NCT#: NCT04149899

Whitecap Biosciences – CONFIDENTIAL

STUDY TITLE

A Phase 1/2a Assessment of WB007 Ophthalmic Solution in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension

Protocol Number:	WB007-001
EudraCT Number:	Not Applicable
Phase:	1/2
Investigational Product:	WB007 (also known as AGN-227535)
Sponsor:	Whitecap Biosciences 6789 Quail Hill Pkwy Suite 719 Irvine, CA 92603
Medical Safety Physician Contact information:	[redacted]
Emergency Telephone Number: (Dr. David)	[redacted]
SAE Reporting:	[redacted]
Whitecap Biosciences, LLC Signatory:	[redacted]

_____ _____

[redacted] Date

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

STUDY LOCATION:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, Good Clinical Practices and all applicable laws and regulations.
- Maintain all information supplied by Whitecap Biosciences in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

RETURN TO WHITECAP BIOSCIENCES WITH ATTACHED PROTOCOL

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Protocol Synopsis

Study Title: A Phase 1/2a Assessment of WB007 Ophthalmic Solution in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension

Investigational Product: WB007 (also known as **AGN-227535)**

Phase: 1/2a

Study Objectives: The objective of this study is to assess the safety, ocular tolerability and IOP-lowering effects of AGN-227535 in adult subjects with bilateral primary open-angle glaucoma or ocular hypertension.

Clinical Hypotheses:

Parts 1/2: AGN-227535 has an acceptable safety and tolerability profile;

Part 1: The safety profile allows for assessing AGN-227535 in Part 2;

Part 2: At least 1 concentration of AGN-227535 demonstrates an IOP lowering effect.

Type of Study: Two-part, multi-centered [(Part 1- single-dose in one eye, open-labeled, dose-escalation), (Part 2 - multiple-dose, randomized, double-masked, active-controlled)], bilateral treatment.

Study Population: Adult (at least 18 years of age) male or female subjects with primary open-angle glaucoma or ocular hypertension in each eye who are otherwise in generally good health. Only one eye must meet all ocular entry criteria.

Number of Subjects and Sites: Approximately 100 subjects will be screened to participate in the study (Part 1 – 25; Part 2 – 75). An expected 95 subjects will be assigned to study treatment such that approximately 18 (Part 1) and 60 (Part 2) subjects complete the study at 3-5 sites. Subjects who do not complete the study may be replaced.

Part 1: Approximately 6 subjects per dose-escalation cohort (up to 3).

Part 2: Up to 2 investigational doses will be chosen based on results from Part 1. Approximately 24 subjects per AGN-227535 group and approximately 12 subjects for the timolol group will be given study treatment.

Duration of Study Participation:

Part 1: Up to 2 months from Screening through Day 2/Exit;

Part 2: Up to 2.5 months from Screening through Day 14/Exit.

Study Treatments: AGN-227535 Ophthalmic Solution (Parts 1 and 2) and timolol 0.5% ophthalmic solution (as a control in Part 2 only)

Part 1: Study Treatments 1-3: AGN-227535 (0.05%; 0.15%; 0.40%);

Part 2: Up to 2 AGN-227535 study treatments and Timolol 0.5% (Study Treatment 4).

Dosage/Dose Regimen:

Part 1: Subjects will be given 1 dose of study treatment to one eye in the morning (administered by site personnel).

Part 2: Subjects will dose study treatment every morning and every evening (approximately 12 hours apart) to each eye for up to 14 days. Site personnel will administer the morning dose at study visits.

Randomization/Stratification:

Part 1: If only one eye qualifies, the study medication will be administered to that eye. If both eyes qualify, the eye with the higher IOP at Baseline (Day -1) Hour 0 will be the study eye and will receive study medication. If both eyes have the same IOP value at this timepoint, the right eye will be the study eye.

Part 2: Part 2: Subjects will be randomly assigned to 1 of up to 3 treatment arms (based on results from Part 1) in a 2(:2):1 allocation ratio to receive 1 of up to 2 AGN-227535 concentrations or timolol 0.5% in each eye. The randomization will be stratified by baseline IOP (IOP ≤ 25 mm Hg and > 25 mm Hg at Hour 0) and performed centrally (ie, across sites). Randomization and stratification will be performed using the Interactive Web Response System (IWRS), a module within the electronic data capture (eDC) system.

Visit Schedule:

Part 1: Screening (days -50 to -4, including washout/waiting period as required); Baseline (Day -1), Day 1, Day 2/Exit

Part 2: Screening (days -50 to -4, including washout/waiting period as required; Baseline (Day -1), Day 1, Day 4 and Day 14/Exit.

Primary Efficacy Endpoint (Part 2 only): Mean change from baseline in IOP

Statistical Method for primary endpoint:

In general, data will be summarized with descriptive statistics which will include sample size, mean, standard deviation, median, minimum and maximum for continuous variables and frequency and percentage for categorical variables.

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. The number and percentage of subjects with adverse event reports will be tabulated for all treatment-emergent adverse events (TEAEs) regardless of causality, treatment-related TEAEs, all serious TEAEs, treatment-related serious TEAEs, and all adverse events leading to premature discontinuation of study treatment.

Analysis populations: Each population will be analyzed based on the treatment received.

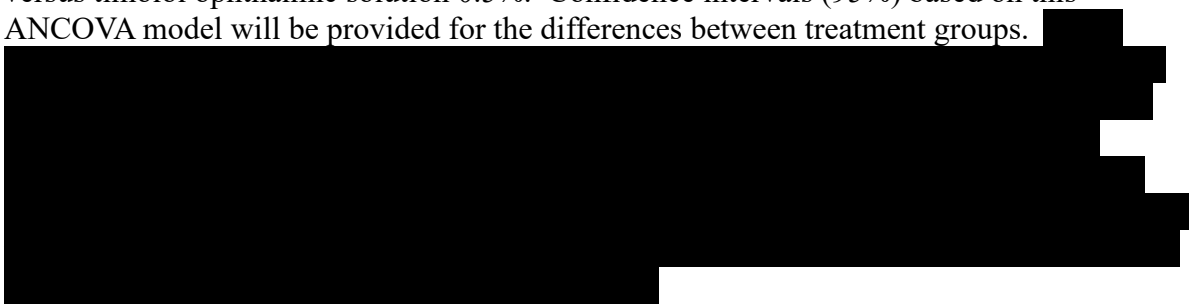
Part 1: The Safety population consisting of all treated subjects will be used for all analyses. All safety and IOP-lowering effects tabulations will provide descriptive statistics by cohort.

Part 2: The Safety population, as defined above, will be used for analyses of all Safety data. In addition to the Safety population two other populations are defined for analyses of Part 2 efficacy data:

The Modified Intent-to-treat (mITT) will consist of all randomized and treated subjects who provide IOP data at baseline and at least one post-baseline IOP assessment. This population will be used for analyses of efficacy data.

The Per-protocol (PP) population is a subset of the mITT population and will consist of subjects who did not have any major protocol violations deemed to have potential impact on the primary endpoint. This population will be used to confirm the primary efficacy analysis.

The primary efficacy endpoints are the Day 14/Exit mean IOP changes from Baseline (Day -1) at each time-matched hour (0, 2, 4, 8) in the study eye. The primary efficacy analysis will be within-group mean change from baseline IOP at hour 2, the time of peak effect of timolol. Between treatment group comparative analyses will be performed in the mITT population via analysis of covariance (ANCOVA) tests which will have treatment as the main effect and the baseline hour-matched IOP as the covariate in the model. Pairwise treatment group comparisons will be performed for each individual dose of AGN-227535 ophthalmic solution versus timolol ophthalmic solution 0.5%. Confidence intervals (95%) based on this ANCOVA model will be provided for the differences between treatment groups.



Additional safety analyses will include evaluation of peak severity of macroscopic hyperemia and hyperemia as evaluated on biomicroscopy at each post-baseline visit (Days 4 and 14) and across all post-baseline time points.

Sample Size Calculation: For each cohort in Part 1 of the study a sample size of 6 patients will provide 83% power to detect a 3 mm Hg within-group change from pre-dose assuming a standard deviation of 2 and two-sided alpha = 0.05.

Part 2 sample size will provide >90% power to detect within-group and between-group treatment differences of mean change from baseline of at least 3 mm Hg for the primary endpoint assuming a standard deviation of 2.5 with two-sided alpha = 0.05. With a treatment group difference of -1 mmHg, the power ranged from 50% for a common SD of 3.5 to 78% for a common SD of 2.5 to conclude non-inferiority based on a 1.5 mmHg margin and a 1-sided alpha = 0.025.

Data Monitoring Committee: No formal Data Monitoring Committee is planned. Between dose-escalation groups in Part 1, all available data collected to date will be used to assist in decision making to continue to the next dose or to stop the study. All data collected in Part 1 will be used to select 1 or 2 concentrations of AGN-227535 to evaluate in Part 2. The decision to proceed or to stop the study will be made by the Medical Monitor, the Head of Clinical and the Chief Executive Officer. All decisions will be documented.

Figure 1 Schematic of Study Design

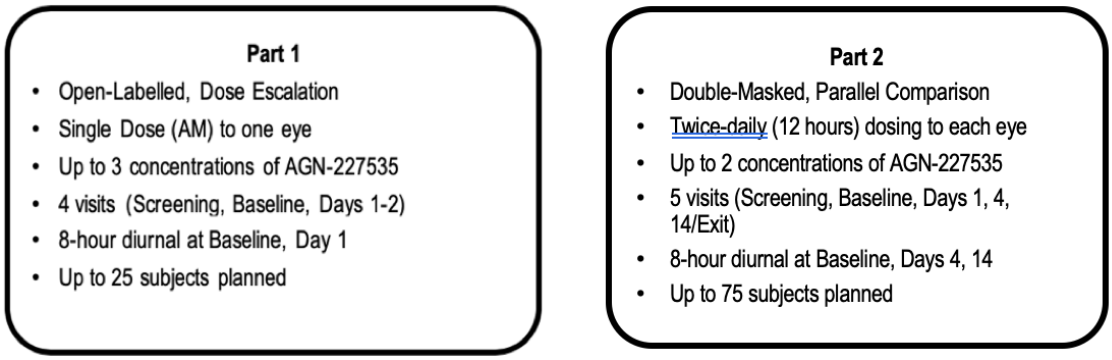
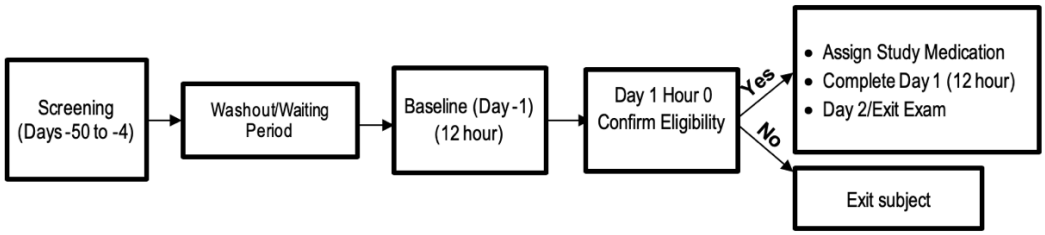


