] testing, rating of drop comfort as assessed by the subject, grading of conjunctival hyperemia by the Investigator);
- Resting heart rate and blood pressure (HR/BP);

- Incidence, severity of adverse events (AEs), serious AEs (SAEs), their relationship to the study drug of AEs, SAEs, and AEs leading to discontinuation of the study drug.

4.2.3. Pharmacokinetic Endpoints

Pharmacokinetic endpoint will include plasma drug concentration measured in a subset of 40 subjects with blood samples collected following dosing at Visit 4/Day 15 and Visit 6/Day 84.

5. STUDY METHODS

5.1. General Study Design and Plan

As background for the statistical methods presented below, this section provides an overview of the study design and plan of study execution. The protocol is the definitive reference for all matters discussed in what follows.

This will be a randomized, multicenter, parallel-group, observer-masked study to evaluate ocular and systemic safety and the efficacy of BTQ-1901-A (nebivolol 0.5%), BTQ-1901-B (nebivolol 1.0%) and BTQ-1902 (timolol 0.5%) ophthalmic suspensions in comparison to timolol 0.5% ophthalmic solution. The study will enroll approximately 240 subjects with POAG or OHT who will be treated for 84 days (12 weeks).

Adult subjects will have POAG or OHT in both eyes (presence of POAG in one eye and OHT in the fellow eye is acceptable). If required, subjects will participate in a minimum washout period of 28 days for prostaglandin analogs, rho-associated protein kinase (ROCK) inhibitors, or beta (β) blockers; 14 days for adrenergic agonists; and 5 days for muscarinic agonists or carbonic anhydrase inhibitors (CAIs).

At least one eye must qualify for the study, but even if only one eye meets all inclusion/exclusion criteria, both eyes will be treated. If both eyes qualify, the qualifying eye with the higher IOP at 8:00 AM at Visit 3/Qualification/Baseline will be designated as the study eye. Should the 8:00 AM IOP be the same in both eyes, then the right eye will be designated as the study eye.

A total of 240 eligible subjects will be randomized in a 1:1:1:1 ratio into 1 of 4 treatment arms: BTQ-1901-A: nebivolol 0.5% ophthalmic suspension; BTQ-1901-B: nebivolol 1.0% ophthalmic suspension; BTQ-1902: timolol 0.5% ophthalmic suspension; and timolol 0.5% ophthalmic solution and receive 1 drop in each eye BID, morning and evening, for 84 days.

The identity of the study medications will be masked to the Investigator and study personnel responsible for endpoint-related study procedures.

The schedule for assessments and timing of events is presented in Table 1.

Table 1 Schedule of Procedures

	Screen-ing	Washout Safety Check[a]	Qualification/ Baseline			Treatment								
Day	**-35 to -1**	**-14 ± 3**	**1**			**15 ± 3**			**42 ± 3**			**84 ± 3**		
Visit	**1**	**2**	**3**			**4**			**5**			**6**		
Hour[b]			**8:00 AM**	**10:00 AM**	**4:00 PM**	**8:00 AM**	**2 h post dose**	**4:00 PM**	**8:00 AM**	**2 h post dose**	**4:00 PM**	**8:00 AM**	**2 h post dose**	**4:00 PM**
Informed consent	X													
Medical/ophthalmic history	X													
Demographics	X													
Adverse events[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X			X			X			X		
Urine pregnancy test[d]	X		X									X		
HR/BP[e]	X			X			X			X			X	
BCVA (logMAR)	X	X	X			X			X			X		
Grading conjunctival hyperemia[f]			X			X			X			X		
Biomicroscopy	X		X	X	X	X	X	X	X	X	X	X	X	X
IOP[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual field test[h]	X											X		
Gonioscopy[i]	X													
Pachymetry[j]	X													
Dilated ophthalmoscopy	X													X
Review eligibility	X				X									
Randomization					X									
Blood collection (PK)[k]							X						X	

