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

Study Phase:	Phase 2
Product Names:	BTQ-1901 (nebivolol) ophthalmic suspension, 0.5% and 1.0% BTQ-1902 (timolol) ophthalmic suspension, 0.5%
Protocol Number:	BTQ-1901-1902-201
Indication:	Treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma
IND:	145479
Sponsor:	Betaliq, Inc.
Sponsor's Medical Consultant	Kenneth Sall, MD
Medical Monitor:	Robert David, MD
Protocol Version:	Original Protocol: 01 June 2020

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Betaliq, Inc.

Barry Butler, MBA Chief Executive Officer Betaliq, Inc.	Date
Kenneth Sall Medical Consultant to Betaliq, Inc.	Date

INVESTIGATOR'S AGREEMENT

I have read the BTQ-1901-1902-201 protocol. The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with International Conference of Harmonisation (ICH) Guidelines, and all applicable United States (US) Federal Regulations and local legal and regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Study Leader	Cynthia Rivali	701-690-3366 (C) 830-626-8002 (Fax)
Medical Monitor	Robert David, MD	949-246-8368 (C)

1. SYNOPSIS

Name of Sponsor/Company: Betaliq, Inc.		
Names of Investigational Products: s		
Names of Active Ingredients: BTQ-1901: Nebivolol 0.5% and 1.0%; BTQ-1902: Timolol 0.5%		
Protocol Number: BTQ-1901-1902-201	**Phase:** 2	**Country:** United States
Title of Study: 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		
Study center(s): Up to 20 sites in the United States		
Studied period (years): Estimated date first patient enrolled: September 2020 Estimated date last patient completed: June 2021		**Phase of development:** 2
Objectives: 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 primary open-angle glaucoma (POAG) or ocular hypertension (OHT).		
Methodology: This will be a randomized, multicenter, parallel-group, observer-masked study with approximately 240 subjects 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) that requires therapy and elevated intraocular pressure (IOP) adequately controlled, in the opinion of the Investigator, on no more than 2 ocular hypotensive medications (fixed dose combinations count as 2 medications). Subjects with OHT on no ocular hypotensive medication are 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). A mid-washout onsite safety check may be conducted for subjects undergoing a 28-day washout period, at the Investigator's discretion. At Visit 3/Qualification/Baseline (Day 1), eligible subjects must have unmedicated IOP measurements ≥ 22 and ≤ 34 mm Hg at 8:00 AM and ≥ 18 and ≤ 34 mm Hg at 10:00 AM and 4:00 PM in the same eye(s) qualifying at the 8:00 AM time point. The IOP must be at least 22 mm Hg at each consecutive measurement at the 8 AM time point. At Visit 3, IOP will be taken bilaterally at 8:00 AM, 10:00 AM, and 4:00 PM (each ± 30 minutes). Even if only one eye meets all inclusion/exclusion criteria, both eyes will be treated. 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 twice daily (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)		

Methodology (Continued):

The study will be observer masked. Randomized study medication will be provided in foil pouches contained in identical-appearing boxes. The pouches will contain 5 mL multidose bottles for the BTQ-1901-A, BTQ-1901-B, and BTQ-1902 treatment arms and 10 mL multidose bottles for the timolol 0.5% treatment arm). An unmasked staff member *not* involved in performing study endpoint-related procedures (i.e., IOP measurement) will be responsible for providing dosing instructions, dispensing study medication, and conducting study medication accountability and dosing compliance assessment. The identity of the study medications will be masked to the Investigator and study personnel responsible for study endpoint-related procedures. Moreover, IOP measurements for a given subject should be performed by the same Investigator/designee who will be masked to the readout of the tonometer, which will be read and entered into the source documentation (whether electronic or paper) by a second staff member once the Investigator/designee reaches the correct applanation effect in the slit lamp.

Study visits will be conducted as follows: Visit 1/Screening/Day -35 to -1, Visit 2/Washout Safety Check/Day -14 ± 3 (optional, but conducted at the Investigator's discretion for subjects undergoing 28-day washout periods), Visit 3/Qualification/Baseline/Day 1, Visit 4/Day 15 ± 3, Visit 5/Day 42 ± 3, and Visit 6/Day 84 ± 3. At Visits 4, 5, and 6, subjects will be evaluated for efficacy and safety at 8:00 AM, at 2 hours after study medication dosing at the clinical site (~10:00 AM), and at 4:00 PM (each ± 30 minutes). All ophthalmic assessments will be performed bilaterally.

Number of Patients (Planned): The sample size is approximately 60 subjects per group, for a total of approximately 240 subjects.

Inclusion Criteria:

Individuals must meet the following criteria:

1. Willing and able to understand and sign an informed consent form prior to any study-related procedures.
2. Able to administer or have a caregiver accurately administer an eye drop.
3. 18 years of age or older, male, or female.
4. Have POAG or OHT in both eyes that requires therapy for IOP and is adequately controlled, in the opinion of the Investigator, on no more than 2 ocular hypotensive medications (fixed dose combinations count as 2 medications). Subjects with OHT on no ocular hypotensive medication are acceptable. Presence of POAG in one eye and OHT in the fellow eye is acceptable.
5. Able, in the opinion of the Investigator, to safely discontinue use of ocular hypotensive medications, if applicable, and undergo the appropriate required washout period for ocular hypotensive medications prior to Visit 3/Qualification/Baseline.
6. At Visit 3/Qualification/Baseline, at least one eye must have unmedicated (post washout) IOP ≥ 22 and ≤ 34 mm Hg at 8:00 AM, *and* ≥ 18 and ≤ 34 mm Hg at 10:00 AM and 4:00 PM (in the same eye[s] qualifying at the 8:00 AM time point). The IOP must be at least 22 mm Hg at each consecutive measurement at the 8:00 AM time point.
7. No significant visual field (VF) loss, defined as a mean deviation in either eye greater than - 12 dB or a central point of fixation < 5 dB in either eye. 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).

Inclusion Criteria (continued):

8. Best corrected visual acuity (BCVA) of +0.6 logMAR or better in both eyes at Visit 1/Screening and Visit 3/Qualification/Baseline.
9. Central corneal thickness ≥ 480 and ≤ 600 μm in both eyes. Pachymetry within 90 days prior to Screening is acceptable.
10. Shaffer gonioscopic grade ≥ 3 (in at least 3 quadrants) in both eyes. Gonioscopy within 90 days prior to randomization is acceptable.
11. Female subjects must be 1-year postmenopausal, surgically sterilized (total hysterectomy, bilateral oophorectomy or bilateral tubal ligation > 90 days prior to Visit 1/Screening), or women of childbearing potential with a negative urine pregnancy test at Visit 1/Screening and Visit 3/Qualification/Baseline who are not breastfeeding or planning a pregnancy during the study. Women of childbearing potential must use an acceptable form of contraception throughout the study. Acceptable methods include the use of at least one of the following:
    - Intrauterine (IUD) device,
    - Hormonal contraceptive (oral, injection, patch, implant, ring); subjects must have been on the same hormonal contraceptive for ≥ 90 days prior to Visit 1/Screening
    - Double barrier method (spermicide used with either a condom or diaphragm),
    - Abstinence

Exclusion Criteria

Ocular

1. Intraocular pressure > 34 mm Hg in either eye at Visit 1/Screening, Visit 2/Washout Safety Check, or Visit 3/Qualification/Baseline.
2. Other forms of glaucoma in either eye, e.g., congenital glaucoma, closed-angle glaucoma, uveitic glaucoma, pseudoexfoliation or pigment dispersion syndrome, or history of angle closure. Narrow angles treated with peripheral iridotomy are allowed if at least 4 months status post iridotomy.
3. Current or recent (within 30 days prior to Visit 1/Screening) clinically significant ocular infection or inflammation, in the opinion of the Investigator, in either eye.
4. History of conjunctivitis within 90 days prior to Visit 1/Screening, or history of herpes simplex or herpes zoster in either eye.
5. Clinically significant ocular disease, in the opinion of the Investigator, in either eye (including, but not limited to corneal edema, uveitis, severe dry eye, proliferative diabetic retinopathy or macular degeneration) that might interfere with the study, confound study results, or put the subject at increased risk.
6. Have a cup-to disc (CD) ratio > 0.8 at Visit 1/Screening in either eye.
7. Intravitreal steroid injections within 6 months prior to Visit 1/Screening. Subconjunctival or subtenon steroid injections within 90 days prior to Visit 1/Screening.
8. Use of topical ocular medications within 30 days prior to Visit 1/Screening other than ocular hypotensive medications and medications used as part of an eye examination (see Table 3). Artificial tears may be used during this period provided the use is not required for severe dry eye disease.