Figure 2 Part 1 Dose Escalation

Visit Flow



Dose Escalation

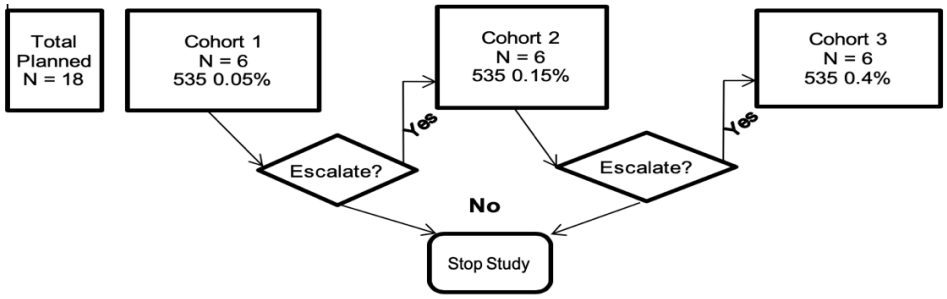


Figure 3 Part 2 (Parallel Comparison)

Visit Flow

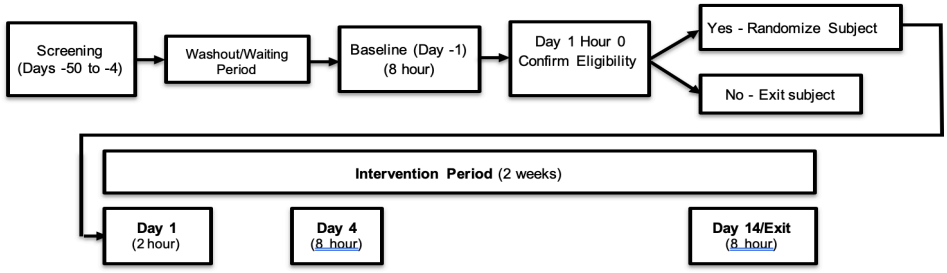


Table 1 Scheduled Visits and Procedures - Screening and Baseline (Parts 1 and 2)

Assessment Visits (Visit Window ± Day)	**Screening Days -50 to -4**	Washout / Waiting Period (-50 to -4 Days) [a]	**Baseline (Day -1)**			
Timepoint: *All examinations for all visits and timepoints should be performed in the order listed below from top to bottom (refer to Attachment 12.2 for details on how to perform procedures)*	**Hour**		**Hour**			
	Not Applicable		**0**	**2**	**4**	**8**
Informed Consent/Authorization	X					
Adverse Event Query	X		X			
(Part 2 only) Subject Comfort of Eye Drops Evaluation (for subjects on IOP lowering medications; evaluation to be administered by designated site personnel)	X					
Concomitant Medications/Treatments	X		X			
Medical and Ophthalmic Histories	X		X			
Prior Medications/Treatments	X		X			
Physical Exam including height and weight	X					
Respiration rate and temperature (seated)	X		X			
Postural (supine/standing) Blood Pressure & Heart Rate	X		X[b]			
Non-fasting Laboratory assessments (CBC with differential, Blood Chemistries, Urinalysis)	X					
Electrocardiogram			X			
Urine Pregnancy Test (for females of childbearing potential)			X			
Macroscopic (Gross) Hyperemia	X		X	X	X	X
[redacted]			X	X		
Visual Acuity (using Manifest Refraction)	X		X			
[redacted]			X			
Slit-Lamp Biomicroscopic Examination	X		X	X	X	X
Intraocular Pressure (IOP)[c]	X		X	X	X	X
Visual Fields[d]	X		X			
Fundus Exam (including cup/disc ratio) (post-pupil dilation)	X					

NOTE: CBC - Complete blood count; H = hour (hour 0 = 07:00 to 09:00 hours)

[a] Washout / Waiting Period (Day -50 to Day -4). For subjects taking IOP-lowering medications, the washout must be completed according to the schedule in Section 6.2. For subjects who are not taking IOP-lowering medications, a 3-day waiting period from Screening to Baseline is required.

[b] At Baseline, blood pressure and heart rate will be measured in the supine position only.

[c] IOP should be measured before pupil dilation (as applicable)

[d] Results of 2 reliable visual field (VF) examinations are required for eligibility. [redacted] 12.2 The same methodology and equipment should be used for all VF examinations.

Table 2 Part 1 - Schedule of Visits and Procedures: Days 1 and 2

Outcome Assessment Visits (Visit window ± day)	Day 1					Day 2
Timepoint: *All examinations for all visits and timepoints should be performed in the order listed below from top to bottom* [redacted] *12.2* [redacted]	**H0**[a]	**30 minutes post-1st dose**	**H2**	**H 4**	**H 8**	**H0**
Adverse Event Query	X	<——————————>				X
Concomitant Medications/Treatments	X					X
Postural (Supine/Standing) Blood Pressure & Heart Rate	X		X			X
Urine Pregnancy Test						X
Macroscopic (Gross) Hyperemia	X	X	X	X	X	X
Visual Acuity[b]	X[b]					X[b]
Slit-Lamp Biomicroscopic Examination	X	X	X	X	X	X
Intraocular Pressure (IOP)[c]	X	X	X	X	X	X
Fundus Exam (including cup/disc ratio) (post-pupil dilation)						X
Confirm Inclusion / Exclusion criteria	X					
Study Medication Assignment	X					
Study medications administered at the site by site personnel	X					
Collect subject EXIT status						X

NOTE: H = hour (hour 0 = 07:00 to 09:00 hours)

[a] Pre-dose

[b] Manifest refraction performed at Baseline (Day -1) should be used at Days 1 and 2 to obtain a correction for visual acuity evaluation. Manifest refraction(s) may be repeated, if in the opinion of the investigator, it is necessary. Visual acuity will be collected in Snellen-equivalent units using a logarithmic (LogMar) visual acuity chart.

[c] IOP should be measured before pupil dilation (as applicable) and at the same time (± 15 minutes) each day as the time established at baseline (day -1, hour 0, between 07:00 and 09:00 hours).

Table 3 Part 2 - Schedule of Visits and Procedures: Day 1 to Day 14/Exit

Outcome Assessment Visits (Visit window ± day)	Day 1 (± 0 day)			Days 4 (± 1 day) and 14 (± 2 days)			
Timepoint: *All examinations for all visits and timepoints should be performed in the order listed below from top to* [redacted] *12.2*	H0	30 minutes post-1st dose[a]	H2	H0	H2	H4	H8
Text or phone call from site reminding subject to dose approximately 12 hours prior to morning Hour 0 appointment				X			
Adverse Event Query	X			X			
Subject Comfort of Eye Drops Evaluation (administered by designated site personnel) (Day 1 and Day 14/Exit only)		X		X			
Concomitant Medications/Treatments	X			X			
Postural (Supine/Standing) Blood Pressure & Heart Rate	X		X	X	X		
Non-fasting Laboratory assessments (CBC with differential, Blood Chemistries, Urinalysis) (Day 14/Exit only, following final dose)				X			
Electrocardiogram (Day 14/Exit only)					X		
Urine Pregnancy Test (Day 14/Exit only, following final dose)				X			
Macroscopic (Gross) Hyperemia	X	X	X	X	X	X	X
[redacted]				X	X		
Visual Acuity[b]	X[b]			X[b]			
[redacted]				X			
Slit-Lamp Biomicroscopic Examination	X	X	X	X	X	X	X
Intraocular Pressure (IOP)[c]	X	X	X	X	X	X	X
Visual Field[d] (Day 14/Exit only)					X		
Fundus Exam (incl. C/D ratio) (post-pupil dilation) (Day 14/Exit only)							X
Confirm Inclusion / Exclusion criteria	X						
Randomize subject / Dispense study medication (for first dose)[e]	X						
Study medication administered by site personnel	X			X			
Collect subject EXIT status (Day 14/Exit only)							X

NOTE: C/D = cup/disc; H = hour (hour 0 = 07:00 to 09:00 hours)

NOTE: The night before postbaseline visits, evening dosing should occur approximately 12 hours (between 19:00 and 21:00 hours) prior to hour 0 of the subject's next morning's visit)

[a] Subject Comfort of Eye Drops Evaluation will be performed within 30 minutes post-morning dose.

[b] Manifest refraction performed at Baseline should be used at the days 1, 4 and 14 visits to obtain a correction for visual acuity evaluation. Manifest refraction(s) may be repeated, if in the opinion of the investigator, it is necessary.

[c] IOP should be measured before pupil dilation (as applicable) and at the same time (± 15 minutes) each day as the time established at baseline (day -1, hour 0, between 07:00 and 09:00 hours).

[d] The same methodology and equipment should be used for examinations of VF performed throughout the study. Visual Field evaluation can occur at any time after the Hour 2 examination and prior to pupil dilation for fundus examination at Hour 8.

[e] Give a single bottle of study medication to subject at the end of the visit

1. Background and Rationale

1.1. Background

Ocular hypertension, or chronically elevated intraocular pressure (IOP), is a major risk factor for optic nerve injury and sight loss associated with glaucoma (AGIS, 2000; Heijl et al, 2002); therefore, a primary goal of glaucoma management is to reduce IOP. [redacted]

Whitecap Biosciences plans to conduct an initial 2-part clinical study to evaluate the safety and IOP-lowering effects of AGN-227535 ophthalmic solution in adult patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT). Part 1 will be an open-label, single-dose, dose-escalation assessment of up to 3 concentrations (0.05% 0.15%, 0.4%) of AGN-227535 administered unilaterally to assess initial safety, tolerability and IOP-lowering effects. Results from Part 1 will determine concentration(s) to assess in Part 2. In Part 2, up to 2 concentrations of AGN-227535 will be administered bilaterally, twice-daily for up to 14 days and compared to timolol as the active control. The non-clinical data package supports twice-daily dosing of AGN-227535 0.4% for up to 28 days in humans.

1.2. Investigational Product

[redacted]

1.3. Summary of Nonclinical Studies

[redacted]

[redacted]

The non-clinical profile of AGN-227535 supports

the planned twice-daily dosing regimen of concentrations of up to 0.4% and the 2-week study duration in this clinical study. This study will be conducted in compliance with the protocol, International Conference on Harmonization guidance and Good Clinical Practices.

1.4. Benefit/Risk Assessment

This is the first clinical study of AGN-227535 in humans; [redacted]

2. Study Purpose, Objectives, and Clinical Hypothesis(es)

Overall Study Purpose

The purpose of this study is to assess initial ocular and systemic safety in humans of AGN-227535 ophthalmic solution and to assess its potential to lower IOP in subjects with glaucoma or ocular hypertension.

Study Objective(s)

The objective of this study is to assess the safety, ocular tolerability and IOP-lowering effects of AGN-227535 in adult subjects with primary open-angle glaucoma or ocular hypertension.

Clinical Hypotheses

Parts 1/2: AGN-227535 has an acceptable safety and tolerability profile.