	Screen-ing	Washout Safety Check[a]	Qualification/ Baseline			Treatment								
Day	**-35 to -1**	**-14 ± 3**	**1**			**15 ± 3**			**42 ± 3**			**84 ± 3**		
Visit	**1**	**2**	**3**			**4**			**5**			**6**		
Hour[b]	**-**	**-**	**8:00 AM**	**10:00 AM**	**4:00 PM**	**8:00 AM**	**2 h post dose**	**4:00 PM**	**8:00 AM**	**2 h post dose**	**4:00 PM**	**8:00 AM**	**2 h post dose**	**4:00 PM**
Study medication dispensed/redispensed					X			X			X			
Drop instillation/ instruction/evaluation					X	X[l]			X[l]			X[l]		
Drop comfort rating[m]					X	X			X			X		
Study medication accountability[n]					X			X			X			X
Compliance assessment[o]							X			X			X	

BP = blood pressure; HR = heart rate: IOP = intraocular pressure; IP = investigational product; PK = pharmacokinetics

NOTE: Subjects using ocular hypotensive medications must have undergone the appropriate required washout period prior to Visit 3/Qualification/Baseline.

NOTE: If a study subject is discontinued from study medication before Visit 6/Day 84 but after Visit 3/Qualification/Baseline/Day 1, every effort should be taken to perform all the procedures listed for Visit 6/Last Day of Treatment (Section 10.4.3). If the subject is willing to remain at the site for the 8-hour visit, it should be conducted as specified, but if the subject is not willing to remain for the full duration, the VF test and the dilated ophthalmoscopy should be conducted as the last ophthalmic assessments in the early discontinuation visit.

[a] Mid-washout safety check for subjects undergoing 28-day washout periods (i.e., prior prostaglandin analogs, rho-associated protein kinase [ROCK] inhibitors, or β-blockers) may be performed at the Investigator's discretion.

[b] The window for each time point is ± 30 minutes. For Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84, the 2 h post-dose timepoint will fall around 10:00 AM, but the timing of the IOP measurement is dependent on the time study medication was administered at the site that day and should be 2 hours (± 30 minutes) after the dose was administered.

[c] All AEs that occur following consent and until the final study visit (Visit 6/Day 84) should be collected and recorded on the AE eCRF page.

[d] Required only for women of childbearing potential. At Visit 3/Qualification/Baseline/Day 1 it must be performed prior to randomization. At Visit 6/Day 84 it may be performed anytime.

[e] HR and BP will be measured seated after at least 5 minutes rest. Vital signs may be repeated once, after at least an additional 5 minutes rest in the seated position, if they are out of range.

[f] It is preferred that conjunctival hyperemia be graded as part of the external eye exam performed prior to biomicroscopy.

[g] At Visit 3/Qualification/Baseline, IOP will be taken bilaterally at 8:00 AM, 10:00 AM, and 4:00 PM (each ± 30 minutes). At Visits 4, 5, and 6, IOP will be taken bilaterally at 8:00 AM, 2 hours after study medication dosing at the clinical site (~10:00 AM), and at 4:00 PM (each ± 30 minutes). Two consecutive IOP measurements of each eye will be performed. If the 2 measurements differ by more than 2 mm Hg, a third measurement will be taken. Consult the Study Manual for specific details.

[h] Visual field measurement may be performed within 90 days prior to Screening if a test meeting the protocol requirements was performed and the results were documented. If the VF performed at or within 90 days prior to Visit 1 does not meet study required parameters, it may be repeated (test should be prior to randomization at Visit 3/Qualification/Baseline). The procedure may be performed at any time during the visit prior to dilation for ophthalmoscopy.

[i] Gonioscopy may be performed within 90 days prior to Screening. The procedure must be performed after IOP measurement and before dilation for ophthalmoscopy.

[j] Pachymetry may be performed within 90 days prior to Screening. The procedure may be performed at any time during the visit after IOP measurement.

[k] Plasma concentration will be measured in a subset of 40 subjects; samples will be collected 2 hours (± 30 minutes) after study medication dosing at the clinical site.

[l] Dose instillation should occur as close as possible to 15 minutes after IOP measurement, but not before 10 minutes after IOP measurement. Artificial tear use is prohibited within 10 minutes of instillation of study medication.

[m] Subjects will be asked to rate the tolerability of the drop according to the following 4-point scale: 0 = No discomfort, 1 = Mild discomfort, 2 = Moderate discomfort, 3 = Severe discomfort. This rating should take place ≥ 10 minutes after the IOP measurement.