Exclusion Criteria

Ocular (continued):

9. Clinically significant ocular trauma or incisional ocular surgery (including routine cataract surgery) in either eye within 6 months prior to Visit 1/Screening. Glaucoma filtering surgery or minimally invasive glaucoma surgery within 12 months prior to Visit 1/Screening. Laser surgery for IOP reduction within 6 months prior to Visit 1/Screening. Non-incisional ocular surgery or non-glaucomatous laser treatment within 90 days prior to Visit 1/Screening.
10. Refractive surgery in either eye (i.e., radial keratotomy, photorefractive keratectomy [PRK], laser-assisted in situ keratomileusis [LASIK], corneal cross-linking, limbal relaxing incision) within 6 months prior to Visit 1/Screening.
11. Any ocular (e.g., corneal) abnormality preventing accurate assessment of IOP.
12. Contact lens wear within 1 week prior to Visit 1/Screening or unwillingness to discontinue wear of contacts lenses prior to and during the study period.
13. Aphakia.

General

14. Pregnancy or lactation.
15. Known hypersensitivity or contraindication to β-blockers (i.e., chronic obstructive pulmonary disease, bronchial asthma, unstable or abnormally low blood pressure or heart rate, second or third degree heart block or congestive heart failure, severe or unstable diabetes mellitus) that in the opinion of the Investigator may put the subject at risk from a topical ocular β-blocker.
16. Have a condition or be in a situation which, in the Investigator's opinion, may put the subject at significant risk, confound study results, or interfere with the subject's participation in the study.
17. Clinically significant systemic disease (myasthenia gravis, hepatic, renal, endocrine, or cardiovascular disorders) that in the opinion of the Investigator might interfere with the study.
18. Use of systemic β-adrenergic antagonists unless the dosage has been stable for 1 month prior to Visit 1/Screening and is expected to remain stable through the study period.
19. Use of systemic (oral, injectable, inhaled) or topical steroids within 30 days prior to Visit 1/Screening. Topical dermatologic or intranasal steroids are acceptable provided the usage meets the criteria outlined in the Summary of Prohibited Medications and Procedures in Table 3.
20. Contraindication to the use of timolol, nebivolol, or any of the components of the investigational products.
21. Changes to systemic medication that could have an effect on IOP within 28 days prior to Visit 3/Qualification/Baseline.
22. Participation in any study of an investigational product within 30 days prior to Visit 1/Screening.
23. History of substance abuse within 1 year prior to Visit 1/Screening.
24. Screening and enrollment of employees or relatives of employees of the clinical site.

Investigational Product, Dosage and Mode of Administration:

BTQ-1901-A (nebivolol 0.5%) or BTQ-1901-B (nebivolol 1.0%) or BTQ-1902 (timolol 0.5%) ophthalmic suspension, 1 drop in each eye BID

Reference Therapy, Dosage and Mode of Administration:

Timolol 0.5% ophthalmic solution, 1 drop in each eye BID

Duration of Treatment:

Twelve (12) weeks (84 days)

Criteria for Evaluation:

Efficacy: Efficacy will be assessed in the study eye at each visit by IOP values at each timepoint as measured by Goldmann applanation tonometry.

Safety: Safety will be assessed at each visit by LogMAR VA, slit lamp examination, resting heart rate (HR)/blood pressure (BP), and adverse event (AE) collection. Ophthalmoscopy/dilated fundus examination and VF testing will occur at Visit 1/Screening and Visit 6/Day 84 (note: VF testing is not mandated at Visit 1/Screening if a test meeting the protocol requirements was performed and the results were documented within 90 days prior to Visit 1/Screening).

Safety/Tolerability Assessments:

Subjective comfort/tolerability data (i.e., rating of drop comfort as assessed by the subject) will be collected at Visit 3/Qualification/Baseline (Day 1), and at each post baseline visit. Conjunctival hyperemia will be assessed by the Investigator using the McMonnies photographic scale at Visit 3/Qualification/Baseline and at each post baseline visit.

Pharmacokinetics:

Plasma concentration will be measured in a subset of 40 subjects; blood samples will be collected following dosing at Visit 4/Day 15 and Visit 6/Day 84.

Study Endpoints:

Primary Efficacy Endpoint: IOP values at each time point (8:00 AM, 2 hours after study medication dosing at the clinical site [~10 AM], 4:00 PM) at Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84.

Secondary Efficacy Endpoints:

- 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.

Statistical Methods:

Primary efficacy analysis will be conducted on the per protocol (PP) population (those subjects in the intent to treat [ITT] population who were both randomized and dosed and who had no major protocol deviations). Efficacy analyses will also be conducted on the ITT population. Safety analyses will be performed using the safety analysis set (all randomized subjects who received at least one dose of the allocated study medication).

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 (ie, a total of 9 between-group comparisons). A hierarchical analysis will be conducted to compare each of the investigational products against the comparator, timolol 0.05%, 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 (ie, 5 of 9).

Statistical Methods (continued): All other efficacy, safety, tolerability and pharmacokinetic variables will be analysed using appropriate statistical techniques and summarized descriptively. Full details will be provided in the Statistical Analysis Plan.
Sample Size Justification: 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.

Table 2: 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	

Table 2: 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**
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.

Table 3: Summary of Prohibited Medications and Procedures

Duration of Restrictions	Medications/Procedures
Ocular	
12 months prior to Visit 1/Screening and throughout the study period	Glaucoma filtering surgery, minimally invasive glaucoma surgery
6 months prior to **Visit 1/Screening** and throughout the study period	Refractive surgery in either eye (i.e., radial keratotomy, photorefractive keratectomy [PRK], laser-assisted in situ keratomileusis [LASIK], corneal cross-linking, limbal relaxing incision).
	Incisional ocular surgery (including routine cataract surgery)
	Laser surgery for IOP reduction
	Intravitreal steroid injections
4 months prior to Visit 1/Screening	Peripheral iridotomy for narrow angles
90 days prior to **Visit 1/Screening** and throughout the study period	Subconjunctival, subtenon steroid injections
30 days prior to **Visit 1/Screening** and throughout the study period	Topical ocular medications other than ocular hypotensives and medications used as part of an eye examination (including but not limited to topical ocular corticosteroids, immunomodulators, NSAIDs, antibiotics, immunosuppressants, antihistamines, antivirals, and LFA-1 antagonists). Artificial tears are allowed if not required for severe dry eye disease. See Study Manual for details.
At least **28 days** prior to **Visit 3/ Qualification/Baseline** and throughout the study period	Prostaglandins/ROCK inhibitors/β-blockers must be washed out for a minimum of 28 days prior to Visit 3/Qualification/Baseline. See Study Manual for details.
At least **14 days** prior to **Visit 3/ Qualification/Baseline** and throughout the study period	Adrenergic agonists must be washed out for a minimum of 14 days prior to Visit 3/Qualification/Baseline. See Study Manual for details.
7 days prior to **Visit 1/Screening** and throughout the study period	Contact lens wear
At least **5 days** prior to **Visit 3/ Qualification/Baseline** and throughout the study period	Muscarinic agonists or CAIs must be washed out for a minimum of 5 days prior to Visit 3/Qualification/Baseline. At the discretion of the Investigator, CAIs may be used during the washout period by any subject if the use is discontinued to allow the appropriate required washout for the CAI (i.e., 5 days). See Study Manual for details.
10 minutes prior to **IP dosing**	Artificial tears are prohibited within 10 minutes of instillation of IP, but otherwise may be used as needed during the study, provided the use is not required for severe dry eye disease.

Table 3: Summary of Prohibited Medications and Procedures (Continued)

Duration of Restrictions	Medications/Procedures
General	
30 days prior to **Visit 1/Screening** and throughout the study period	Systemic corticosteroids (oral, injectable, inhaled). Topical dermatologic steroids are acceptable if used for less than 3 consecutive days on no more than 3 separate areas of the body within 30 days of Visit 1/Screening and the dosage is not expected to increase during the study. Intranasal steroids are acceptable if used less than or equal to 3 times per week within 30 days of Visit 1 and the dosage is not expected to increase during the study. See Study Manual for details.
	Any investigational product other than BTQ-1901 and BTQ-1902.
Within **28 days of Visit 3/Qualification/Baseline** and throughout the study period	Any change in dosage of systemic medication that could have an effect on IOP. See Study Manual for details.
Throughout the study period	Systemic β-adrenergic antagonists unless the dose has been stable for 1 month prior to Visit 1/Screening and is expected to remain stable through the study period.