Part 1: The IOP-lowering effects of at least 1 concentration of AGN-227535 are sufficient for evaluation to proceed to Part 2;

Part 2: The IOP effects of at least 1 concentration of AGN-227535 demonstrate adequate IOP lowering;

3. Study Design and Rationale

Study Design Description: This is a 2-part study designed to evaluate the safety, tolerability and IOP-lowering effects of AGN-227535 in subjects with primary open-angle glaucoma (POAG) or ocular hypertension (OHT). Approximately 100 subjects are planned to be enrolled at up to approximately 5 study centers in the United States.

In Part 1, an open-label dose-escalation of AGN-227535 0.05%, 0.15% and 0.4% is planned in order to assess initial safety, tolerability and IOP-lowering effects. Approximately 6 subjects will be exposed to a single dose (to one eye) at each concentration level. Between

cohorts, all available data will be used to assess the appropriateness to pursue the next concentration. Approximately 25 subjects will be screened so that 18 subjects complete the study.

In Part 2, In addition to the primary analysis of the within-group mean IOP change from baseline, a parallel comparison of AGN-227535 with timolol 0.5% is planned. Study treatments will be administered twice-daily for 14 days. Up to 2 investigational doses will be chosen based on results from Part 1. Subjects will be randomized in a 2(:2):1 ratio to receive one of up to two concentrations of AGN-227535 (based on results from Part 1) or timolol ophthalmic solution 0.5% and will be stratified based on IOP at Baseline, Hour 0 (≤ 25 mm Hg versus > 25 mm Hg). Approximately 24 subjects per AGN-227535 group and 12 subjects for the timolol group will be given study treatment. If 2 investigational doses are selected: approximately 75 subjects will be screened so that 60 subjects complete the study.

For both Parts 1 and 2, potential subjects will be screened within the 50 days prior to initiation of treatment. Thus, the total duration of study participation for each subject is up to 2.5 months which includes 4 (Part 1) and 5 (Part 2) in-clinic visits. The visit schedule requires day-long visits at some time points to perform sufficient clinical assessments. The primary efficacy endpoint (Part 2) is IOP change from baseline at each time-matched hour at Day 14/Exit.

Subject safety will be monitored throughout the study.

Rationale for the Study Design: Part 1 of this first in-human study will be conducted in a dose-escalation approach to assess the initial safety, tolerability and IOP-lowering effects of AGN-227535 following a single dose. Part 2 will be conducted as a 14-day assessment of the safety, tolerability and IOP-lowering effects of AGN-227535 dosed bilaterally BID to evaluate the short-term potential to lower IOP with an acceptable safety/tolerability profile. Timolol, an accepted standard of care treatment, will be used as the control in Part 2.

Rationale for Dose and Route of Administration: [redacted] As a topical eyedrop, the route of administration is considered appropriate.

Rationale for Duration of Observation: As the first-in-humans study, it is appropriate to take a measured approach with limited exposure to confirm the non-clinical results. [redacted]

3.1. Study Endpoints

3.1.1. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is mean change from baseline in IOP at each time-matched hour of Day 14/Exit (Hours 0, 2, 4 and 8).

3.1.2. Secondary Efficacy Endpoint(s)

Mean IOP at Day 14/Exit.

3.2. Methods for Randomization, Stratification, Masking, and Minimization of Bias

3.2.1. Randomization and Stratification (Part 2 Only)

Subjects will be randomly assigned to 1 of up to 3 treatment arms (based on results from Part 1) in a 2(:2):1 allocation ratio to receive 1 of up to 2 AGN-227535 concentrations or timolol.

To ensure balance of elements that could influence the IOP-lowering effects across treatment groups, the randomization will be stratified by baseline (Hour 0) IOP (≤25 mm Hg; >25 mm Hg).

The randomization scheme will be prepared by Whitecap Biosciences Biostatistics or its' designee. The IWRS, a module within eDC, will be used to confirm Baseline IOP eligibility and in Part 2 only, stratification and randomization of subjects.

3.2.2. Masking

Part 1: Subject treatment will not be masked. If both eyes qualify, the eye with the higher IOP at Baseline (Day -1) Hour 0 will be the study eye and will receive study medication. If both eyes have the same IOP value at this timepoint, the right eye will be the study eye.

Part 2: Subject treatment will be double-masked; neither the investigator nor the staff or subject will be aware of treatment assignment. All study treatments will be provided in similarly-appearing bottles with the same colored bottle caps and identical cartons to maintain masking of the study.

3.2.3. Minimization of Bias

The study design is that of a well-controlled clinical trial that includes elements necessary for a valid ascertainment of the effectiveness of treatment. Part 2 of the study is randomized and double-masked to minimize investigator and subject bias. A parallel-group design eliminates possible confounding effects that are inherent in other study designs (eg, crossover). The selection of subjects, study endpoints, and therapy are in general similar to studies that established the safety and efficacy of other IOP-lowering treatments of subjects with glaucoma or ocular hypertension. Subjects who are chronically treated with ocular hypotensive medications will be required to undergo appropriate washout periods prior to study entry to eliminate residual effects of other active ocular hypotensive medications.

3.3. Treatment Stopping Rules and Discontinuation Criteria

3.3.1. Treatment Stopping Rules

There are no specific treatment stopping rules. On an ongoing basis, all available safety data will be reviewed by the sponsor. If two or more adverse events of the same kind that are severe in nature and considered possibly study drug related occur, a decision will be made as to whether to stop enrollment of the cohort (Part 1 only), to add subjects to a lower concentration cohort (Part 1 only), to stop the study and exit all subjects, or to continue the study and proceed as planned (see Section 3.4 for details on decision making).

3.3.2. Discontinuation Criteria

Subject Discontinuation

Whitecap Biosciences, or the investigator, may decide to discontinue subjects who are enrolled into the study but who had significant deviation from protocol-specified inclusion/exclusion criteria.

If a subject meets any of the following criteria, s/he must be exited from the study (see Early Exit Procedures, Section 8.9).

- The investigator or Whitecap Biosciences deems that it is unsafe for the subject to continue in the study;
- Subject indicates that s/he no longer want to participate in the study.

Subjects will be discontinued from the study under the following circumstances: if a female subject becomes pregnant during the study, the investigator will notify Whitecap Biosciences immediately after the pregnancy is confirmed, the subject should not receive further study treatment and she must be exited from the study and the pregnancy followed to term (see

Section 8.9 for Early Exit Procedures and Section 6.4.3 for Procedures for Pregnancy Follow-up and Reporting).

Subjects who are exited before completing the study may be replaced following consultation with sponsor.

Study Discontinuation

The study may be stopped at a study site at any time by the site investigator. Whitecap Biosciences may stop the study (and/or the study site) for any reason with appropriate notification.

3.4. Decision Making During Parts 1 and 2

No formal Data Monitoring Committee will be established for this study. Prior to each dose-escalation step in Part 1, all available data will be reviewed to determine if the next dose should be assessed or if the study should be stopped. If the study proceeds to Part 2, the determination of doses to evaluate will be based on an unmasked review of all available data from Part 1.

All decisions to proceed or stop the study at any time will be made by a committee comprised of the Medical Monitor, the Head of Clinical and the Chief Executive Officer. Dose selection to be studied in Part 2 will be made by the same committee: an unmasked review of all Part 1 safety, tolerability and IOP effect results will be performed to determine if Part 2 should be performed and if yes, which dose(s) should be assessed. All decisions will be documented.

4. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population consists of adult subjects with POAG or OHT (but who are otherwise healthy). Subject eligibility will be based on the entry criteria below.

4.1. Inclusion Criteria

The following are requirements for enrollment into the study:

General:

1. Male or female at least 18 years of age at the time of consent.

2. Female subjects must agree to use an acceptable method of contraception (see Section 6.4 for pregnancy considerations and contraceptive requirements).

Type of Participant and Disease Characteristics:

3. Subject who:

   a. Is able and willing to follow study instructions and likely to complete all required study visits;

   b. Has chronic POAG or OHT in each eye and IOP is likely to be controlled on monotherapy;

   c. If on IOP-lowering medication, is willing to withhold his/her IOP-lowering treatments for the duration of the study and can do so without significant risk, in the opinion of the investigator;

   d. If on IOP-lowering medication, has been appropriately washed out of all IOP-lowering medications prior to Baseline (Day - 1) (see Section 6.2);

   e. At Baseline (Day -1), meets the following criteria in at least 1 eye (and in the same eye for all hours indicated below):

      1. An IOP $\geq$ 24 mm Hg and $\leq$ 34 mm Hg at Hour 0; and

      2. An IOP $\geq$ 22 mm Hg and $\leq$ 34 mm Hg at Hours 2, 4 and 8.

   f. Has an IOP $\leq$ 34 mm Hg in the fellow eye at Baseline (Day-1) Hours 0, 2, 4 and 8

   g. Has a best-corrected visual acuity (BCVA) score equivalent (using a logarithmic (LogMar) visual acuity chart) to Snellen acuity of 20/100 or better in at least 1 eye and of 20/200 or better in the fellow eye, using a logarithmic visual acuity chart at Screening and Baseline (Day -1);

   h. Is in good general health [as determined by the investigator from medical history and physical examination findings, non-fasting blood analysis (complete blood count with differential, blood chemistry), urinalysis], and 12 lead-ECG results are within reference range or acceptable to the investigator prior to randomization. Note: For the screening laboratory evaluation, subjects may have laboratory tests repeated once for reassessment at the discretion of the investigator prior to randomization. The investigator must review the screening results to confirm subject qualification for study entry.

Informed Consent and Written Authorization

4. Written informed consent of the subject has been obtained prior to any study-related procedures.

5. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information).

4.2. Exclusion Criteria

If any of the following criteria are met, the subject is not eligible for participation in the study:

Medical Conditions

1. Uncontrolled systemic disease.
2. History of orthostatic hypotension.
3. Female who is pregnant, nursing, or planning a pregnancy, or female of childbearing potential not using a reliable means of contraception (see Section 6.4).
4. Abnormal anatomy of nasolacrimal drainage system (eg, nasolacrimal duct obstruction).
5. History of chronic alcohol consumption or drug addiction.
6. Contraindications to topical beta-blocker therapy including bronchial asthma; a history of bronchial asthma; chronic obstructive pulmonary disease; second- or third-degree atrioventricular block; overt cardiac failure; cardiogenic shock.
7. History of or current diagnosis of cardiac arrhythmia.
8. Heart rate < 55 beats per minute while in a resting supine position.
9. Blood pressure decrease from the supine measurements of at least 20 mm Hg (systolic) or of at least 10 mm Hg (diastolic) after 3 minutes of standing.
10. Systolic blood pressure < 90 mm Hg while in a resting supine position.