[n] Study medication accountability may be performed at any time during the visit.

[o] Compliance will be monitored via subject-reported missing doses in the Missed Doses Log. Documentation of compliance may be performed at any time during the visit.

5.2. Inclusion – Exclusion Criteria and General Study Population

The general study population will include a total of 240 subjects with POAG or OHT. The inclusion and exclusion criteria defined in the protocol apply to all subjects and are not repeated herein the SAP. Reference is made to the final protocol for the specific inclusion and exclusion criteria for study subjects.

5.3. Randomization and Masking

A total of 240 eligible subjects will be randomized in a 1:1:1:1 ratio into 1 of 4 treatment arms and receive 1 drop in each eye BID, morning, and evening, for 84 days:

- BTQ-1901-A (nebivolol 0.5% ophthalmic suspension) (N = 60)
- BTQ-1901-B (nebivolol 1.0% ophthalmic suspension) (N = 60)
- BTQ-1902 (timolol 0.5% ophthalmic suspension) (N = 60)
- Timolol 0.5% ophthalmic solution (N = 60) [active comparator]

A randomized block design will be used, and the randomization will be created by a biostatistician independent of the trial. Randomization will not be stratified by any factors.

If subjects meet eligibility criteria at Visit 1/Screening as well as at Visit 3/Qualification/Baseline, sites will access the Interactive Web Response System (IWRS) to randomize subjects to study treatment and assign the study medication kit to be dispensed. The drug kit and randomization numbers will be recorded in the subject's eCRF. Study medication from the IWRS-assigned kit will be dispensed to the subject after initial dosing at the study site on Day 1 (Visit 3/Qualification/Baseline). The study will be observer masked.

Rules for unmasking a subject for safety reasons are fully described in the protocol and not repeated herein this SAP.

5.4. Analysis Variables

Variables to be analyzed include demographics and baseline characteristics, efficacy variables (IOP values at each timepoint and change from baseline), safety/tolerability variables (adverse events, bilateral ophthalmic examinations, vital signs, rating of drop comfort, and conjunctival hyperemia grading) and PK concentrations.

6. SAMPLE SIZE

The sample size is not based on a formal sample size calculation; this study is planned to provide sufficient data to power the Phase 3 study.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

There will be 4 (four) analysis populations defined for this study.

7.1.1. Intent-to-Treat Population (ITT)

The ITT population is defined as all randomized subjects. Supplemental efficacy analyses will be conducted on the ITT population.

7.1.2. Per-Protocol Population (PP)

The PP population consists of those subjects in the ITT population who were randomized and dosed and had no major protocol deviations. The primary efficacy analysis will be conducted on the PP population. Subjects who are members of the PP population will be analyzed as randomized.

7.1.3. Safety Population (SAF)

The safety population is defined as all randomized subjects who received at least one dose of the allocated study medication. All safety analyses will be performed using the safety population. Subjects who are members of the safety population will be analyzed as treated.

7.1.4. Pharmacokinetic Population (PK)

The PK population will consist of the subjects who were randomized, dosed, and have at least one PK value. It is planned that plasma concentration will be measured in a subset of 40 subjects. Subjects who are members of the PK population will be analyzed as treated.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

Planned covariates include baseline IOP for the efficacy analyses.

7.2.2. Planned Subgroups

There are no planned subgroup analyses.

7.3. Management of Analysis Data

7.3.1. Data Handling

At least one eye must qualify for the study. Even if only one eye meets all inclusion/exclusion criteria, both eyes will be treated. If both eyes qualify, the qualifying eye with the higher IOP

at 8:00 AM at Visit 3/Qualification/Baseline will be designated as the study eye. Should the 8:00 AM IOP be the same in both eyes, then the right eye will be designated as the study eye.

At each IOP measurement time point, 2 consecutive IOP measurements of each eye will be performed. If the 2 measurements differ by more than 2 mm Hg, a third measurement will be taken. Mean IOP is calculated as the mean of 2 measurements or as the median of 3 measurements.