Abbreviations: BTQ-1901 = nebivolol 0.5% and 1.0% ophthalmic suspensions; BTQ-1902 = timolol 0.5% ophthalmic suspension; CAI = carbonic anhydrase inhibitors; IOP = intraocular pressure; IP = investigational product; LFA-1 = lymphocyte function-associated antigen 1; NSAID = non-steroidal anti-inflammatory drug; ROCK = rho-associated protein kinase

2. TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS

Abbreviation	Explanation
β	Beta
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BCVA	Best-corrected visual acuity
BID	Twice daily
BP	Blood pressure
BTQ-1901	Nebivolol
BTQ-1902	Timolol
CAI	Carbonic anhydrase inhibitor
CI	Confidence interval
CRO	Clinical research organization
CS	Clinically significant
eCRF	Electronic case report form
eDC	Electronic data capture
F6H8	Perfluorohexyloctane
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IOP	Intraocular pressure
ITT	Intent-to-treat population
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LASIK	laser-assisted in situ keratomileusis
LOCF	Last observation carried forward
LogMAR	Logarithm of the minimum angle of resolution
MMRM	Mixed models for repeated measures
NCS	Non-clinically significant

Abbreviation	Explanation
OHT	Ocular hypertension
OU	Both eyes
PK	Pharmacokinetics
POAG	Primary open angle glaucoma
PP	Per protocol population
PRK	photorefractive keratectomy
ROCK	Rho-associated protein kinase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
US	United States
VA	Visual acuity
VF	Visual field

4. INTRODUCTION

BTQ-1901 (nebivolol) and BTQ-1902 (timolol) ophthalmic suspensions are being developed by Betaliq, Inc. (the Sponsor) for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension (OHT) or primary open-angle glaucoma (POAG). Glaucoma is a leading cause of blindness worldwide. The global prevalence is estimated to be 64 million people in 2013 and it is expected to increase to nearly 112 million in 2040 (Tham et al, 2014).

Intraocular pressure is balanced between the secretion of aqueous humor by the ciliary body and drainage of aqueous humor through 2 independent pathways—the trabecular meshwork and uveoscleral outflow pathways. In POAG, the most common form of glaucoma, there is increased resistance to aqueous outflow through the trabecular meshwork. The same mechanism applies to OHT, in which IOP is elevated without visual field (VF) deficits or clinically apparent damage to the optic nerve. Mechanical stress from continued elevated IOP may result in progressive damage to the optic nerve, which can result in visual disability leading to blindness.

Elevated IOP in eyes with POAG is typically treated with topical ophthalmic medications. Many patients with OHT are untreated, but topical hypotensive medication has been found effective in delaying or preventing the onset of POAG; in the Ocular Hypertension Treatment Study, the incidence of OAG after 60 months of follow-up was 9.5% in the observation group vs 4.4% in the treated group (Kass et al, 2002). The most frequently used medications are prostaglandin analogues, which increase uveoscleral outflow of aqueous humor, and beta(β)-adrenergic blockers, which reduce aqueous humor production. While β-blockers are well tolerated locally, they may have important systemic adverse events (AEs), such as bronchospasm, decreased heart rate, and congestive heart failure, all of which may limit their use.

The Sponsor is developing two β-blockers, BTQ-1901 and BTQ-1902, in a unique vehicle composed of one excipient, the inert and anhydrous semifluorinated alkane, perfluorohexyloctane (F6H8). F6H8 is a clear, colorless, chemically inert liquid without pharmacologic activity. Both BTQ-1901 and BTQ-1902 are free of other excipients like oils, surfactants, buffers, and preservatives, and are administered in a multidose bottle rather than a unit dose vial. Due to the low surface tension of F6H8, the resulting eye drops are relatively small, with a volume of approximately 11 µL/drop.

The active ingredient of BTQ-1901 is nebivolol, a β_1 selective β-blocker. The chief advantage of β_1 selectivity is the absence of β_2-adrenergic inhibition which minimizes the risk of respiratory side effects. Nebivolol also stimulates nitric oxide release via stimulation of the β_3 receptor which produces a vasodilatory effect (Kuroedov et al, 2004) that may improve blood flow to the optic nerve. While extensively used as a systemic blood pressure medication (Bystolic® was approved by the United States [US] Food and Drug Administration [FDA] in 2007 [Bystolic package insert, 2019]), nebivolol has not been evaluated for ocular use as an ocular hypotensive therapy.

The active ingredient of BTQ-1902 is timolol. Timolol was the first topical ocular β-blocker approved by the FDA (1978), and it is still an integral part of the standard of care for glaucoma. Utilizing F6H8 as the vehicle for the BTQ-1901 and BTQ-1902 ophthalmic suspensions allows development of these products as non-preserved suspensions in a multi-dose bottle, thus minimizing tolerability and ocular irritation issues that may arise when eye drops contain preservatives or phosphates. This quality may potentially result in fewer ocular AEs.

Importantly, it is postulated that the resulting drug products might have less systemic absorption and fewer negative systemic AEs because of the smaller drop size.

Nonclinical pharmacology, pharmacokinetics, and toxicology studies were conducted in support of the development of timolol (topical ocular route) and nebivolol (systemic route). Based on the results of the 28-day and 6-month repeat dose toxicology studies in albino rabbits, the pharmacological and toxicological data for BTQ-1901-A, BTQ-1901-B, and BTQ-1902 are considered adequate to support their safe clinical use for this initial Phase 2 clinical trial. There were no significant macroscopic or microscopic findings observed in rabbits dosed with nebivolol 1.0% ophthalmic suspension (BTQ-1901-B) 4 times daily for 28 days or twice daily (BID) for 6 months, or with timolol 0.5% ophthalmic suspension (BTQ-1902) BID for 6 months. Moreover, systemic accumulation of nebivolol 1.0% and timolol 0.5% was very low after the 6-month treatment period (around the lower limits of quantification [LLOQ]). Therefore, ocular instillation of BTQ-1901 or BTQ-1902 twice daily to subjects with a maximum clinical concentration of 1.0% nebivolol or 0.5% timolol for up to 12 weeks is considered safe for the initial Phase 2 clinical study.

BTQ-1901 and BTQ-1902 ophthalmic suspensions are topical treatments for POAG or OHT that have not been previously evaluated in clinical trials. The planned first in human (FIH) study is 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% ophthalmic solution in subjects with POAG or OHT in both eyes over a 12-week (84-day) treatment period. For additional information regarding BTQ-1901 and BTQ-1902 ophthalmic suspensions, please refer to the Investigator's Brochure.

5. STUDY OBJECTIVE

5.1. Primary Objective

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.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

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) that requires therapy and elevated IOP adequately controlled, in the opinion of the Investigator, on no more than 2 ocular hypotensive medications (fixed dose combinations count as 2 medications). Subjects with OHT on no ocular hypotensive medications are 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). A mid-washout onsite safety check may be conducted, at the Investigator's discretion, for subjects undergoing a 28-day washout period.

Eligible subjects must have unmedicated IOP measurements at Visit 3/Qualification/Baseline ≥ 22 and ≤ 34 mm Hg at 8:00 AM and ≥ 18 and ≤ 34 mm Hg at 10:00 AM and 4:00 PM (each qualifying eye must fall within the required IOP range at all 3 time points and must be at least 22 mm Hg at each consecutive measurement at the 8:00 AM time point).

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.

Randomized study medication will be provided in foil pouches contained in identical-appearing boxes to conceal the differences in presentation (5 mL multidose bottles for the BTQ-1901-A, BTQ-1901-B, and BTQ-1902 treatment arms versus 10 mL multidose bottles for the timolol 0.5% treatment arm). The identity of the study medications will be masked to the Investigator and study personnel responsible for endpoint-related study procedures. Moreover, Goldmann IOP measurements should be performed by the same Investigator/designee throughout the study who will be masked to the readout of the tonometer, which will be read and entered into the source documentation (whether electronic or paper) by a second staff member once the Investigator/designee reaches the correct applanation effect in the slit lamp.

Study visits will be conducted as follows: Visit 1/Screening/Day -35 to -1, Visit 2/Washout Safety Check/Day -14 ± 3 (conducted for subjects undergoing 28-day washout periods at the Investigator's discretion), Visit 3/Qualification/Baseline/Day 1, Visit 4/Day 15 ± 3, Visit 5/Day 42 ± 3, and Visit 6/Day 84 ± 3. At Visits 4, 5, and 6, subjects will be evaluated for

efficacy and safety at 8:00 AM, at 2 hours after study medication dosing at the clinical site (~10:00 AM), and at 4:00 PM (each ± 30 minutes). All ophthalmic assessments will be performed bilaterally.

The Schedule of Procedures (Table 2) provides a tabular summary of all scheduled visits and procedures to be performed during the clinical study.

6.2. Number of Subjects

A total of 240 subjects are planned: 60 subjects in each treatment arm.