Ophthalmic History / Conditions

11. Types of glaucoma other than chronic POAG (eg, uveitic; pigmentary; PXE, traumatic; angle-closure, including those who have had an iridectomy and/or iridotomy).
12. Surgical intervention for glaucoma at any time or laser intervention for glaucoma within the 12 months prior to Screening.
13. History of ocular neoplasia, uveitis, or herpetic ocular diseases.
14. History (within 6 months prior to Baseline [Day -1]) of any intraocular or refractive surgery in either eye.
15. Evidence of cataract surgery resulting in complications (eg, capsular rupture) in the study eye.
16. History or evidence of severe ocular trauma in the study eye.
17. Moderate or advanced findings of glaucoma on visual field examination; visual field loss which, in the opinion of the investigator, is functionally significant or shows evidence of progression (based on 2 visual field examinations) (see Sections 8.2 and 8.3 for timing of visual field examination requirements).

Prior/Concomitant Therapy

18. Current or anticipated use of any ocular medications (including periocular, intraocular, or sub-Tenon's administration) or other medications (eg, oral) for ophthalmic indications outside of those of the study protocol **from 2 months prior to Screening through Day 2/Exit (Part 1) or Day 14/Exit (Part 2).** NOTE: If required, IOP-lowering medications with shorter washout durations may be used during the washout period shown in Table 5.
19. Introduction or anticipated alteration of existing chronic systemic medications that may have a substantial effect on IOP (eg, systemic beta-blockers, carbonic anhydrase inhibitors or cholinergic agonists) **from 2 months prior to Screening through Day 2/Exit (Part 1) or Day 14/Exit (Part 2)**.
20. Current or anticipated use of oral, intramuscular, intravenous, intravitreal, periocular, or topical ophthalmic corticosteroids **from 2 months prior to Screening through Day 2/Exit (Part 1) or Day 14/Exit (Part 2)** (see Sections 6.1 and 6.3).
21. Treatment with any non-ocular alpha agonists, alpha antagonists (including medications for benign prostate hyperplasia), anticholinergics, sedative medications (including antihistamines, benzodiazepines, or opiate-type medications), or cold medications that could confound the study results **within 2 weeks prior to Baseline (Day -1) or anticipated use during the study** (see Sections 6.1 and 6.3).
22. Use of adrenergic augmenting antidepressant drugs, monoamine oxidase inhibitors (MAOIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) **within 30 days prior to Screening or anticipated use during the study** (see Sections 6.1 and 6.3).
23. Subject has a sleep disorder or has had excessive daytime somnolence **within 30 days prior to Screening**.
24. Use of sedative-hypnotics or other agents (including over the counter) for insomnia **within 10 days prior to Screening or anticipated use during the study** (see Sections 6.1 and 6.3).
25. Consumption of alcohol-containing beverages or products **within 72 hours prior to dosing on Day 1** or anticipated consumption **within 72 hours prior to a study visit**.
26. Blood donation or equivalent blood loss of ≥450 mL within 90 days prior to Day 1.

Prior/Concurrent Clinical Study Experience

27. Previous randomization in Part 2 of this study.
28. Concurrent enrollment in an investigational drug or device study or participation in such a study **within the 30 days prior to Screening**.

Diagnostic Assessments

29. Known allergy or hypersensitivity to the study medication or their components.

30. Known allergy, hypersensitivity or lack of efficacy with brimonidine (ALPHAGAN®, ALPHAGAN® P).
31. Known allergy or contraindication to use of any diagnostic agents.
32. Anticipated wearing of contact lenses in either eye during the study:
    - Use of rigid gas permeable (RGP) lenses or hard contact lenses should be discontinued at least 1 week prior to Baseline (Day -1);
    - Discontinue use of soft contact lenses at least 24 hours prior to Baseline (Day -1).
33. The following ocular surface findings:
    - Ocular hyperemia in either eye, on either macroscopic or slit-lamp examination, greater than +1 (mild) at Screening or greater than or equal to +1 (mild) at Baseline (Day -1) at Hour 0, based on a bulbar hyperemia grading guide (standard photographs) provided by the sponsor;
    - Active ocular surface findings other than hyperemia in either eye, on either macroscopic or slit-lamp examination, greater than or equal to +0.5 (trace) at Baseline (Day -1) at Hour 0.
34. Any ocular symptom at Baseline (Day -1) at Hour 0.
35. Active ocular disease (eg, blepharitis, dry eye, ocular seasonal allergies) that would interfere with the interpretation of the study data in either eye.
36. Corneal or other ocular abnormalities that would preclude accurate reading with an applanation tonometer (eg, corneal ectasias, corneal graft, significant corneal scarring).
37. Contraindication to pupil dilation.

Other Exclusions

38. Anticipated need to participate in any activity that may cause irritation to the eye (eg, swimming, smoking) during the study.
39. Anticipated need to engage in strenuous physical activity/exercise within 24 hours prior to a study visit, or to change an established exercise routine during the study.
40. Subject has a condition or is in a situation which, in the investigator's opinion, may put the subject at significant risk, confound the study results, or interfere significantly with the subject's participation in the study.

4.3. Lifestyle Considerations

During the study, subjects will be advised to:

- Refrain from activities that may cause irritation to the eye (eg, swimming or smoking);

- Refrain from engaging in strenuous physical activities/exercise within 24 hours prior to a study visit or changing established exercise routine during the study; subjects may participate in light recreational activities during the study (eg, watching television, reading);
- Refrain from use of types of medications listed in exclusion criteria. If used, document, in subject's Source Document /Case Report Form;
- Refrain from drinking more than ½ cup of liquid for one hour prior to IOP measurements on study visit days.

4.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet certain eligibility criteria (eg, IOP) for participation in this study (screen failure) may be re-screened once. Each case must be discussed with Whitecap Biosciences for re-screening consideration. Re-screened subjects should be assigned the same participant number as for the initial screening.

4.5. Rationale for Inclusion and Exclusion Criteria

The inclusion criteria and exclusion criteria [11-17] are designed to enroll adult subjects with OHT or mild POAG, as these subjects will be unlikely to require other treatment interventions during the study.

Exclusion criteria [18-26] are designed to exclude subjects whose study results could interfere with the interpretation of the efficacy results. Exclusion criteria [29-38] are designed to avoid including subjects with ocular conditions that may interfere with the interpretation of the study results.

5. Study Treatments

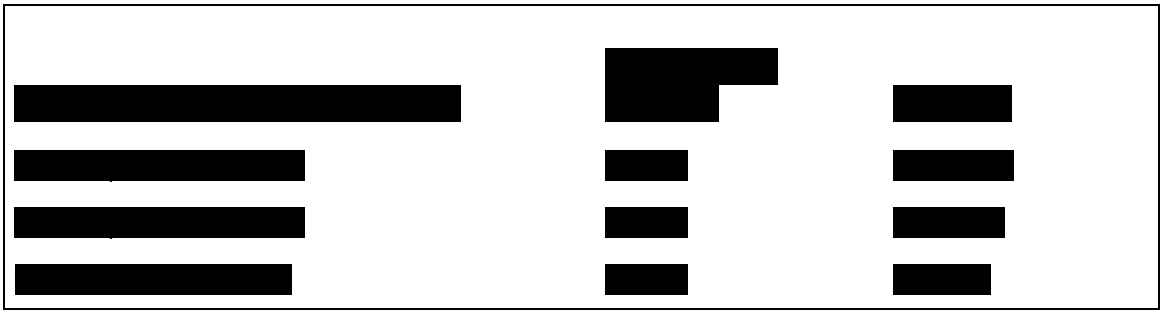
5.1. Investigational Product

Investigational Product Description

The following study treatments will be used in this study (Study treatments 1, 2 and 3). For study purposes, these treatments are referred to as Investigational Products (IP). AGN-

227535/WB007 ophthalmic solutions at concentrations of 0.05%, 0.15% and 0.4% are the planned study treatments. In Part 2, Timolol maleate ophthalmic solution 0.5% will be used as a control (Study treatment 4). [redacted]

[redacted]



*w/v = mass/volume

[redacted]

Study Treatment #4 - Timolol maleate ophthalmic solution 0.5%: contains timolol 0.5% (6.8 mg timolol maleate), mono basic and dibasic sodium phosphate, hydrochloric acid and/or sodium hydroxide to adjust pH, purified water and benzalkonium chloride 0.005%.

5.1.1. Preparation/Handling/Storage/Accountability

Investigational Product Storage

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study medications. Study product must be stored in a secure, environmentally controlled, and monitored (automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. [redacted]

Investigational Product Kit

Each IP kit will contain a single bottle of study treatment (Part 1) and 2 bottles of study treatment (Part 2). Each subject will be allocated 1 kit. Additional kits will be provided to the site in the event of loss/damage. In Part 2, each bottle of study treatment will be packaged in a unit carton. Each IP kit will be stored in secondary packaging. Clinical supplies for each subject will be labeled with a kit number associated with the subject randomization.

To assign kits in Part 1, designated site personnel will pull a kit from the provided inventory for the given cohort. To assign kits in Part 2, designated site personnel will use IWRS to obtain the specific kit number(s). The site will receive the IWRS confirmation notification for transactions. All notifications are to be maintained with the study source documents [redacted]

Appropriately qualified study site personnel will administer/dispense study medications as indicated in Section 8.4.

Investigational Product Preparation

Not applicable.

Investigational Product Inventory

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused investigational product are provided [redacted]

5.2. Study Treatment Administration

5.2.1. Study Treatment Regimen and Dosing

The principal investigator or delegated study personnel will instruct subjects on proper dosing techniques of ocular medications. In Part 1 and on study visit days in Part 2, the morning dose of study medications will be administered by the site, and dosing will occur at approximately the same time of day (hour 0 between the hours of 07:00 and 09:00) for a given subject. Also in Part 2, subjects will self-administer the study medication as follows: all other morning doses (between 07:00 and 09:00 hours) and all evening doses (between 19:00 and 21:00 hours) at approximately the same time of day each morning and evening.

Study visits should be scheduled to occur approximately 12 hours following the evening dose the night before a study visit.

5.2.2. Treatment Compliance

The IP must be dispensed/ administered only to the study subject by appropriately qualified site personnel. The IP is to be used in accordance with the protocol for subjects who are under the direct supervision of an investigator.

Part 1: The study treatment will be administered by site personnel.

Part 2: Subjects will be instructed on proper dosing techniques and site personnel will periodically remind subjects to take their treatments (via text message or phone call), (at a minimum, the night before a scheduled follow-up visit).

6. Concomitant Treatments and Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving after study treatment dosing is initiated must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant treatments and medications.

6.1. Prohibited Treatments and Medications

The decision to administer a prohibited treatment and/or medication is done with the safety of the study participant as the primary consideration. When possible, Whitecap Biosciences should be notified before the prohibited treatment or medication is administered.

The following medications, classes of medications, and treatment procedures are not permitted as concurrent therapy during the study:

- [redacted]
- [redacted]

- [redacted]
- Use of oral, intramuscular, intravenous, intravitreal, periocular, or topical ophthalmic corticosteroids. NOTE: intra-articular, inhaled, nasal, and dermal corticosteroids are permitted;
- [redacted]
- Use of any other ophthalmic topical medications or oral medications for ophthalmic indications. NOTE: artificial tears are allowed during study (see Section 6.3 for acceptable usage);
- Excessive consumption of alcohol or caffeine;
- Wearing of contact lenses.