7.3.2. Missing Data

All data recorded on the electronic case report form (eCRF) will be included in data listings that will accompany the clinical study report. All efficacy analyses will be based on observed cases (without imputation). Multiple imputation methods and single imputation methods (e.g., last observation carried forward [LOCF]) will be utilized for sensitivity analyses for select variables.

7.3.2.1. Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for AEs and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates
   1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
   2) If the month is unknown, then:
      i) If the year matches the first dose date year, then impute the month and day of the first dose date.
      ii) Otherwise, assign ‘January.’
   3) If the day is unknown, then:
      i) If the month and year match the first dose date month and year, then impute the day of the first dose date.
      ii) Otherwise, assign the first day of the month.

B. Stop Dates
   1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
   2) If the month is unknown, then assign ‘December.’
   3) If the day is unknown, then assign the last day of the month.

7.3.2.2. Baseline

Except for specific analyses noted later (e.g., IOP), baseline values will be the last observation measured prior to dosing. If a repeat value is measured prior to dosing this value can be used for baseline.

7.3.2.3. Missing Baseline Data

Every effort will be made to ensure that accurate baseline information on the subjects is collected. In the event that a subject is missing baseline information the subject will be included in the safety population for assessment of safety and excluded from the primary analyses. All baseline data will be observed cases, without imputation.

7.3.2.4. Imputation Methods

Multiple imputation methods and single imputation methods (e.g., LOCF) will be utilized for sensitivity analyses that include repeating the primary analysis with the ITT population.

7.3.2.4.1. Last Observation Carried Forward (LOCF)

Subjects with missing post-baseline efficacy data will be imputed using the LOCF method for the sensitivity analysis for all primary and secondary efficacy endpoints. For LOCF imputation, missing post-baseline efficacy data will be carried forward from the last non-missing post-baseline value for that endpoint. Baseline efficacy data will not be carried forward to any missing post-baseline value.

7.3.2.4.2. Multiple Imputation

An alternative method of handling missing efficacy data in sensitivity analyses will be the method of multiple imputation. The pattern of missing observations in each treatment group will not influence the missing value estimation in the other because the imputation will be conducted independently for each treatment group. Missing data will be assumed to be missing at random (MAR).

For the imputation step, missing values will be separated into non-monotone missing values (i.e., intermittent missing values between completed assessments) and monotone missing values (i.e., missing values after the subject dropped out). SAS PROC MI procedure will sequentially estimate an imputation model for the IOP values at each post-baseline timepoint where IOP values are collected, separated between the treatment groups.

For the imputation of intermediate missing values, the missing IOP values in each data set will be filled in using the Markov-Chain Monte Carlo (MCMC) method with multiple chains and monotone imputing. A total number of imputations will be 100. The seed used for these imputations will be 2021.

Once the intermediate missing data are imputed, the monotone missing data will be imputed for all subjects with monotone regression. The dataset is the output dataset of the partial imputation. Since this dataset already has 100 imputed values at each visit, only one imputation will be performed.

Analysis timepoint results will be combined for overall inference to account for the uncertainty associated with the imputed values. This will be done using SAS PROC MIANALIZE.

7.3.3. Handling of Early Termination Visit Information

In the event that a subject is terminated early from this study the early termination visit data for safety variables will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

7.3.4. Pooling of Investigational Sites

The data from all study centers will be pooled together for all planned analyses.

7.3.5. Coding Conventions for Events and Medications

All adverse events, and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 24.1) system for reporting (preferred term and body system).

Prior and Concomitant medications will be coded using WHO-DD (Drug Dictionary) (Version date September 2021 B2/B3).

7.3.6. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

7.3.7. Study Data

Study data identified in the schedule for time and events (Table 1) are collected, and source verified, on the electronic data capture (EDC) tool: Laboratory data are not collected in the EDC tool and are provided from external laboratories.

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n) mean, standard deviation, median, minimum, and maximum will be tabulated by treatment. For categorical variables, the counts and percentage of each value will be tabulated by treatment. Expansion of descriptive table categories within each treatment may occur if such elaborations are thought to be useful.

All study related data collected will be presented in listings. Study related data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

7.4.2. Interim Analyses

No formal interim analysis is planned for this study.