6.3. Treatment Assignment

The treatment regimens will be as follows:

- BTQ-1901-A: nebivolol 0.5% ophthalmic suspension administered BID to both eyes for 84 days (12 weeks)
- BTQ-1901-B: nebivolol 1.0% ophthalmic suspension administered BID to both eyes for 84 days (12 weeks)
- BTQ-1902: timolol 0.5% ophthalmic suspension administered BID to both eyes for 84 days (12 weeks)
- Timolol 0.5% ophthalmic solution administered BID to both eyes for 84 days (12 weeks)

6.4. Criteria for Study Termination

The study may be terminated at any time by the Sponsor, following appropriate notification.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Inclusion Criteria

1. Willing and able to understand and sign an informed consent form prior to any study related procedures.
2. Able to administer or have a caregiver accurately administer an eye drop.
3. 18 years of age or older, male, or female.
4. Have POAG or OHT in both eyes that requires therapy for IOP and is adequately controlled, in the opinion of the Investigator, on no more than 2 ocular hypotensive medications (fixed dose combinations count as 2 medications). Subjects with OHT on no ocular hypotensive medication are acceptable. Presence of POAG in one eye and OHT in the fellow eye is acceptable.
5. Able, in the opinion of the Investigator, to safely discontinue use of ocular hypotensive medications, if applicable, and undergo the appropriate required washout period for ocular hypotensive medications prior to Visit 3/Qualification/Baseline.
6. At Visit 3/Qualification/Baseline, at least one eye must have unmedicated (post washout) IOP ≥ 22 and ≤ 34 mm Hg at 8:00 AM *and* ≥ 18 and ≤ 34 mm Hg at 10:00 AM and 4:00 PM in the same eye(s) qualifying at the Visit 3 8:00 AM time point. The IOP must be at least 22 mm Hg at each consecutive measurement at the 8:00 AM time point.
7. No significant VF loss, defined as a mean deviation in either eye greater than - 12 dB or a central point of fixation < 5 dB in either eye. 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).
8. Best corrected visual acuity (BCVA) of +0.6 logMAR or better in both eyes at Visit 1/Screening and Visit 3/Qualification/Baseline.
9. Central corneal thickness ≥ 480 and ≤ 600 μm in both eyes. Pachymetry within 90 days prior to Screening is acceptable.
10. Shaffer gonioscopic grade ≥ 3 (in at least 3 quadrants) in both eyes. Gonioscopy within 90 days prior to randomization is acceptable.
11. Female subjects must be 1-year postmenopausal, surgically sterilized (total hysterectomy, bilateral oophorectomy or bilateral tubal ligation > 90 days prior to Visit 1/Screening), or women of childbearing potential with a negative urine pregnancy test at Visit 1/Screening and Visit 3/Qualification/Baseline who are not breastfeeding or planning a pregnancy during the study. Women of childbearing potential must use an acceptable form of contraception throughout the study. Acceptable methods include the use of at least one of the following:
    - Intrauterine (IUD) device
    - Hormonal contraceptive (oral, injection, patch, implant, ring); subjects must have been on the same hormonal contraceptive for ≥ 90 days prior to Visit 1/Screening

- Double barrier method (spermicide used with either a condom or diaphragm)
- Abstinence

7.2. Exclusion Criteria

Ocular

1. Intraocular pressure > 34 mm Hg in either eye at Visit 1/Screening, Visit 2/Washout Safety Check, or Visit 3/Qualification/Baseline.
2. Other forms of glaucoma in either eye, e.g., congenital glaucoma, closed-angle glaucoma, uveitic glaucoma, pseudoexfoliation or pigment dispersion syndrome, or history of angle closure. Narrow angles treated with peripheral iridotomy are allowed if at least 4 months status post iridotomy.
3. Current or recent (within 30 days prior to Visit 1/Screening) clinically significant ocular infection or inflammation, in the opinion of the Investigator, in either eye.
4. History of conjunctivitis within 90 days prior to Visit 1/Screening, or history of herpes simplex or herpes zoster in either eye.
5. Clinically significant ocular disease, in the opinion of the Investigator, in either eye (including, but not limited to corneal edema, uveitis, severe dry eye, proliferative diabetic retinopathy or macular degeneration) that might interfere with the study, confound study results, or put the subject at increased risk.
6. Have a cup-to disc (CD) ratio > 0.8 at Visit 1/Screening in either eye.
7. Intravitreal steroid injections within 6 months prior to Visit 1/Screening. Subconjunctival or subtenon steroid injections within 90 days prior to Visit 1/Screening.
8. Use of topical ocular medications within 30 days prior to Visit 1/Screening other than ocular hypotensive medications and medications used as part of an eye examination (see Table 3). Artificial tears may be used during this period provided the use is not required for severe dry eye disease.
9. Clinically significant ocular trauma or incisional ocular surgery (including routine cataract surgery) in either eye within 6 months prior to Visit 1/Screening. Glaucoma filtering surgery, or minimally invasive glaucoma surgery within 12 months prior to Visit 1/Screening. Laser surgery for IOP reduction within 6 months prior to Visit 1/Screening. Non-incisional ocular surgery or non-glaucomatous laser treatment within 90 days prior to Visit 1/Screening.
10. Refractive surgery in either eye (i.e., radial keratotomy, photorefractive keratectomy [PRK], laser-assisted in situ keratomileusis [LASIK], corneal cross-linking, limbal relaxing incision) within 6 months prior to Visit 1/Screening.
11. Any ocular (e.g., corneal) abnormality preventing accurate assessment of IOP.
12. Contact lens wear within 1 week prior to Visit 1/Screening or unwillingness to discontinue wear of contacts lenses prior to and during the study period.
13. Aphakia.

General

14. Pregnancy or lactation.
15. Known hypersensitivity or contraindication to β-blockers (i.e., chronic obstructive pulmonary disease, bronchial asthma, unstable or abnormally low blood pressure or heart rate, second or third degree heart block or congestive heart failure, severe or unstable diabetes mellitus) that in the opinion of the Investigator may put the subject at risk from a topical ocular β-blocker.
16. Have a condition or be in a situation which, in the Investigator's opinion, may put the subject at significant risk, confound study results, or interfere with the subject's participation in the study.
17. Clinically significant systemic disease (myasthenia gravis, hepatic, renal, endocrine, or cardiovascular disorders) that in the opinion of the Investigator might interfere with the study.
18. Use of systemic β-adrenergic antagonists unless the dosage has been stable for 1 month prior to Visit 1/Screening and is expected to remain stable through the study period.
19. Use of systemic (oral, injectable, inhaled) or topical steroids within 30 days prior to Visit 1/Screening; topical dermatologic or intranasal steroids are acceptable provided the usage meets the criteria outlined in the Summary of Prohibited Medications and Procedures in Table 3.
20. Contraindication to the use of timolol, nebivolol, or any of the components of the investigational products.
21. Changes to systemic medication that could have an effect on IOP within 28 days prior to Visit 3/Qualification/Baseline.
22. Participation in any study of an investigational product within 30 days prior to Visit 1/Screening.
23. History of substance abuse within 1 year prior to Visit 1/Screening.
24. Screening and enrollment of employees or relatives of employees of the clinical site.

7.3. Criteria for Withdrawal from the Study/Criteria for Discontinuation of Study Medication

The following are the criteria for considering withdrawal from the study:

- Withdrawal of subject consent. The subject may request for any reason at any time to be withdrawn from the study.
- Subject lost to follow-up.
- The Sponsor terminates the study (see Section 6.4).

If a subject withdraws from the study, the principal reason for withdrawal will be recorded in the electronic case report form (eCRF). Subjects who are withdrawn will not be replaced.

If a study subject fails to attend a study visit at any point during the study period, every effort should be made to keep the subject in the study and conduct all study visits as scheduled; all attempts to contact the subject must be documented. If the subject relocates during the study period, the clinical research organization (CRO), should be contacted to determine if there is a possibility that the subject could continue at another clinical site.

The following are criteria for considering discontinuation from study medication:

- Pregnancy: If a subject becomes pregnant during the study, the subject will be withdrawn from study medication and followed through the conclusion of the pregnancy (Section 9.5.3).
- Adverse event: A clinically significant or serious AE (SAE) that in the Investigator's or Medical Monitor's judgment, suggests that continued administration of study medication is not in the subject's best interests for safety reasons. Additionally, if an AE requires treatment, the Investigator in consultation with the Medical Monitor may determine that study medication should not be concurrently administered with a required concomitant medication.
- Intraocular pressure in either eye >34 mm Hg during the treatment period.
- Subject request: Subject requests to be withdrawn from study medication.

When possible, a decision to discontinue a subject from study medication should first be discussed with the Medical Monitor. If a subject is discontinued from study medication, every effort should be made to encourage the subject to continue to attend study visits to be followed for safety, rather than withdrawing the subject from the study or, failing that, to perform all early discontinuation assessment procedures at the visit the subject is withdrawn (Section 10.5).

In case a subject must be withdrawn from the trial, the sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator until satisfactory health has returned or the subject´s health has reached a stable condition.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drugs

BTQ-1901-A (nebivolol 0.5%), BTQ-1901-B (nebivolol 1.0%), and BTQ-1902 (timolol 0.5%) are formulated for topical ocular delivery as sterile, preservative-free ophthalmic suspensions and contain the active ingredient (as specified) in a vehicle composed of one excipient, the inert and anhydrous semifluorinated alkane, perfluorohexyloctane (F6H8). These study drugs are packaged in identical 5 mL multidose bottles to maintain masking of treatment identity.