6.2. Washout/Waiting Period

The washout/waiting period between Screening and Baseline is 4 to 50 days. The duration of this period is dependent upon whether a subject is taking IOP-lowering medications at Screening.

6.2.1. Washout Period

Eligible subjects who are being treated with IOP-lowering medication(s) in either eye will begin washout of these medication(s) following the screening visit. The minimum washout period will be 4 days to 6 weeks depending on the washout schedule below (Table 5). Note: The time from Screening to Baseline should not exceed 50 days.

Table 5 Minimum Washout Period

Ophthalmic Medication(s)	Minimum
Carbonic anhydrase inhibitors (topical or systemic) (eg, acetazolamide [Diamox®], dorzolamide [eg, Trusopt®], brinzolamide [eg, Azopt®], methazolamide [eg, Neptazane])	4 days
Sympathomimetics (eg, Dipivefrin, [PROPINE®]) or Epinephrine [eg, Epifrin®])	2 weeks
Alpha-agonists (eg, brimonidine [ALPHAGAN® P], apraclonidine [Iopidine®])	2 weeks
Beta-adrenergic blocking agents (eg, timolol [Timoptic®, Timoptic XE®], levobunolol [BETAGAN®], betaxolol [Betoptic®, Betoptic-S®], metipranolol [Opti-Pranolol®], carteolol [Ocupress®] and generics)	4 weeks
Fixed-combination therapy (eg, Cosopt®, COMBIGAN®)	4 weeks
Prostamides, prostaglandins, and prostaglandin analogs (eg, bimatoprost [LUMIGAN®], latanoprost [Xalatan®], travoprost [Travatan®], unoprostone [Rescula®], tafluprost [Taflotan®])	6 weeks
Rho Kinase (ROCK) Inhibitors	6 weeks

6.2.2. Considerations During Washout Period

For a subject on IOP-lowering medication(s), to minimize the effect of the absence of IOP-lowering therapy during the washout period, the investigator (at his/her discretion) may choose to modify a subject's medication regimen to a medication with a shorter washout duration rather than stop all IOP-lowering medications at once (eg, while undergoing the washout of a prostaglandin analog [PGA] (6 weeks), a subject may be switched to a carbonic anhydrase inhibitor which has shorter washout duration (4 days) than the PGA). The duration of the washout period must adhere to the requirements summarized in Table 5 based on the medications used at the time of Screening. At the discretion of the investigator, for subjects undergoing a washout period, consideration should be given to interim safety evaluation of IOP at some time during the washout period.

6.2.3. Waiting Period

Subjects who are not taking any IOP-lowering medications at Screening must have a minimum of 3 days between the Screening and Baseline visits. If a subject has taken IOP‑lowering medications prior to the screening visit, then s/he must also adhere to the appropriate washout period (See Table 5).

6.3. Permissible Medications and Treatments

During the study, therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the Medical Safety Physician.

Use of intra-articular, inhaled, nasal, and dermal corticosteroids are permitted.

Use of artificial tears is permitted providing the artificial tear is not given within 30 minutes pre- or post-study treatment administration. Use of artificial tears will be documented in the appropriate eCRF.

Existing use of chronic systemic medications that may have a substantial effect on IOP (eg, systemic beta-blockers, carbonic anhydrase inhibitors cholinergic agonists) are allowed providing the dosage has been stable for at least 3 months prior to randomization and remains stable throughout the study.

6.4. Pregnancy and Contraception Considerations

Definition of Female of Child-bearing Potential

For purposes of this study, a female will be considered of childbearing potential unless she is permanently sterilized (ie, hysterectomy) or is naturally postmenopausal. Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman who is at least 40 years of age has experienced 12 months or more of amenorrhea without any other obvious pathological or physiological cause. Female subjects who have had a hysterectomy or are naturally postmenopausal will not be required to perform a urine pregnancy test or to use contraceptives during the study.

6.4.1. Pregnancy Considerations

All female subjects who are of child-bearing potential will be advised to avoid pregnancy and are required to use methods of contraception considered acceptable to Whitecap Biosciences during the study.

For information about pregnancy reporting procedures, see Section 6.4.3.

6.4.2. Acceptable Contraception

The investigator will review the contraception requirements for the study with each subject.

The following methods of contraception, if properly used, are considered acceptable for use to avoid pregnancy during this study: hormonal contraceptives for females, (ie, oral, patch, injection, implant); sterilization (ie, bilateral salpingectomy, bilateral tubal ligation, vasectomy with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate); intrauterine devices/systems, sexual abstinence (when this is the lifestyle of the subject), and the following barrier methods (male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring). Note: spermicide alone is not an acceptable barrier method.

6.4.3. Procedures for Pregnancy Follow-up and Reporting

If a female subject becomes pregnant during the study (or within 30 days post-study exit), the investigator will notify Whitecap Biosciences (or designee) immediately after the pregnancy is confirmed. The subject should not receive further study treatment and she must be exited from the study (see Section 8.9 for Early Study Exit Procedures).

The investigator will (1) notify the subject's physician that the subject was enrolled in the study and treated with an investigational drug AGN-227535 ophthalmic solution or with timolol ophthalmic solution, and (2) follow the progress of the pregnancy to term. The

investigator must document the outcome of the pregnancy and provide a copy of the documentation to Whitecap Biosciences.

7. Study Assessments

This section provides a high-level summary of the study assessments to be performed. For details as to when these assessments are performed, see Section 8. [redacted]

For an explanation of terms and abbreviations, see Tables 6 and 7.

7.1. Demographics and Baseline Characteristics

- Age, race (including categories for ethnicity), sex, iris color;
- Medical and ophthalmic histories;
- Prior medications and treatments;
- Physical Examination;
- Ophthalmic Examination.

7.2. Efficacy Assessments

- IOP: IOP will be measured using a Goldmann Applanation Tonometer (GAT) and a 2-person reading method.

7.3. Safety Assessments

- **Adverse Events**: Adverse events will be monitored throughout the study;
- **Physical Examination**: A physical examination including height and weight;
- **Respiratory rate and temperature** in a resting seated position;
- **Postural (Supine and Standing) blood pressure and heart rate** will be assessed at specified timepoints and visits;
- **Electrocardiogram (ECG)**: A standard 12-lead ECG will be performed at the specified visits and timepoints. ECGs will be collected as triplicate recordings (within approximately 1 minute apart) and reviewed by the investigator. A consulting cardiologist will confirm the qualification of the subject prior to dosing of subject;
- **Non-Fasting Laboratory Tests**: Complete blood count with differential, blood biochemistry, and urinalysis will be measured;
- **Urine Pregnancy Test**: Female subjects of childbearing potential will have urine pregnancy tests performed;

- **Macroscopic Hyperemia Evaluations**: Macroscopic bulbar conjunctival hyperemia will be graded by the investigator upon gross inspection and compared with standard images;

[redacted]

- **Visual Acuity**: Visual acuity (in Snellen equivalents) will be measured for each eye using a logarithmic visual acuity chart (4-meter distance). Manifest refraction will be performed;

[redacted]

- **Slit-lamp Biomicroscopy**: Biomicroscopic examinations will be performed using a slit lamp through an undilated pupil. The examinations will include evaluation of the condition of the conjunctiva, cornea, anterior chamber, iris/pupil, and lens. The lens will also be evaluated following dilation for the cataract assessment;
- **Visual Field Examinations**: Visual field examinations (including historical tests used for screening) will be performed using Humphrey automated perimetry. Acceptable test methods are the Humphrey 24-2 full-threshold or Swedish Interactive Threshold Algorithm (SITA) Standard tests. The same test methodology will be used for all study-related examinations for a given subject;
- **Dilated fundus exam**: Stereoscopic fundus assessments should be conducted through a dilated pupil. The examination will include evaluation of the macula, optic nerve, vitreous, and retina. The cup/disc (C/D) ratio will also be assessed using the Armaly Cup-Disc grading card.

7.4. Other Assessments

- **Patient Comfort of Eye Drops Evaluation** (questionnaire administered by designated site personnel) (Part 2 only): Subjects are asked to rate the overall comfort of the eye drops.

7.5. Methods of Data Collection

This protocol will use electronic case report forms (eCRFs) with remote data capture through a qualified third-party vendor [redacted]. Data entered into the eCRF will correspond to, and be supported by, source documentation maintained at the sites (See Section 10.4.1, for investigator responsibilities regarding source documentation requirements). The data will be entered on the eCRFs by appropriately trained personnel in a timely manner and on an ongoing basis.

IWRS will be used to manage study treatment inventory. In Part 2 only, IWRS will also stratify and randomize subjects and assign study treatment kit numbers.

A qualified third-party laboratory will be used for the analysis of blood and urine samples. Laboratory results will be provided to the sites by the vendor. For statistical analysis purposes, laboratory data will be transferred to Whitecap Biosciences (or designee) at the end of each part of the study; detailed laboratory data will not be captured in EDC.

8. Study Conduct

This section provides a high-level summary of when during the study the procedures are to be performed. [redacted] The procedures should be performed in the order as listed on the Schedule of Visits and Procedures (see Tables 1, 2 and 3). The order of the following procedures (Medical and ophthalmic histories, Prior medications/treatments, concomitant medications/treatments) can be completed at any time during the study visit. For a glossary of terms and abbreviations, see Table 7; for a glossary of subject status definitions and other definitions, see Table 8. For a list of other study supplies besides the IP, see Attachment 12.3.

This study consists of the following scheduled visits:

- Part 1 (4 visits): Screening (Days -50 to -4); Baseline (Day -1); Days 1, 2/Exit;
- Part 2 (5 visits): Screening (Days -50 to -4); Baseline (Day -1); Days 1, 4, 14/Exit; designated site personnel will phone the subject on the evenings before Days 4 and 14/Exit to remind subjects of dosing requirements (See Section 8.4.2 for details).

Several visits (Part 1: Baseline [Day -1], Day 1; Part 2: Baseline [Day -1], Day 4, Day 14/Exit) will consist of an 8-hour diurnal assessment.

The following subsections provide details on the conduct of the study and list of procedures for each scheduled visit. Listed ocular procedures should be performed on both eyes. The procedures are listed in the order in which they should be performed (unless otherwise specified.

The Screening visit will occur between 4 and 50 days prior to Baseline (Day -1). Final subject qualification for the study will be determined at Baseline (Day -1). Subjects who qualify for the study will be considered eligible for study treatment administration and be assigned to one of the cohorts in a sequential manner (Part 1) or randomly assigned to one of the treatment groups (Part 2).

To minimize diurnal variation across study visits, particularly for IOP, the time of examinations for each subject's post-screening study-related activities and examinations should remain consistent over the course of the study. IOP measurements should be performed at approximately the same time each day based on the time of day established at the corresponding Baseline visit. Hour 0 should occur between 0700 and 0900 hours. At the Baseline visit, IOP measurements should occur 2, 4 and 8 hours from the time of the Hour 0 IOP evaluation. At post-Baseline visits, IOP measurements should be obtained as close as possible to the same time of day as the corresponding timepoint at Baseline.