7.4.3. Final Analysis and Publication of Study Results

The final analysis will be completed after all subjects have completed Visit 6 or prematurely discontinued the study.

7.5. Multiple Testing Procedures

The primary efficacy analysis will be the between-group comparison of the mean IOP values in the study eye at each time point at each of the Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84 visits (i.e., a total of 9 between-group comparisons). A hierarchical analysis will be conducted to compare each of the investigational products against the comparator, timolol 0.5%, as follows: (1) BTQ-1902, (2) BTQ-1901B, and (3) BTQ-1901A.

To demonstrate noninferiority, the upper limits of the 2-sided 95% confidence interval (CI) for the difference between each comparison should be lower than 1.5 mm Hg at all timepoints. Additionally, the upper limits of the 95% CI should be lower than 1.0 mm Hg for the majority of time points measured (i.e., 5 of 9).

All other comparisons are considered exploratory.

8. SUMMARY OF STUDY DATA

8.1. Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects for the following categories: subjects screened, subjects screen failed, subjects randomized, subjects in ITT Population, subjects in Safety Population, subjects in the PP Population, and subjects in the PK Population. All percentages will be based on the number of subjects randomized.

End of trial information will also be summarized in this table, including the number of subjects completing the study/treatment and the number of subjects that prematurely discontinued the study/treatment with reasons for withdrawal. All percentages will be based on the number of subjects randomized.

A by-subject data listing of study completion information including the reason for premature study withdrawal and also treatment completion status, if applicable, will be presented.

8.2. Protocol Deviations

Major protocol deviations, as determined by a Sponsor masked review of the data prior to database lock and unmasking of the study, may result in the removal of a subject's data from the PP Population. The Sponsor or designee will be responsible for producing the final deviation file; this file will include a description of the protocol deviation and clearly identify whether or not this deviation warrants exclusion from the PP Population. This file will be finalized prior to database lock.

All protocol deviations will be presented in a data listing, with a flag to indicate if a deviation was considered major and resulted in the exclusion of the subject from the PP Population. A summary table will be generated based on the classification of protocol deviations.

8.3. Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively by treatment group and overall. The demographic data and baseline characteristics will be summarized for all analysis populations (ITT, SAF, PP, and PK). Individual subject demographics and baseline characteristics will be provided in listings.

The demographics consist of age (year), sex, race, ethnicity, and iris color. The baseline characteristics consist of baseline diagnosis of Primary Open-Angle Glaucoma and Ocular Hypertension by eye (right eye [OD] and left eye [OS]), designated study eye (OD, OS), baseline systolic/diastolic BP (mm Hg), baseline HR (beats/min), baseline Visual Field testing results (mean deviation), baseline LogMAR BCVA, and pachymetry.

Age, baseline systolic/diastolic blood pressure, baseline heart rate will be summarized using descriptive statistics. The number and percentage of subjects by sex, race, ethnicity, and iris

color will also be reported. Percentages will be based on the total number of subjects in the study population presentation.

All demographic and baseline information will be listed by subject.

8.4. Concurrent Illness and Medical Conditions

The number and percent of subjects with medical/ophthalmic histories will be summarized for all subjects by the type of history and eye (ophthalmic history: study eye, ophthalmic history: non-study eye, non-ocular medical history) and treatment group. Individual subject listings will also be provided for concurrent illness and medical history.

Medical history will be coded using the MedDRA Version 24.1. The number and percentage of subjects with any medical history will be summarized overall and for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of subjects in the Safety Population.

Subject medical history data including gonioscopy will be presented in a listing.

8.5. Prior and Concomitant Medications

The number and percentages of all ocular concomitant medications will be summarized by study/non-study eye and treatment group, Anatomical Therapeutic Chemical (ATC) level 2, and PT. The total number of concomitant medications and the number and percentages of subjects with at least 1 concomitant medication will be summarized by treatment group. All summaries will be performed using the Safety Population.

A concomitant medication is defined as any medication taken on or after the day of first exposure to study drug up until 7 days after last dose of study drug.

Prior medications are defined as any medications started and stopped prior to the day of first exposure to any study drug.

Non-ocular medications will be summarized similarly.