The active comparator, timolol, is a sterile, preserved ophthalmic solution that contains timolol 0.5% and is packaged in 10 mL multidose bottles (Timolol maleate ophthalmic solution prescribing information, 2016).

8.2. Randomization and Masking

Study medication will be randomized in a 1:1:1:1 ratio into 1 of 4 treatment arms (BTQ-1901-A, N = 60; BTQ-1901-B, N = 60; BTQ-1902, N = 60; timolol 0.5%, N = 60). 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 (see Section 7) 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. The study medication will be provided in foil pouches contained in identical-appearing boxes. The pouches will contain 5 mL bottles for the BTQ-1901-A, BTQ-1901-B, or BTQ-1902 treatment arms and 10 mL bottles for the timolol 0.5% treatment arm (see Section 8.1). An unmasked staff member not involved in performing study endpoint-related procedures (i.e., IOP measurement) will be responsible for providing dosing instructions, dispensing study medication, and conducting study medication accountability and dosing compliance assessment. The identity of the study medications will be masked to the Investigator and study personnel responsible for study endpoint-related procedures. Moreover, IOP measurements should be performed by the same Investigator/designee who will be masked to the readout of the tonometer, which will be read and entered into the source documentation (whether electronic or paper) by a second staff member once the Investigator/designee reaches the correct applanation effect in the slit lamp.

8.2.1. Unmasking During the Study Period

Should it be necessary to unmask a subject's treatment assignment in case of emergency, the Investigator may obtain the treatment code for a given randomized subject from the IWRS. The treatment code is to be obtained only if a medical emergency exists and knowledge of the medication being taken will influence the medical management of the subject.

The following procedure should be followed:

1. The Investigator should attempt to contact the Medical Monitor via phone before unmasking a subject unless it is not possible to do so without risk to the subject.
2. The Investigator should document the AE and justification for unmasking in the eCRF.
3. If the subject is to be discontinued from study medication, then ALL procedures described in the Early Discontinuation Visit (Section 10.5) should be completed.
4. The Investigator should contact the CRO at safety@trialrunners.com within 24 hours with the subject number and details of the AE or SAE and any action taken.

8.3. Concomitant Medications

8.3.1. Permitted Medications and Treatments

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the Investigator. If there is any question as to whether the medication may interfere, the Investigator should contact the Medical Monitor or Sponsor. Whenever possible, medications should be administered in dosages that remain constant throughout the study duration. Note: Artificial tear use is permitted prior to and during the study period as needed provided the use is not required for severe dry eye disease. Artificial tears should not be instilled within 10 minutes of administration of study medication.

8.4. Treatment Compliance

Treatment compliance will be monitored by subject-reported missed doses assessed at each treatment visit (Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84) via response to the Missed Doses Log. Subjects will be asked to log if they have missed any doses since the previous visit, and if so, the date of missed dose, which dose was missed (AM and/or PM), which eye was not dosed (right, left, both), and the reason for the missed dose. These data will be analyzed to determine an estimate of compliance over the duration of the study.

8.4.1. Prohibited Medications

The Medical Monitor should be notified before prohibited medication or therapy is administered unless the safety of the subject requires immediate action. The decision to administer a prohibited medication or therapy should be done with the safety of the subject as the primary consideration. The Medical Monitor MUST be contacted to determine whether the subject should continue with study medication.

Prohibited medications and therapies are summarized in Table 3 and specific details are found in the Study Manual.

8.5. Study Medication Materials and Management

8.5.1. Packaging and Labeling

Study medication will be packaged and labeled at a central packaging facility. Study sites will utilize the IWRS to assign kits to subjects. Each kit has 3 boxes (subkits). Contents of the boxes

(subkits) will differ depending upon treatment allocation (either 5 mL multidose bottles or 10 mL multidose bottles).

- Box 1, dispensed at Visit 3/Qualification/Baseline, includes either 1 bottle (5 mL) of BTQ-1901-A, BTQ-1901-B, BTQ-1902 OR 1 bottle of timolol 0.5% (10 mL)
- Box 2, dispensed at Visit 4/Day 15, includes either 2 bottles (5 mL each) of BTQ-1901-A, BTQ-1901-B, BTQ-1902 OR 2 bottles of timolol 0.5% (10 mL)
- Box 3, dispensed at Visit 5/Day 42, includes either 3 bottles (5 mL each) of BTQ-1901-A, BTQ-1901-B, BTQ-1902 OR 3 bottles of timolol 0.5% (10 mL)

8.5.2. Storage and Administration

Study medication must be stored at room temperature, 15°C - 25°C, or 59°F - 77°F, under temperature monitored conditions. Subjects should be instructed not to store or place the study medication where it can be exposed to extreme temperatures (e.g., refrigeration or leaving it in a hot car) or light.

An unmasked staff member *not* involved in performing study endpoint-related procedures will instruct the subject on proper instillation technique and dispense the first study medication kit at Visit 3/Qualification/Baseline. At each study visit during the treatment period (Visit 4/Day 15 , Visit 5/Day 42, and Visit 6/Day 84) the subject (or caregiver, if the subject is not able to self-administer the medication) will administer the morning dose of study medication at the study site, instilling 1 drop in each eye. Before administering the eye drops, the hands should be washed. The steps described in detail in the Subject Dosing and Storage Instructions will be followed.

Each day of dosing, the subject will administer one drop to each eye BID (morning and evening).

8.5.3. Study Medication Accountability

An unmasked staff member *not* involved in performing endpoint procedures will maintain full accountability records for the study medication and will be responsible for recording the receipt, dispensing, and return of all supplies of the study medication using the inventories supplied by the Sponsor. At each visit subsequent to Visit 3/Qualification/Baseline (i.e., Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84) all bottles that were dispensed at the previous visit (empty, used, or unused) should be returned to the site in the kit. At Visits 4 and 5, study medication accountability procedures will be conducted, and new study medication kits will be dispensed for the next study period. At Visit 6 all study medication materials will be returned to the study site, and final study medication accountability will be conducted. Visit 6 will be the last day of study treatment; no further study medication will be dispensed at this visit. The monitor will review dispensing and study medication accountability records at the completion of the study and note any discrepancies. All investigational study medication must be stored in a secure facility with limited access.

9. STUDY ASSESSMENTS

Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign, and date the current Institutional Review Board (IRB)-approved version of the informed consent form (ICF). A full discussion of informed consent is presented in Section 13.3. Ophthalmic procedures should be performed in the order specified in Table 2.

9.1. Demographic and Background Characteristics

9.1.1. Demographic/Medical History

A complete medical history will be obtained from each subject. Demographic information including date of birth, gender, race, ethnicity, iris color, and date of informed consent will be recorded.

9.1.2. Concomitant Medications History

All concomitant medications (prescription and over-the-counter [OTC]) taken at Visit 1/Screening and for 90 days prior to Visit 1 and throughout the course of the study will be recorded in the Concomitant Medications page of the eCRF. Information regarding the dates of first and last dose, site of dosing (e.g., right eye, left eye, both eyes [OU], systemic), and the reason the concomitant medication is being taken must be recorded in the eCRF. When a concomitant medication has been taken at a stable dose for longer than 6 months, an estimation of the year of the start date is adequate. Standard procedural medications will not be captured in the eCRF but are recorded on a standard procedural medication log provided by the CRO.

9.1.3. Ophthalmic History and Ophthalmic Intervention History

Clinically significant ophthalmic history and ophthalmic intervention history will be documented and will include any clinically significant previously diagnosed ophthalmic abnormalities and ocular surgeries, including laser procedures.

9.1.4. Urine Pregnancy Test

A urine pregnancy test will be performed for females of childbearing potential at Visit 1/Screening, Visit 3/Qualification/Baseline, and Visit 6 or Early Discontinuation Visit.

9.2. Efficacy Assessment

The efficacy of BTQ-1901-A (nebivolol 0.5%), BTQ-1901-B (nebivolol 1.0%) or BTQ-1902 (timolol 0.5%) ophthalmic suspensions will be compared to the active comparator (timolol 0.5% ophthalmic solution) as measured by 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 (ie, a total of 9 between-group comparisons).

9.2.1. Intraocular Pressure

Intraocular pressure will be measured utilizing a calibrated Goldmann tonometer and using the standard of care. NOTE: For 3 through 6, IOP measurements must be made within 30 minutes of the protocol-specified time points (8:00 AM, 10:00 AM, and 4:00 PM for Visit 3 and 8:00

AM, 2 hours after study medication dosing at the clinical site [~10:00 AM], and 4:00 PM for Visits 4, 5, and 6). For any given subject, IOP should be measured with a calibrated tonometer and by the same Investigator/designee, if possible, throughout the study who will be masked to the readout of the tonometer, which will be read and entered into the source documentation (whether electronic or paper) by a second staff member once the Investigator/designee reaches the correct applanation effect in the slit lamp. 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.