Evaluations should be performed in the order listed in the Schedule of Visits and Procedures (see Tables 1, 2 and 3). Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the subject, then evaluations should overlap (ie, examine the subject together and discuss findings) for at least one visit.

If a female becomes pregnant during the study, the investigator will notify Whitecap Biosciences immediately after the pregnancy is confirmed and the subject will stop taking study treatment. The subject will be discontinued from the study after appropriate safety follow-up. See Section 6.4.3 for Procedures for Pregnancy Follow-up and Reporting.

8.1. Informed Consent

The study will be discussed with potential subjects. Those who are interested must give written informed consent prior to being subjected to any study-related procedures. Written documentation will be obtained in accordance with relevant country requirements (ie, Written Authorization for Use and Release of Health and Research Study Information and local privacy requirements, where applicable. See Section 10.1.3 for details on the Informed Consent process.

After obtaining consent and authorization, potential subjects will undergo a series of preliminary screening procedures to assess qualification for the study. At Screening, each subject will be assigned a subject number.

8.2. Subject Screening Visit /Screening Period (Days –50 to –4)

Subjects who provide informed consent will be assigned a subject identification number that will be used on all study documents. For each subject, the start of the study is defined as the time the informed consent is signed. Study-related procedures and data collection for study purposes may commence only after the informed consent has been obtained. All subjects (Part 1 and Part 2) will undergo screening that includes procedures for initial qualification at

the Screening visit followed by a Screening period (washout/waiting period, see Section 6.2) for those who meet required Screening visit eligibility criteria (see Sections 4.1 and 4.2 for inclusion/exclusion criteria). For subjects who screen fail, the reason for screen failure, as well as demographic and AE data will be collected and reported on the appropriate eCRF.

Once informed consent has been provided, the following procedures should be performed in the order below:

- Informed consent and authorization;
- Query to screen for any recent event that could jeopardize the subject's safety prior to further screening;
- Subject comfort of eye drops evaluation (for IOP-lowering agent(s) subject is taking at Screening) (Part 2 only);
- Medical and ophthalmic histories (including demographic data);
- Prior medications and treatments (current as well as those that have been stopped within 3 months prior to the Screening visit);
- Physical exam (including height and weight);
- Respiratory rate and temperature (seated);
- Postural (supine/standing) blood pressure and heart rate;
- Clinical laboratory evaluation (non-fasting), including CBC with differential, blood chemistries and urinalysis. Note: The Screening labs will be used to determine subject eligibility. If repeat testing is required, a non-fasting sample should be drawn at least 3 days prior to the scheduled Baseline visit to ensure results are available for review prior to randomization;
- Macroscopic (gross) hyperemia evaluation;
- Visual acuity (VA): Manifest refraction required to obtain a correction for VA evaluation;
- Slit-Lamp Biomicroscopy;
- IOP (GAT);
- Visual field: May be performed up to 12 months prior to or at Screening using the protocol-required testing method. For subjects requiring pupil dilation, the visual field should be performed after the IOP measurement or the next day. The same test methodology should be used throughout the study for a given subject;
- Fundus exam (including cup/disc ratio, post-pupil dilation);
- Begin washout of all IOP-lowering medication (see Section 6.2);
- Enter subject as "in Screening" in eDC;

- Preliminary determination of eligibility.

Washout Period (Days –50 to –4)

Eligible subject who are being treated with IOP-lowering medication(s) in either eye will enter the Screening Period and begin washout of these medication(s) following the Screening visit. Details of the washout requirements and options to minimize the absence of treatment during washout can be found in Section 6.2 and Table 5. The Baseline visit will occur following the completion of the washout period.

Waiting Period (Days –4 to –1)

There is a minimum of 3 days waiting between the Screening and Baseline visits for all subjects. Additionally, for subjects who have taken IOP-lowering medications prior to/at the screening visit, then they must also adhere to the appropriate washout period (See Table 5).

8.3. Subject Enrollment – Baseline Visit (Day -1)

A subject is considered to be enrolled in the study when s/he has completed all screening and qualification procedures and meets all eligibility criteria at the Baseline (Day -1) visit based on the inclusion/exclusion criteria (see Section 4.1 and 4.2) and confirmed eligibility on the morning of Day 1 (Part 1) AND has been randomized at Day 1 (Part 2).

Baseline - Hour 0:

- Adverse event (AE) query
- Medical and ophthalmic histories (including demographic data)
- Prior medications and treatments (between Screening and Baseline)
- Concomitant medications and treatments
- Respiratory rate and temperature (seated)
- Postural (supine) blood pressure and heart rate
- 12 lead-ECG
- Urine Pregnancy Test - Results of pregnancy tests (required for female subjects of childbearing potential only) must be obtained prior to treatment and must be negative for the subject to be eligible
- Macroscopic (gross) hyperemia evaluation

[redacted]

- Visual acuity (VA): Manifest refraction required to obtain a correction for VA evaluation

[redacted]

- Slit-Lamp Biomicroscopy
- IOP (GAT)
- Visual field: The 2nd VF examination can be performed at any time prior to pupil dilation
- Confirm 2 reliable fields are available and meet entry criteria.

Baseline - Hours 2, 4, 8

- Macroscopic (gross) hyperemia evaluation

[redacted]

- Slit-Lamp Biomicroscopy
- IOP (GAT)

8.3.1. Procedures Prior to Randomization (Part 2 only)

At the end of the Screening period, subjects will be assessed at the Baseline (Day -1) visit for eligibility. Qualified subjects will return the morning of Day 1 where eligibility will be confirmed. Eligible subjects may then be randomized. (Note: Subjects who do not meet eligibility criteria at Baseline (Day -1) or confirmation of eligibility on Day 1 before dosing occurs will be exited from the study as screen failures).

Only eligible subjects will be randomized.

8.3.2. Randomization Procedures (Part 2 only)

Prior to randomization of a subject, the site will be required to enter certain data into eDC. For IOP, each of the Baseline (Day -1) IOP measurements (either 2 or 3 per eye per hour) will need to be entered into IWRS, within eDC. These measurements will be used to confirm that the subject meets IOP inclusion criterion numbers 3 e and f (see Section 4.1). For confirmed qualified IOP, IWRS will assign a stratification code based on the IOP value(s) entered, randomize the subject and assign a study kit number. The kit number corresponds to the assigned study treatment for the subject. See Study Randomization Procedures in the IWRS section [redacted]

8.4. Study Visits and Procedures for Enrolled Subjects

8.4.1. Part 1 - Study Visits and Procedures for Enrolled Subjects

See Table 2 for the Schedule of Visits and Procedures in Part 1. Visits in Part 1 should occur on the designated day. No windows will be allowed.

Part 1 - Day 1 (Hour 0, pre-1st dose)

- Adverse event (AE) query
- Concomitant medications and treatments
- Postural (supine/standing) blood pressure and heart rate
- Macroscopic (gross) hyperemia evaluation
- Visual acuity (VA): Manifest refraction performed at Baseline (Day -1) should be used for visual acuity evaluation. Manifest refraction(s) may be repeated, if in the opinion of the investigator, it is necessary.
- Slit-lamp biomicroscopy
- IOP (GAT)
- Confirm Inclusion/Exclusion Criteria are still met
- Study medication assignment
- Enter Treatment Assignment form in eDC
- Site to administer study medication

Part 1 - Day 1 (30 minutes post-dose)

- Macroscopic (gross) hyperemia evaluation
- Slit-lamp biomicroscopy
- IOP (GAT)

Part 1 - Day 1 (Hour 2)

- Postural (supine/standing) blood pressure and heart rate
- Macroscopic (gross) hyperemia evaluation
- Slit-lamp biomicroscopy
- IOP (GAT)

Part 1 - Day 1 (Hours 4 and 8)

- Macroscopic (gross) hyperemia evaluation
- Slit-lamp biomicroscopy
- IOP (GAT)

Part 1 - Day 2 (Hour 0)

- Adverse event (AE) query

- Concomitant medications and treatments
- Postural (supine/standing) blood pressure and heart rate
- Urine pregnancy test (females of child-bearing potential only)
- Macroscopic (gross) hyperemia evaluation
- Visual acuity (VA): Manifest refraction performed at Baseline (Day -1) should be used for visual acuity evaluation. Manifest refraction(s) may be repeated, if in the opinion of the investigator, it is necessary.
- Slit-lamp biomicroscopy
- IOP (GAT)
- Fundus exam (including cup/disc ratio, post-pupil dilation)

Following the completion of the Day 2/Exit examination, the subject will exit the study.

8.4.2. Part 2 - Study Visits and Procedures for Enrolled Subjects

Visit windows will be applied in Part 2 only. Visit windows of ±1 day will be allowed. In Part 2, for each subject, the schedule of all post-baseline visits should be determined using the date of the Baseline visit.

Part 2 - Day 1 (Hour 0, Pre-1st Dose)

- Adverse event (AE) query
- Concomitant medications and treatments
- Postural (supine/standing) blood pressure and heart rate
- Macroscopic (gross) hyperemia evaluation
- Visual acuity (VA): Manifest refraction performed at Baseline (Day -1) should be used for visual acuity evaluation. Manifest refraction(s) may be repeated, if in the opinion of the investigator, it is necessary.
- Slit-lamp biomicroscopy
- IOP (GAT)
- Confirm Inclusion/Exclusion Criteria still met
- Randomize subject / obtain kit assignment / dispense a single bottle of study medication for first dose
- Site to administer 1st dose of study medication to each eye

Part 2 - Day 1 (30 minutes post-dose) (±5 minutes)

- Subject Comfort of Eye Drop Evaluation

- Macroscopic (gross) hyperemia evaluation
- Slit-lamp biomicroscopy
- IOP (GAT)

Part 2 - Day 1 (Hour 2) (±10 minutes)

- Postural (supine/standing) blood pressure and heart rate
- Macroscopic (gross) hyperemia evaluation
- Slit-lamp biomicroscopy
- IOP (GAT)
- Review instillation technique and give study medication to the subject to take home

Part 2 – Evening before Day 4 and Day 14/ Exit

- On the evenings before Day 4 and Day 14/Exit, designated site personnel will remind subjects to dose their evening dose approximately 12 hours prior to their next morning Hour 0 timepoint and to not dose the following morning (study medications will be administered by designated site personnel at the end of the Hour 0 timepoint).

Part 2 - Days 4 and 14/Exit (Hour 0) (±10 minutes)

- Adverse event (AE) query
- Concomitant medications and treatments
- Postural (supine/standing) blood pressure and heart rate
- Macroscopic (gross) hyperemia evaluation

[redacted]

- Visual acuity (VA): Manifest refraction performed at Baseline (Day -1) should be used for visual acuity evaluation. Manifest refraction(s) may be repeated, if in the opinion of the investigator, it is necessary.