8.6. Treatment Compliance

Continuous descriptive summaries will be presented for the Safety Population by treatment level and will include number of doses, number of doses missed, and study dosing compliance (%). Compliance is calculated for each subject using the following formula:

((Date of last dose – Date of first dose + 1) x2 doses – Missed doses) / ((Date of last visit [Visit 6 or ET] – Date of Visit 3 + 1) x 2 doses) x100%

9. EFFICACY ANALYSES

Unless otherwise noted, all efficacy analyses will be completed using PP and ITT Populations. All efficacy analyses will be completed using the planned dose that the subject was randomized to.

Efficacy data will be presented in tables of descriptive statistics and frequency distribution. All summary tables will be supported with individual subject data listings.

In general, and unless otherwise noted, data summaries will be presented by treatment.

9.1. Primary Efficacy Analysis

The primary efficacy analysis will be the between-group comparison of the mean IOP values in the study eye at each time point at each of the Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84 visits (i.e., a total of 9 between-group comparisons).

A summary of the efficacy endpoints will be prepared at each time point.

The between-treatment comparison will employ a mixed model for repeated measures (MMRM) with treatment, visit/time, treatment-by-visit/time interaction, and average baseline value as fixed effects, and actual IOP value in the study eye as the outcome variable of the model. Visit/time will include the following 9 timepoints: Visit 4/Day 15 (8:00 AM, 10:00 AM, 4:00 PM), Visit 5/Day 42 (8:00 AM, 10:00 AM, 4:00 PM), and Visit 6/Day 84 (8:00 AM, 10:00 AM, 4:00 PM). Average baseline value is the average result of IOP assessments performed at Visit 3/Day 1 (8:00 AM, 10:00 AM, and 4:00 PM).

An unstructured correlation matrix will be used thus allowing adjustment for correlations between time points within patients. A Kenward-Roger approximation will be used for the denominator degrees of freedom. If the model with the unstructured correlation matrix fails to converge then the following correlation structures will be fitted: variance components, compound symmetry, first order autoregressive and Toeplitz. The value of the Akaike Information Criteria (AIC) should be considered to choose the most appropriate model (the model with the smallest AIC is preferred). In case of inadequate results, further modification of the model may be required.

Example SAS code is provided below.

```
proc mixed data=eff method=reml;
    class trt visittime subjid;
    model actual=trt visittime trt*visittime avgbase/ddfm=kr;
    repeated visittime/type=UN subject=subjid;
    lsmeans trt*visittime/cl pdiff;
    run;
```

Where actual is the actual IOP value measured at each visit/time point, trt is treatment (BTQ-1901-A, BTQ-1901-B, BTQ-1902, or Timolol 0.5% ophthalmic solution), visittime is the combination of visit/timepoint (9 total values), and avgbase is the average baseline value.

Treatment comparisons will be performed for the treatment difference in least squares means (LS mean) compared with the Timolol 0.5% treatment group. LS mean (standard error [SE]) by treatment group, visit and time, the LS mean difference between treatment groups, along with 2-sided 95% CI of the treatment differences and the p-value for the treatment comparison will be displayed. To demonstrate noninferiority, the upper limits of 95% CI for the difference between each comparison should be lower than 1.5 mm Hg at all timepoints. Additionally, the upper limits of the 95% CI should be lower than 1.0 mm Hg for the majority of time points measured (i.e., 5 of 9).

Linear contrasts will be used to calculate the confidence intervals at all visit/times.

9.2. Secondary Efficacy Analysis

Similar analysis methods to those used for the primary efficacy endpoints will be utilized for the secondary efficacy endpoints.

Secondary efficacy endpoint #1: MMRM will be used for between-treatment comparison of change from baseline IOP in the average of the 3 daily IOP measurements at each post baseline visit. Treatment, visit, treatment by-visit interaction, and average baseline value will be considered as fixed effects, and change from average baseline IOP value in the study eye will be considered as the outcome variable of the model. Visits to be analyzed will include Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84. Average baseline value is the average result of IOP assessments performed at Visit 3/Day 1 (8:00 AM, 10:00 AM, and 4:00 PM). Change from baseline IOP value is a difference between average result of IOP assessments performed at post-baseline visit and baseline value (defined above).