9.3. Pharmacokinetic Assessments

Plasma concentration will be measured in a subset of 40 subjects; 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. Consult the Study Manual for specific details.

9.4. Safety Assessments

Safety will be assessed at each visit by LogMAR VA, biomicroscopy, resting heart rate (HR)/blood pressure (BP), and AE collection. Ophthalmoscopy/dilated fundus examination and VF testing will be performed at Visit 1/Screening and Visit 6/Day 84. Safety/tolerability assessments at each visit will include grading of conjunctival hyperemia by the Investigator and subjective assessment of comfort/tolerability data by the subject. Ophthalmic assessments should be performed in the order in which they appear in the Schedule of Procedures (Table 2).

9.4.1. Visual Acuity

Best corrected visual acuity measurement will be performed in each eye at all study visits with the logMAR eye chart. Consult the Study Manual for specific details.

9.4.2. Biomicroscopy

A slit-lamp examination will be conducted at each study visit to assess the anterior ocular structures. Abnormalities will be documented as abnormal, non-clinically significant (NCS) or abnormal, clinically significant (CS). Consult the Study Manual for specific details.

9.4.3. Grading of Conjunctival Hyperemia

Conjunctival hyperemia will be graded using the McMonnies photographic scale (McMonnies and Chapman, 1987a; McMonnies and Chapman, 1987b). Please note that this scale was designed for contact lens wearers but validated for non-contact lens wearers (McMonnies and Ho, 1991). Consult the Study Manual for specific details.

9.4.4. Vital Signs

Blood pressure and HR will be measured after at least 5 minutes rest in the sitting position. Vital signs may be repeated once, after at least an additional 5 minutes rest in the seated position, if they are out of range. Consult the Study Manual for specific details.

9.4.5. Ophthalmoscopy/Dilated Fundoscopy

Ophthalmoscopy/dilated fundoscopy will be conducted, and the structures will be graded as normal or abnormal, NCS, or abnormal, CS. Consult the Study Manual for specific details.

9.4.6. Visual Field Testing

Automated perimetry will be performed at Visit 1/Screening and Visit 6/Day 84. The site should perform the automated perimetry assessments following the investigator's standard practices. 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/ Day 1).

The preferred equipment for the VF is the Humphrey Perimeter using the full threshold 24-2 test with the SITA Standard or SITA Fast strategy. The same strategy used for the initial test should be used for any subsequent VF test. Visual field results should be reliable. Subjects with a functionally significant VF loss, defined as mean deviation greater than -12 dB or a central fixation point less than 5 dB in either eye, are excluded from the study. Other equipment may be used after approval by the Sponsor. Consult the Study Manual for specific details.

9.4.7. Subjective Grading of Comfort/Tolerability

Subjective comfort/tolerability data (i.e., rating of drop comfort as assessed by the subject) will be collected at each post baseline visit (≥ 10 minutes after the IOP measurement). Consult the Study Manual for specific details.

9.5. Adverse and Serious Adverse Events

9.5.1. Definition of Adverse Events

9.5.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a study medication (pharmaceutical/biological product) that does not necessarily have a causal relationship to this medication. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study medication, whether or not related to the study medication. Study medication includes the investigational drug under evaluation and the comparator product or vehicle placebo that is given during any phase of the study.

Adverse events are collected from the time the subject signs the ICF through the final study visit. Medical conditions/diseases present before starting the investigational treatment are only considered AEs if they worsen any time after the subject signs the ICF. Abnormal test results constitute AEs only if they induce clinical signs or symptoms or require therapy.

The occurrence of AEs should be sought by open-ended questioning of the subject at each visit during the study. At each clinic visit, study personnel should ask the following question: "Have you had any problems since your last visit?" AEs also may be detected when they are volunteered by the subject during or between visits or through study assessments.

9.5.1.2. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

  Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity (excluding progression/outcome of the disease under study),
- Is a congenital anomaly/birth defect,
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Is medically significant, i.e., defined as an event that jeopardizes the health of the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Treatment on an outpatient emergency basis that does not result in hospital admission, or a hospitalization that is elective or is a preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study, is not considered an SAE.

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.

9.5.2. Relationship to Study Drug

The relationship of AEs to the study medication should be assessed by the Investigator using the definitions below.

Not related: The temporal relationship of the event to the study medication makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Related: The temporal relationship of the event to the study medication makes a causal relationship possible or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study medication and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined by the Sponsor to be “related,” the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

9.5.3. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation, regardless of severity or potential association with the study medication or study procedures, will be recorded in the eCRF. Changes from baseline assessments that are part of the disease being studied will not necessarily be recorded as AEs unless the Investigator deems them as such. Clinically significant changes in BP and HR should be reported as AEs. 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. Serious adverse events will be followed until the event is resolved or stabilized.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the following:

- Onset (date)
- Resolution (date)
- Severity grade (mild, moderate, severe)
- Relationship to study medication (not related, related)
- Action taken regarding study medication (none, study medication temporarily interrupted, study medication permanently discontinued)
- Action taken regarding the event (concomitant medication taken; hospitalization/prolonged hospitalization; other)
- Serious (yes/no)

The severity grade should be determined by the Investigator using the definitions below.

- **Mild**: Discomfort noticed but no disruption of normal daily activity
- **Moderate**: Discomfort sufficient to cause interference with normal daily activity
- **Severe**: Incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity (as defined directly above) whereas seriousness is defined by the criteria under Section 9.5.1.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form. Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. The subject will be withdrawn from study medication and followed through conclusion of pregnancy. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented.

9.5.4. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded following consent and until the final study visit, Visit 6/Day 84, following the end of treatment exposure. Any SAEs suspected to be related to the investigational product should be reported.

Any SAE that occurs must be reported to Trial Runners, the CRO, within 24 hours of its occurrence or within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported to Trial Runners as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the subject should be maintained at the site with a copy emailed to safety@trialrunners.com. The Investigator must assess the SAE relationship and complete and sign the SAE form. Trial Runners/the Sponsor may request additional information. Follow-up information (e.g., discharge summary) will be retained in the subject's chart and a copy will be emailed to safety@trialrunners.com.

In addition, all SAEs should be recorded on the Adverse Event eCRF page with the serious question marked "Yes".

It is the Investigator's responsibility to notify the approving IRB of any SAEs on a timely basis as instructed by the Sponsor following the Sponsor's determination of causality.

All subjects who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event.

The Sponsor will report all SAEs to the US Food and Drug Administration (FDA) on the appropriate schedule depending if the event is drug related or not drug related, expected or unexpected (based on the available information in the Investigator's Brochure).

Any death occurring during the study and follow up period should be reported as an SAE. For any death occurring through the end of the study, regardless of the degree of relationship to study medication, the SAE resulting in the death must be reported to Trial Runners. A death occurring after completion of the study does not require completion of the SAE form.

10. STUDY ACTIVITIES

Table 2 provides a tabular summary of all scheduled visits and procedures to be performed during the clinical study. Ophthalmic procedures should be performed in the order in which they are shown in the Schedule of Procedures. Please note that per Section 10.1.1, procedures performed at Visit 1/Screening may be split and conducted at a separate visit (preferably within 1 week after Visit 1) to be scheduled before Visit 3/Qualification/Baseline/Day 1.

10.1. Screening Visit

Screening eligibility assessments are obtained during the Screening Visit conducted on or between Day -35 to -1 (Visit 1), which is dependent on the required washout period for prior ocular hypotensive medications.

10.1.1. Visit 1/Screening (Day -35 to -1)

At Visit 1/Screening, (Day -35 to -1), subjects will provide informed consent before any study-related procedures are conducted. Subjects will then participate in screening procedures to establish eligibility for the study.

If necessary, Visit 1 may be split and a separate visit (preferably within 1 week after Visit 1) may be scheduled to allow all required screening procedures to be performed before Visit 3/Qualification/Baseline. For example, if dilated ophthalmoscopy is not performed because the subject prefers not to be dilated at this visit, the subject may return on another day. Also, 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).

At the end of the visit/split visit, inclusion/exclusion criteria will be reviewed. Eligible subjects will begin the washout period that is required for the ocular hypotensive medication the subject was receiving or, if medication naïve, be scheduled for Visit 3/Qualification/Baseline.