[redacted]

- Slit-lamp biomicroscopy
- IOP (GAT)
- Site to administer study medication at end of Hour 0 examination
- Site to collect study medication following final dose (Day 14/Exit only)

Part 2 - Day 14/Exit only, once final dose has been administered

- Clinical laboratory evaluation (non-fasting)

- Urine pregnancy test (females of child-bearing potential only)

Part 2 - Day 14/Exit only (30 minutes post-dose) (±5 minutes)

- Subject Comfort of Eye Drops Evaluation (administered by designated site personnel)

Part 2 - Days 4 and 14/Exit (Hour 2) (±10 minutes)

- Postural (supine/standing) blood pressure and heart rate
- ECG (Day 14/Exit only)
- Macroscopic (gross) hyperemia evaluation
- [redacted]
- Slit-lamp biomicroscopy
- IOP (GAT)
- Visual Field (may occur at any time from Hour 2 prior to pupil dilation) (Day 14/Exit only)

Part 2 - Days 4 and 14/Exit (Hours 4 and 8) (±10 minutes)

- Macroscopic (gross) hyperemia evaluation
- Slit-lamp biomicroscopy
- IOP (GAT)
- Fundus exam (including cup/disc ratio, post-pupil dilation) (Day 14/Exit, Hour 8 only)

Following the completion of the Day 14/Exit examination, the subject will exit the study.

8.5. Unscheduled Visits and Associated Procedures

Additional examinations may be conducted as necessary to ensure the safety and well-being of subjects during the study period. eCRFs should be completed for each unscheduled visit. For all parameters not measured, indicate "Not Done".

Subjects may experience adverse events that necessitate their returning for unscheduled visits. The adverse event and all required information should be recorded on the appropriate eCRF and the subject's record should include all relevant information.

8.6. Instructions for Subjects

The principal investigator or designated study personnel will instruct the subject on proper dosing techniques prior to dispensing the study treatment to the subject. The sites will contact subjects routinely to remind them to administer their study treatment as instructed.

After each subject has signed the informed consent, s/he will be instructed as follows:

- To provide a list of all medications (prescription, non-prescription, vitamins, herbal supplements), taken within the 3 months prior to Screening and those that will be continued during the study period, including the dose and the reason for taking the medication and a list of any non-medicinal treatments;
- At Screening, subjects whose IOP is currently being treated with IOP-lowering medication(s) will be instructed by the site to stop taking the IOP-lowering meds (ie, begin the washout period) following the Screening visit. The washout period will be a minimum of 4 days to 6 weeks depending on the schedule in Table 5. Subjects may be instructed to return for a visit during the washout period so that the investigator may assess their IOP;
- To return to the study site, at approximately the same time of day established at Baseline (Day -1);
- To remain at the site to complete the remainder of the day's study-related procedures as explained to them by the study site personnel;
- To refrain from swimming and smoking, being exposed to smoke or other exposure that might cause eye irritation during the study;
- To refrain from drinking more than ½ cup of liquid within 1 hour prior to IOP measurement;
- To avoid discussing side effects (if any experienced) with other subjects in the trial;
- If spectacles are worn for vision correction, subjects should remember to bring the spectacles each time they visit the doctor's office;
- Females of childbearing potential should be reminded that they are to maintain the agreed to contraception method throughout the study and notify the site in the event of a pregnancy, up to 30 days after exiting from the study (see Section 6.4.3);
- Subjects should also be reminded to contact the study site if they are experiencing any difficulties during their study participation.

In Part 2 only, subjects will also be instructed as follows:

- On proper dosing of ocular medications and to dose study medication as directed: administer one drop in each eye each evening (between 1900 and 2100 hours) starting the evening of Day 1 and each morning (between 0700 and 0900 hours) through the evening of Day 13. The final dose of study medication on the morning of Day 14/Exit will be administered by site personnel after the Hour 0 examination. Subjects will be reminded to take their study medications approximately 12 hours before their Hour 0 appointments the evening prior to a post-baseline study visit and to not dose in the morning of Days 4 and 14. If desired, subjects will also be given the option for periodic (eg, daily) reminders from the Site to take their study medications each morning and evening;
- On proper storage conditions for study medications. The study medications should be kept in their unit carton (box). Do not show the bottles to other subjects or study staff (except the individual who dispenses the study medication to the subject). The study medications may be stored at room temperature during the study period (between 59°F and 77°F);
- To bring all used and unused study medication to all visits and to remind subjects that all study medications will be collected by the site at the Day 14/Exit visit.

8.7. Safety Monitoring

Investigators are responsible for identifying, monitoring and reporting adverse events that occur throughout the study (from subject signing of informed consent through study exit). Any adverse event that is marked 'ongoing' at the exit visit should be followed-up as appropriate until the event is resolved or deemed chronic or stable by the Study Investigator.

8.7.1. Procedures for Collecting and Reporting Adverse Events

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each subject a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

If, after obtaining the subject's informed consent but prior to administration of study product/treatment, a medical condition is identified via a study entry protocol assessment or procedure (eg, screening ECG test) which, based on the Investigator's judgment (and in consultation with the subject), is determined to be a pre-existing condition (ie, a condition existing prior to the time of the subject's informed consent), it should be documented on the

appropriate eCRF. Otherwise, the condition should be reported as a pre-treatment adverse event.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities.

8.7.2. Severity

A clinical determination will be made of the intensity of an AE. The severity assessment for an AE must be completed using the following definitions as guidelines:

Mild	Awareness of signs or symptoms, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity
Not Applicable	In some cases, an AE may be an 'all or nothing' finding that cannot be graded (eg, death)

8.7.3. Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an AE and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the study drug or study procedure.

8.7.4. Procedures for Reporting a Serious Adverse Event

Any serious adverse event must be immediately reported but no later than 24 hours after learning of the serious adverse event. The first report should be submitted even if the available information is minimal. All subjects with a serious adverse event must be followed up and the outcomes reported. The investigator must supply Whitecap Biosciences and the IRB/IEC with any additional requested information (eg, autopsy reports, discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Whitecap Biosciences (or designee) immediately by email using the Serious Adverse Event Form; phone numbers and relevant Whitecap Biosciences (or designee) personnel contacts are on the front page of this protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3. Provide Whitecap Biosciences (or designee) with a complete, written description of the adverse event(s) on the Serious Adverse Event Form describing the event chronologically, including any treatment given (eg, medications administered, other treatments given) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Provide follow-up SAE reports to Whitecap Biosciences (or designee) as more information becomes available
5. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

[redacted] additional details.

8.8. Procedures for Stopping Study Treatment

Part 1- There are no specific procedures for stopping treatment.

Part 2 - When the study treatment is stopped for an individual subject prior to the protocol defined duration for study treatment administration, the Day 14/Exit (Hour 0) procedures, at a minimum should be performed. The reason that the study treatment is stopped should be documented on the appropriate eCRF.

8.9. Early Study Exit Procedures

8.9.1. Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons;
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent;
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records;
- A subject who is enrolled, but who had significant deviation from protocol-specified inclusion/exclusion criteria, may be discontinued from participation in the study;

- If a female becomes pregnant during the study, the investigator will notify Whitecap Biosciences immediately after the pregnancy is confirmed and the subject will stop taking study treatment. The subject will be discontinued from the study after appropriate safety follow-up. See Section 6.4.3 for Procedures for Pregnancy Follow-up and Reporting;
- Subjects who are exited before completing the study may be replaced.

See Schedule of Visits and Procedures for specific data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. If a subject is discontinued prior to completing the study, the procedures outlined for the Day 2/Exit visit (for Part 1) or the Day 14/Exit visit (Hour 0 timepoint at a minimum) for Part 2 should be performed at the last visit attended.

When a subject exits before completing the study, the reason for the early exit will be clearly documented on the appropriate eCRF.

If the subject exits before completing the study, any serious adverse events or treatment-related non-serious adverse events occurring within 14 days after the last dose of study treatment should be reported to the Site.

8.9.2. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to be lost to follow up and exited from the study;
- When a subject is lost to follow-up, the reason for the early exit will be clearly documented on the appropriate eCRF.

8.10. Procedures for Unmasking of Study Medication

When necessary for the safety and proper treatment of the subject, the investigator can unmask the subject's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, Whitecap Biosciences (or designee) should be notified prior to unmasking study medication. The investigator should inform Whitecap Biosciences (or designee) of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the subject can be determined by designated site personnel through the IWRS via password protected access. The reason for breaking the code must be recorded in the subject's source documents. [redacted]

9. Statistical Procedures

One database lock will occur when all subjects (both Part 1 and Part 2) have either completed the study or discontinued from the study prematurely, and all data queries have been resolved. Randomization release will occur following the database lock. A detailed statistical analysis plan (SAP) will be approved prior to database lock.

9.1. Analysis Population(s)

Each population will be analyzed based on the treatment received.

Part 1: The Safety population consisting of all treated subjects will be used for all analyses.

Part 2: The following populations will be used for analysis:

- The Safety population will consist of all treated subjects. All safety analyses will be performed using the safety population;
- The Modified Intent-to-treat (mITT) will consist of all randomized and treated subjects who provide IOP data at baseline and at least one post-baseline IOP assessment. This population will be used for analyses of efficacy data;
- The Per-protocol (PP) population is a subset of the mITT population and will consist of subjects who did not have any major protocol violations deemed to have potential impact on the primary endpoint. This population will be used to confirm the primary efficacy analysis and will be determined prior to database lock.

9.2. Sample Size Calculation

For each cohort in Part 1 of the study a sample size of 6 patients will provide 83% power to detect a 3 mmHg within-group change from pre-dose assuming a standard deviation of 2 and two-sided alpha = 0.05, based on a one-sample t-test. With larger standard deviations (≥2.5) the power to detect this difference is <66%.

For Part 2, a sample size of 24 has > 90% power to detect a within-group mean changes from baseline IOP of 3 mm Hg, assuming a SD of 2.5 mm Hg. Also, power calculations were performed for the comparison of each dose of AGN–227535 versus Timolol. These calculations consider treatment differences (AGN–227535 minus Timolol) mean changes from baseline in study eye IOP in the mITT population at Day 14/Exit.

The power to detect treatment group differences from -1 to -4 mm Hg with common standard deviations (SDs) ranging from 2.5 to 3.5, based on a two-sample t-test are shown in Table 6.

Table 6 Power Calculations for Study Part 2 Tests of Treatment Differences
(AGN-227535 N = 24; Timolol N = 12; alpha = 0.05)

Treatment Group Difference	Common SD	Power (%)
-4	2.5	99
	3	96
	3.5	88
-3	2.5	91
	3	78
	3.5	65
-2	2.5	59
	3	45
	3.5	35
-1	≥2.0	<20

Additional sample size calculations were performed for tests of non-inferiority of either dose of AGN-227535 to Timolol. These calculations considered a non-inferiority margin of 1.5 mm Hg and one-sided $\alpha = 0.025$. With a treatment group difference of -1 mm Hg, the power ranged from 50% for a common SD of 3.5 to 78% for a common SD of 2.5.

The calculation was based on the non-inferiority tests for the difference between two means using t-test as implemented in the commercial software PASS version 16.0.3 (2018).

9.3. Methods of Analyses

In general, data will be summarized with descriptive statistics which will include sample size, mean, standard deviation, median, minimum and maximum for continuous variables and frequency and percentage for categorical variables.