Example SAS code is provided below.

```
proc mixed data=eff method=reml;
    class trt visit subjid;
    model change=trt visit trt*visit avgbase/ddfm=kr;
    repeated visit/type=UN subject=subjid;
    lsmeans trt*visit/cl pdiff;
    run;
```

Where change is the IOP change from average baseline value using the average of the 3 daily IOP measurements at each visit, trt is treatment (BTQ-1901-A, BTQ-1901-B, BTQ-1902, or Timolol 0.5% ophthalmic solution), visit is the visit (Visit 4/Day 15, Visit 5/Day 42, or Visit 6/Day 84), and avgbase is the average baseline value.

Treatment comparisons will be performed for the treatment difference in LS mean. LS mean (SE) by treatment group, visit and time (applicable for time-matched IOP change from

baseline), the LS mean difference between treatment groups, along with 2-sided 95% CI of the treatment differences and the p-value for the treatment comparison and within-treatment difference will be displayed.

Secondary efficacy endpoint #2: For the analysis of time-matched change from baseline in study eye IOP measurements at all time points MMRM will include treatment, visit/time, treatment-by-visit/time interaction, and average baseline value as fixed effects. Visit/time will include the following 9 timepoints: Visit 4/Day 15 (8:00 AM, 10:00 AM, 4:00 PM), Visit 5/Day 42 (8:00 AM, 10:00 AM, 4:00 PM), and Visit 6/Day 84 (8:00 AM, 10:00 AM, 4:00 PM). The average baseline value is the average result of IOP assessments performed at Visit 3/Day 1 (8:00 AM, 10:00 AM, and 4:00 PM). Time-matched change from baseline is a difference between actual IOP and baseline IOP taken at the same time of Visit 3/Day 1 (e.g. Visit 4/Day 15 8:00 AM change from baseline will be based on Visit 3/Day 1 8:00 AM result).

Example SAS code is provided below.

```
proc mixed data=eff method=reml;
    class trt visittime subjid;
    model timematchchg=trt visittime trt*visittime avgbase/ddfm=kr;
    repeated visittime/type=UN subject=subjid;
    lsmeans trt*visittime/cl pdiff;
    run;
```

Where timematchchg is the time-matched change from baseline value measured at each visit/time point, trt is treatment (BTQ-1901-A, BTQ-1901-B, BTQ-1902, or Timolol 0.5% ophthalmic solution), visittime is the combination of visit/timepoint (9 total values), and avgbase is the average baseline value.

Treatment comparisons will be performed for the treatment difference in LS mean. LS mean (SE) by treatment group, visit and time (applicable for time-matched IOP change from baseline), the LS mean difference between treatment groups, along with 2-sided 95% CI of the treatment differences and the p-value for the treatment comparison and within-treatment difference will be displayed.

9.3. Sensitivity Analysis

Sensitivity analyses will be based on ITT population and will be performed for primary and secondary efficacy endpoints. This will include the same statistical methodology as in the primary and secondary analyses, however when using imputed data preliminary imputation steps will have to be completed prior to applying the methods from the primary and secondary analyses.

The following analyses will be performed:

- repeating the primary and secondary analyses;

- utilizing LOCF imputed data (see Section 7.3.2.3.1) and analysis of covariance (ANCOVA) model at each visit/time point;
- imputing missing data using multiple imputation techniques (see Section 7.3.2.3.2) and repeating the primary and secondary analyses;
- using Wilcoxon rank sum tests to compare treatments at each time point.

10. SAFETY ANALYSES

All Safety analyses will be conducted using the Safety population. Categories for data presentation and analysis will consist of each treatment group (BTQ-1901-A, BTQ-1901-B, BTQ-1902, timolol 0.5%) and overall treatments summary. All safety analyses will be completed using the actual treatment a subject received.

10.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1.

Treatment-emergent adverse events (TEAEs) are defined as any AE or worsening of an existing condition after initiation of the investigational product and through the subject's last study visit (study completion or early termination). Serious adverse events (SAE) will be recorded from the date of informed consent, throughout the clinical trial. All SAEs that are ongoing at the time of completion or discontinuation from the study will be followed until stabilization or resolution of the event.