Screening procedures include the following:

- Informed consent/assent
- Demographics
- Medical and ophthalmic histories
- Prior and concomitant medications/therapies
- Urine pregnancy test (females of childbearing potential only)
- BP/HR
- BCVA (logMAR)
- Biomicroscopy
- IOP
- Visual field test (may be performed at any time during the Screening visit prior to dilation for ophthalmoscopy, or within 90 days prior to Screening)
- Gonioscopy (may be performed during the Screening visit at any time after IOP and before dilation for ophthalmoscopy, or within 90 days prior to Screening)
- Pachymetry (may be performed during the Screening visit at any time after IOP, or within 90 days prior to Screening)
- Dilated ophthalmoscopy
- Review eligibility criteria
- Provide instructions regarding the washout period

10.2. Washout Period

A washout period will occur for all subjects using ocular hypotensive medications at Screening. If required, subjects will participate in a minimum washout period of 28 days for prostaglandin analogs, ROCK inhibitors, or β-blockers, 14 days for adrenergic agonists, and 5 days for muscarinic agonists or CAIs.

10.2.1. Visit 2/Optional Washout Safety Check (Day -14 ± 3)

A mid-washout onsite safety check may be conducted for subjects undergoing a 28-day washout period, at the Investigator's discretion.

Procedures performed at Visit 2 include the following:

- AE assessment
- Concomitant medication review

- BCVA
- IOP

10.3. Qualification Visit

One qualification visit will be conducted, Visit 3/Qualification/Baseline/Day 1.

At Visit 3, subjects must have unmedicated IOP measurements in at least one eye ≥ 22 and ≤ 34 mm Hg at 8:00 AM and ≥ 18 and ≤ 34 mm Hg at 10:00 AM and 4:00 PM (each timepoint is ± 30 minutes). The IOP must be at least 22 mm Hg at each consecutive measurement at the 8:00 AM time point.

10.3.1. Visit 3/Qualification/Baseline/Day 1

This visit will be scheduled so that IOP can be taken at 8:00 AM, 10:00 AM, and 4:00 PM (± 30 minutes). If the subject has not discontinued using their prior ocular hypotensive medications for the required washout period duration (28 days for prostaglandin analogs, ROCK inhibitors or β-blockers, 14 days for adrenergic agonists, and 5 days for muscarinic agonists or CAIs), the visit will need to be rescheduled.

Procedures performed at Visit 3 include the following:

8 AM (± 30 minutes):

- AE assessment
- Concomitant medication review
- Urine pregnancy test (females of childbearing potential only); must be performed prior to randomization
- BCVA
- Grading conjunctival hyperemia (grading of conjunctival hyperemia must be performed prior to randomization)
- Biomicroscopy/
- IOP

10 AM (± 30 minutes):

- AE assessment
- HR/BP
- Biomicroscopy
- IOP

4 PM (± 30 minutes):

- AE assessment
- Biomicroscopy

- IOP
- Review eligibility criteria
- Randomize eligible subjects
- Dispense study medication
- Provide instruction and supervise guided practice of drop instillation by subject/caretaker (no evening dose should be administered at home after this visit)
- Conduct drop comfort rating following instillation of study medication (≥ 10 minutes after the IOP measurement)
- Study medication accountability (i.e., document that Kit 1 was dispensed)

10.4. Treatment Visits

These treatment visits (Visit 4/Day 15, Visit 5/Day 42, and Visit 6/Day 84), will be scheduled so that IOP can be taken at 8:00 AM, at 2 hours after the dosing of study medication at the clinical site (~10:00 AM), and at 4:00 PM (each ± 30 minutes).

Subjects should be reminded before each visit not to dose in the morning before coming to the site and to bring their box containing all study medication materials (opened and unopened bottles/vials and pouches) to the study site for drug accountability/treatment compliance assessment. When the subject arrives, confirm that the previous day's evening dose of study medication *was* administered, and the morning dose of study medication *has not* been administered. Subjects who did not dose the evening before or who dosed prior to the morning visit MUST be rescheduled, even if the next appointment is out of window.

10.4.1. Visit 4/Day 15 ± 3

Procedures performed at Visit 4 include the following:

8 AM (± 30 minutes):

- AE assessment
- Concomitant medication review
- BCVA
- Grading conjunctival hyperemia
- Biomicroscopy
- IOP
- Drop instillation (should occur as close as possible to 15 minutes after IOP measurement, but not before 10 minutes after IOP measurement)
- Conduct drop comfort rating following instillation of study medication (≥ 10 minutes after the IOP measurement)

2 hours ± 30 minutes after drop instillation:

- AE assessment
- HR/BP
- Biomicroscopy
- IOP
- Blood collection for pharmacokinetics (PK) assessment (subset of subjects only)
- Compliance assessment (may be performed at any time during the visit)

4 PM (± 30 minutes):

- AE assessment
- Biomicroscopy
- IOP
- Study medication dispensing
- Study medication accountability (may be performed at any time during the visit)

10.4.2. Visit 5/Day 42 ± 3

8 AM (± 30 minutes):

- AE assessment
- Concomitant medication review
- BCVA
- Grading conjunctival hyperemia
- Biomicroscopy
- IOP
- Drop instillation (should occur as close as possible to 15 minutes after IOP measurement but not before 10 minutes after IOP measurement)
- Conduct drop comfort rating following instillation of study medication (≥ 10 minutes after the IOP measurement)

2 hours ± 30 minutes after drop instillation:

- AE assessment
- HR/BP
- Biomicroscopy
- IOP
- Compliance assessment (may be performed at any time during the visit)

4 PM (± 30 minutes):

- AE assessment
- Biomicroscopy
- IOP
- Study medication dispensing
- Study medication accountability (may be performed at any time during the visit)

10.4.3. Visit 6/Last Day of Treatment (Day 84 ± 3)

At Visit 6, subjects will undergo final efficacy and safety assessments and rate the ocular tolerability of study medication.

Visit 6 procedures include the following:

8 AM (± 30 minutes):

- AE assessment
- Concomitant medication review
- Urine pregnancy test (females of childbearing potential only)
- BCVA
- Grading conjunctival hyperemia
- Biomicroscopy
- IOP
- Drop instillation (should occur as close as possible to 15 minutes after IOP measurement, but not before 10 minutes after IOP measurement)
- Conduct drop comfort rating following instillation of study medication (≥ 10 minutes after the IOP measurement)
- Visual field test (may be performed at any point in the visit prior to dilation for ophthalmoscopy)

2 hours ± 30 minutes after drop instillation:

- AE assessment
- HR/BP
- Biomicroscopy
- IOP
- Blood collection for PK assessment (subset of subjects only)
- Compliance assessment (may be performed at any time during the visit)

4 PM (± 30 minutes):

- AE assessment
- Biomicroscopy
- IOP
- Dilated ophthalmoscopy
- Study medication accountability (may be performed at any time during the visit)

10.5. Early Discontinuation Assessment Procedures

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 (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.

11. STATISTICS

11.1. General Considerations

This is a Phase 2 study 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.

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)

A biostatistician will perform statistical analyses as agreed with the Sponsor according to the Statistical Analysis Plan (SAP).

Primary efficacy analysis will be conducted on the per protocol (PP) population. Efficacy analyses will also be conducted on the intent to treat (ITT) population. Safety analyses will be performed using the safety analysis population. Definitions for all of the analysis populations can be found in Section 11.3.

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.

A detailed SAP will be finalized prior to database lock. The analysis of continuous and ordinal variables will use the applicable parametric methods (t-test, analysis of variance [ANOVA], and analysis of covariance [ANCOVA], and mixed models for repeated measures [MMRM]). Descriptive statistics will be used to summarize continuous outcomes (number of subjects [N], mean, standard deviation or standard error of the mean, median, maximum, and minimum) and categorical variables (frequency and percentage) at each assessment time point (the time points at which data are collected are specified in the Schedule of Procedures—see Table 2).

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 (ie, a total of 9 between-group comparisons).

Final analyses of efficacy will be conducted when all subjects complete Visit 6.

11.1.1. Handling of Missing Data

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. Full details will be provided in the SAP.

11.2. Determination of 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.

11.3. Analysis Populations

Three populations will be used for analysis, as described below.

11.3.1. Populations for Efficacy Analysis

11.3.1.1. Intent-to-Treat (ITT) Population

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

11.3.1.2. Per-Protocol (PP) Population

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.

11.3.2. Safety Population

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.

11.4. Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized for all analysis populations. Summary tables will be supported with individual subject data listings.

11.5. Efficacy Analysis

Efficacy analyses will be performed on the PP population for the primary efficacy endpoint using observed data only. Analysis of the efficacy endpoints will also be conducted with the ITT population.

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

The efficacy measures (IOP) taken at Visit 3/Day 1 at 8:00 AM, 10:00 AM, and 4:00 PM will serve as baseline.

11.5.1. Hypothesis Testing

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 (ie, 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 (ie, 5 of 9).

All other comparisons are considered exploratory.

11.5.2. Primary Efficacy Endpoints

The primary efficacy endpoint will be 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.