If the onset of an AE is on Day 1, then the time of first dose will be compared to the time of onset to determine if the AE is treatment-emergent.

The number and percent of subjects with any TEAEs will be summarized by system organ class and preferred term by dose level (and overall). At each level of tabulation (e.g. at the preferred term level) subjects will be counted only once if they had more than one such event reported during the AE collection period.

The following summary tables and subject level listings will be presented for TEAE data:

- Overall summary of TEAEs
- Summary table of TEAE descending incidence by PT
- Summary table of TEAEs by SOC and PT
- Summary table of serious TEAEs by SOC and PT
- Summary table of TEAEs by highest relationship level to study drug by SOC and PT
- Summary table of serious TEAEs by highest relationship level to study drug by SOC and PT

- Summary table of TEAEs by maximum intensity by SOC and PT
- Summary table of TEAEs leading to study discontinuation by SOC and PT
- Summary table of TEAEs leading to study drug discontinuation or interruption by SOC and PT

Ocular (by study and non-study eye) and non-ocular AE/TEAE will be summarized and listed separately.

10.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

10.2.1. Deaths

All deaths, regardless of causality, will be provided in a table listing and written clinical narratives will also be provided.

10.2.2. Serious Adverse Events

A table listing of SAEs and a table listing of related SAEs will be provided.

Furthermore, the number and percent of subjects with SAEs will be displayed by SOC and PT, and relationship to study medication, for each treatment group. Within each PT, subjects will be counted only once if they had more than one SAE event reported during the treatment period.

10.2.3. Adverse Events Leading to Discontinuation of Study Drug

A table listing of all AEs leading to study discontinuation, or discontinuation/ interruption of study drug will be presented.

Furthermore, the number and percent of subjects with AE's leading to study discontinuation, or discontinuation/interruption of study drug will be displayed by SOC and PT for each treatment group. Within each PT, subjects will be counted only once if they had more than one AE leading to study discontinuation, or discontinuation/interruption of study drug reported during the treatment period.

10.3. Bilateral Ophthalmic Examinations

Bilateral ophthalmic examinations (LogMAR BCVA, slit lamp biomicroscopy, dilated ophthalmoscopy, VF testing) including grading of conjunctival hyperemia by the Investigator and assessment of comfort/tolerability by the subject (drop comfort rating) will be summarized descriptively for each treatment group by time point. Assessments done on both eyes will be summarized separately by study and non-study eye.

Continuous results will be summarized descriptively for the observed value as well as for the change from baseline value. Categorical results will be summarized by counts and percentage.

Unscheduled visit results will not be summarized but will be included in patient data listings.

10.4. Vital Signs

Descriptive statistics of observed values will be presented for vital sign data by scheduled study visit, including systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), heart rate (beats/min) by treatment group for subjects in the Safety Population. Changes from baseline to each scheduled post-baseline visit will be presented.

All vital sign data by subject will be presented in a listing. Unscheduled visit results will not be summarized but will be included in patient data listings.

10.5. Other Safety Measures

All collected measures and assessments will be listed. No other safety analyses have been prospectively defined. If, however, after study results are reviewed, they will be fully described and documented in the final clinical study report. The SAP does not need to be amended to complete any other safety measures identified as post-hoc.

11. PHARMACOKINETIC (PK) ANALYSES

All PK analyses will be conducted using the PK population and actual treatment a subject received. Plasma concentration will be measured in this population, blood samples will be collected 2 hours (± 30 minutes) after study medication dosing at the clinical site at Visit 4/Day 15 and Visit 6/Day 84.

Descriptive summary statistics of concentration data by visit/time and treatment will include n, mean, standard deviation, coefficient of variation (%CV), median, minimum, maximum, and geometric mean.

For each analyte, the plasma concentration at each timepoint will be analyzed using analysis of variance (ANOVA), considering treatment as fixed effect. For each treatment, LS means will be calculated. Mean differences between the test treatments and the comparator (timolol 0.5%) and the corresponding 90% CI will be calculated.

All available concentration-time data will be listed by treatment.

12. REFERENCES

ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline, September 1998