11.5.3. Primary Efficacy Analysis

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

The between-treatment comparison will employ an MMRM with treatment, visit/time, treatment-by-visit/time interaction, and baseline values as fixed effects. Linear contrasts will be used to calculate the confidence intervals at all visit/times.

Sensitivity analyses include repeating the primary analysis with the ITT population, imputing missing data using multiple imputation techniques and repeating the primary analysis; utilizing LOCF imputed data and ANCOVA models at each visit/time point; and using Wilcoxon rank sum tests to compare treatments at each time point. Full details will be provided in the SAP.

11.5.4. Secondary Efficacy Endpoints

Secondary 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.

11.5.5. Secondary Efficacy Analysis

Similar analysis methods to those used for the primary efficacy endpoints will be utilized for the secondary efficacy endpoints. Full details will be provided in the SAP.

11.6. Safety Analyses

The safety of BTQ-1901 and BTQ-1902 will be compared to timolol 0.5% with analysis of safety variables including bilateral ophthalmic examinations (LogMAR BCVA, slit lamp

examination, resting HR/BP, ophthalmoscopy/dilated fundus examination, VF testing), and AEs. The ocular tolerability of study medication will be rated by the subject. Safety data will be presented in tables of descriptive statistics and frequency distribution. All summary tables will be supported with individual subject data listings.

11.7. Pharmacokinetic Analyses

Pharmacokinetic variables will be analyzed using appropriate statistical techniques and summarized descriptively. Full details will be provided in the SAP.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and/or their contracted agents utilize standard operating procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs require compliance with FDA regulations and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance.

The study will be monitored by clinical research associates (CRAs)/monitors provided by Trial Runners, the CRO, to verify that the rights and well-being of human subjects are being protected, the reported data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, with ICH GCP, and with the applicable regulatory requirements.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its agent may conduct a quality assurance audit at any time during or after completion of a study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include but is not limited to a review of all informed consent/assent forms, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the study materials receipt, storage, and administration. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the findings of the audit.

13. ADMINISTRATIVE CONSIDERATIONS

13.1. Institutional Review Board (IRB) Approval

The IRB must review, approve, and provide continuing review of the clinical study protocol, protocol amendments, the informed consent documents, subject recruitment advertisements, and any other written information to be provided to the subjects. Initial IRB approval is an affirmative decision that the clinical study has been reviewed and may be conducted at the study site within the constraints set forth by the IRB, the institution, GCP, and applicable regulatory requirements. A copy of the IRB approval letter for the protocol, the informed consent, the intended advertising, and any written material to be provided to the subject must be submitted to the Sponsor or designee prior to release of investigational supplies to the study site. Progress reports and notifications of serious adverse reactions will be provided to the IRB according to local regulations and guidelines. The IRB must be notified of completion or termination of the study. The study site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol.

13.2. Ethical Conduct of the Study

The study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with ICH guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

13.3. Subject Information and Consent

A sample ICF containing the required elements of informed consent will be provided by the Sponsor or designee. Any changes made to this sample must be approved by Betaliq or designee prior to submission to the IRB. After approval by the Sponsor or designee, the ICF must be submitted to and approved by the IRB. The informed consent must be written in a language in which the subject is fluent. Regulations require that foreign language informed consent forms be submitted to the IRB for approval. The foreign language translation is required to contain a statement of certification of the translation. The Investigator must forward a copy of the consent forms, the certified foreign language translation, and an IRB approval letter to the Sponsor or designee.

It is the responsibility of the Investigator to inform each subject of the purpose of this clinical trial, including possible risks and benefits, and to document the informed consent process. Prior to undergoing any study-related procedures, the subject must read, sign, and date the current IRB-approved version of the informed consent form. The original informed consent form is to be retained by the study site, and a copy of the signed consent form is to be given to the subject.

13.4. Subject Confidentiality

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, the Sponsor, Trial Runners, the IRB, and FDA/relevant regulatory agencies. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. No information that can be related to a specific individual

subject will be released or used in any fashion without the signed written consent of that subject. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the Investigator for purposes of long-term follow-up, if needed. This information will be treated with strict adherence to professional standards of confidentiality.

13.5. Study Monitoring

The study will be monitored by Trial Runners on behalf of the Sponsor in accordance with current GCP to assure compliance with the study protocol and the quality of the data collected. Monitoring visits will occur as required and could include a study initiation visit, monitoring visit(s), and a study close-out visit. Training will be provided for key investigative personnel in all aspects of study conduct. The Investigator will be responsible for making sure that site personnel are provided adequate training on conducting delegated tasks.

Before a site can enter a subject into the study, a representative of the Sponsor will:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence and the responsibilities of the Sponsor and or its representatives

This study will utilize electronic data capture (eDC) to optimize the eCRF source verification process with limited separate source documentation. Monitors will review e-source data and overall study data/consistency remotely and query discrepancies based upon eCRF entries (eCRF initial entry is the source). During this monitoring, data are reviewed as entered by the site, and the monitors will flag any abnormalities, trends, or safety signals for Medical Monitor review and monitor follow-up onsite, if necessary. Refer to the Study Manual for details regarding the direct data entry of study assessments and requirements for maintaining additional source documentation via paper/medical record.

During visits to the study site, the monitor may review the source documents including but not limited to signed informed consent forms, inclusion/exclusion checklist, medical/ocular history, concomitant medications, study material accountability and storage, the reporting procedures for AEs, SAEs, and protocol deviations. The CRA will review the study documents to ensure all documentation is current and only qualified and trained staff are appropriately delegated study related tasks. The CRA will also review the site-specific processes and research-related SOPs to ensure appropriate Investigator oversight is being maintained and documented as required by GCP/ICH.

All data generated during this study and the medical records/documents from which they originated are subject to inspection by the Sponsor or designee, the FDA, and other regulatory agencies. The Investigator must notify the Sponsor or designee promptly of any inspections scheduled by regulatory authorities.

Upon completion of the study, the clinical monitor will conduct a final visit (closeout) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that the investigational product (IP) and other supplies have been accounted for (returned/destroyed), and ensure that the Investigators are aware of their responsibilities once the study ends.

The Investigator is responsible for permitting the Sponsor or designee direct access to any study documents for monitoring and auditing purposes, for providing adequate space for monitoring, and for addressing any questions or issues that might be raised by the monitor or auditor on a timely basis.

13.6. Case Report Forms and Study Records

Data relating to study procedures may be entered by site personnel directly onto eCRFs available in the study's eDC system. When the eCRF is the first place study data are recorded, it will be the source document; exceptions are detailed in the Study Manual. Paper source documents will be retained at the study site when appropriate.

13.7. Protocol Deviations

The Investigator should not deviate from the requirements of this protocol except in the event of a medical emergency.

A major protocol deviation is defined as nonadherence to the protocol that involves inclusion/exclusion criteria, affects subject safety, or has the potential to affect the integrity of the data, for example, enrollment of a subject who does not meet key eligibility criteria, or failing to collect data necessary to interpret primary endpoints. All protocol deviations will be reported to the Sponsor by entering the event in the appropriate eCRF page. Protocol deviations should be reported to the IRB in accordance with IRB-specific guidelines. If there is any question as to whether the deviation is reportable, the Sponsor or designee and the IRB should be contacted. If subjects are enrolled in error they may be removed after review by the Medical Monitor, but removal is not required. Major and minor protocol deviations will be defined before unmasking.

All changes to the protocol will be made by the Sponsor or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation.

13.8. Access to Source Documentation

A trial-related monitoring audit, review by the IRB, and/or regulatory inspection may be conducted at any time during or after completion of a study (Section 12). The Investigator will be given adequate notice if he/she is selected for an audit and must provide direct access to study documentation. The audit may include, but is not limited to, a review of all informed consent forms; a review of medical records; a review of regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the study materials receipt, storage, and administration.

13.9. Data Generation and Analysis

Management of data and the production of the clinical study report will be the responsibility of the Sponsor or its designee.

During the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Such clarifications and corrections will be

discussed with and approved by site personnel and appropriately documented. Prior to database lock, data listings will be generated, and anomalous values investigated.

13.9.1. Retention of Data

Investigators should retain study-related records at the site until informed by the Sponsor. The Investigator will not move study documents or discard any records without notifying the Sponsor. If the Principal Investigator moves from the current clinical site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the clinical site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation. If it becomes necessary for the Sponsor or designee, or the FDA or relevant regulatory authorities to review any documentation relating to the study, the Investigator must permit access to such records.

13.10. Publication and Disclosure Policy

All information concerning BTQ-1901, BTQ-1902 and the operations of the Sponsor, such as patent applications, formulas, manufacturing processes, basic scientific data or formulation information not previously published, are considered CONFIDENTIAL and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of the Sponsor.

The publication policy is addressed in a separate agreement.

14. REFERENCES

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