Part 1: All safety and IOP-lowering effects tabulations will provide descriptive statistics by cohort.

Part 2: For continuous variables, treatment groups will be compared using analysis of variance covariance techniques or two-sample t-tests. Nominal variables will be analyzed using Pearson's chi-square test or Fisher's exact test.

Analyses performed for the mITT population will use the method of last observation carried forward (LOCF) to impute missing values. No imputation for missing data will be performed for the PP or safety populations.

As this is an exploratory trial, all treatment comparisons will be made at the two-sided $\alpha = 0.05$ level without adjustment for multiple comparisons.

9.3.1 Efficacy (Part 2)

9.3.1.1. Primary Efficacy Endpoint(s)

The primary response measure is IOP. Two consecutive measurements of IOP will be taken for each eye, with the right eye measured first. If the first two measurements of either eye differ by more than two mm Hg, a third measurement will be taken for the eye. Depending on the number of measurements required and obtained, the IOP for a given eye will be represented by either the average or the median of the readings. Details will be provided in the SAP.

The change from baseline for each eye at each post-baseline assessment is calculated as the IOP at that assessment minus the IOP at the corresponding hour at baseline. Efficacy will be evaluated in the study eye. The study eye is the eye that meets the inclusion/exclusion criteria. If both eyes meet the criteria, the study eye will be the eye with the worse (highest) IOP at Day -1 Hour 0. If both eyes have the same IOP value at this timepoint, the right eye will be the study eye.

The primary efficacy endpoints are the Day 14/Exit mean IOP changes from Baseline (Day -1) at each time-matched hour (0, 2, 4, 8). The primary hypothesis is that AGN-227535 ophthalmic solution effectively lowers IOP. The primary efficacy analysis is the within-

group mean change from baseline at Hour 2, the time of peak efficacy of timolol. This study will also assess if AGN-227535 is non-inferior to Timolol ophthalmic solution 0.5% with respect to change from baseline (follow-up minus baseline) in study eye IOP at each time-matched hour evaluated (hours 0, 2 4, and 8) at Day 14/Exit in the mITT population. The analyses will be performed via analysis of covariance (ANCOVA) which will have treatment as the main effect and the Baseline hour-matched IOP as the covariate in the model.

Pairwise treatment group comparisons will be performed for each individual dose of AGN-227535 versus timolol ophthalmic solution 0.5%. A 2-sided 95% confidence interval (CI) for the treatment difference (AGN-227535 Ophthalmic Solution minus Timolol ophthalmic solution 0.5%) will be constructed based on this ANOVA model for each AGN-227535 dose. [redacted] If AGN-227535 ophthalmic solution is determined to be non-inferior to Timolol ophthalmic solution 0.5%, a further attempt to show superiority of AGN-227535 over Timolol will be made.

Primary efficacy will be evaluated in the mITT population.

9.3.1.2. Secondary Efficacy Endpoint(s)

Mean IOP at Day 14/Exit.

Mean IOP change from baseline at each time-matched hour via analysis of variance (ANOVA) which will have treatment and the Baseline IOP stratum (IOP ≤25 mm Hg and > 25 mm Hg as the main effects in the model.

9.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. A detailed definition of treatment emergent adverse events (TEAEs) will be provided in the SAP. The number and percent of subjects with adverse event reports will be tabulated for all treatment emergent adverse events (TEAEs) regardless of causality, treatment-related TEAEs, all serious TEAEs, treatment-related serious TEAEs, and all adverse events leading to premature discontinuation of study treatment.

For Part 2, analyses of macroscopic hyperemia and hyperemia as evaluated on biomicroscopy will include evaluation of peak severity at each post-baseline visit (Days 4 and 14) and across all post-baseline time points.

Detailed methods for analyses of all safety variables will be provided in the SAP.

9.4. Other Analyses

[redacted]

9.5. Subgroup Analyses

For Part 2, descriptive statistics for the primary analyses will be provided by Baseline IOP stratum. Additional subgroup analyses may be specified in the SAP.

9.6. Interim Analyses

No interim statistical analysis is planned.

10. Supporting Documentation and Operational Considerations

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable ICH Good Clinical Practice (GCP) Guidelines;
- Applicable laws and regulations;
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated;

- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects;
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of US 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study;
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of US 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center;
- The medical record/source document must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF;
- If the ICF is modified during the subject's participation in the study, it may be required for the subject to be re-consented;
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred;
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject;
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

10.2. Protection of Human Subjects

10.2.1. Subject Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to Whitecap Biosciences or the governing health authorities (eg, US FDA, Canadian Committee for Medicinal Products for Human Use [CHMP], US Pharmaceutical and Medical Devices Agency, Japan PMDA) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.2.2. Subject Privacy

Written authorization and other documentation in accordance with the country and local privacy requirements (where applicable) is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA").

In accordance with country-specific requirements, additional purposes of this study may include publishing of anonymized subject data from the study.

10.2.3. Compliance with Informed Consent Regulations and Relevant Country Regulations

Following informed consent regulations (eg, US 21 CFR Part 50) Written informed consent is to be obtained from each subject prior to any study-related activities or procedures in the study, and/or from the subject's legally authorized representative.

1. That the study involves research;
2. The objectives of the study;
3. The study procedures;
4. The expected duration of the subject’s participation in the study;
5. The approximate number of subjects involved in the study;
6. The reasonably foreseeable risks or inconveniences to the subject;
7. The alternative procedures or courses of treatments that may be available to the subject, and their important potential benefits and risks;
8. The compensation and/or treatment available to the subject in the event of study-related injury;
9. That the subject’s participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled;
10. That subject will be informed in a timely manner if information becomes available that may be relevant to the subject’s willingness to continue participation in the study;
11. The foreseeable circumstances and/or reason under which the subject’s participation in the study may be terminated;
12. That the monitors, auditors, the IRB, and the regulatory authorities may provide direct access to the subject’s original medical records. In such cases, the confidentiality of the subject should be protected, and by signing and sealing an informed consent form, the subject is authorizing such access;
13. If the results of the study are published, the subject’s identity will remain confidential;
14. The anticipated expenses, if any, to the subject for participating in the study;
15. The anticipated prorated payment, in any, to the subject for participating in the study;
16. The name, title, and address of the investigator to contact;
17. The person(s) to contact for further information regarding the clinical study and the rights of subjects, and whom to contact in the event of study-related injury;

18. The type of the IRB engaged in the assessment and deliberation about the acceptability of the study, items subject to the assessment of each IRB, and other IRB-related items relating to the study;
19. The subject's responsibilities.

10.2.4. Compliance with IRB Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and reapproval or review at least annually. Whitecap Biosciences is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB correspondence with the investigator should be provided to Whitecap Biosciences.

10.2.5. Compliance with Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.3. Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Whitecap Biosciences and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects.

10.4. Documentation

10.4.1. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the eCRFs serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record /source notes:

- Subject’s contact information;
- The date that the subject entered the study, subject number and for Part 2, subject study treatment kit number;
- Sites will receive the IWRS confirmation notification for each transaction. All notifications are to be maintained with the study source documents;
- The study title and/or the protocol number of the study and the name of Whitecap Biosciences;
- A statement that informed consent was obtained including the date. A statement that written authorization (HIPAA authorization; US sites only) and any local subject privacy required documentation for this study has been obtained (including the date) A statement that informed consent was obtained (including the date);
- Reasons for screen failure;
- Dates of all subject visits;
- All prior and concurrent medications (see Table 7 for definitions and timeframes). List all prescription and non-prescription medications being taken. At each subsequent visit, changes to the list of medications should be recorded;
- All prior and concurrent procedures and/or non-medication treatments (see Table 7 for definitions and timeframes). List all procedure and non-medication treatments being taken. At each subsequent visit, changes to the list of medications should be recorded;
- Occurrence and status of any adverse events (including onset date, assessments of severity, seriousness, and relationship with study drug, treatment instigated (if any), action taken regarding study drug, outcome, and stop date);
- The date the subject exited the study, and a notation as to whether the subject completed the study or reason for early exit;
- The results of protocol-required laboratory tests performed by the site (ie, results of urine pregnancy tests, hematology including complete blood count and differential, blood chemistry panel and urinalysis);
- Patient medical and surgical histories (including demographics);
- Patient ophthalmic history (including iris color);
- Results of physical examination performed by site (including height and weight);
- For females, documentation of non-childbearing potential or results of pregnancy test and documentation of subject’s stated birth control method when applicable;

- Ophthalmic examination results of subject visits including all IOP measurements and times, macroscopic bulbar hyperemia evaluations, [redacted], visual acuity, [redacted], slit-lamp biomicroscopy, visual field and fundus exams;
- Subject comfort of eye drop evaluations responses (Part 2 only);
- Respiratory rate, and temperature measurements (seated);
- Postural (supine/standing) blood pressure and heart rate;
- Electrocardiogram findings;
- Source notes should also include any subject counseling/education (when applicable) regarding contact lens usage, activities that would interfere with ocular surface evaluation, permissible mediations/treatments, prohibited medications/treatments, and timing in relation to scheduled study visits and study compliance including instruction provided to subject for administration and storage of study medication.

10.4.2. Compliance with Electronic Records; Electronic Signatures Regulations

This study is to be conducted in compliance with the regulations on electronic records and electronic signature (US 21CFR Part 11).

10.4.3. Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. An investigator who has signed the protocol signature page should personally electronically sign the eCRFs to ensure that the observations and findings are recorded on the eCRFs correctly and completely. A certified electronic copy of the eCRFs including data corrections will be provided to the site for archiving at the end of the study. [redacted]

10.4.4. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF;
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF;
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents;
- The sponsor or designee is responsible for the data management of this study including quality checking of the data;

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.4.5. Study and Site Closure

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of subjects by the investigator;
- Discontinuation by the sponsor of further development of the study treatment.

10.4.6. Final Report by Investigator

An investigator's summary, in compliance with US 21 CFR Part 312.64(c), will be provided to Whitecap Biosciences (or designee) within a short time after the completion of the study, or as designated by Whitecap Biosciences. A summary of the study's outcome is also to be provided to the responsible IRB and, if applicable, the investigator's institution.

10.4.7. Retention of Documentation

All study-related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of all investigational products, and copies of case report forms should be maintained on file.

For countries falling within the scope of the ICH guidelines, the Whitecap Biosciences-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Whitecap Biosciences.

Whitecap Biosciences requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5. Monitoring by Whitecap Biosciences

Authorized representatives of Whitecap Biosciences will monitor the study on a periodic basis. The determination of the extent, frequency and nature of monitoring will be based on such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Whitecap Biosciences or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.6. Publications

The results of this study may be published or presented at scientific meetings; the investigator shall agree to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results, in accordance with standard editorial and ethical practice. Whitecap Biosciences, as the sponsor, has proprietary interest in this study and thus will be involved in reviewing, at a minimum, any abstract or manuscript prior to submission in order to allow the sponsor to protect proprietary information and to provide comments. Authorship and manuscript composition will reflect joint cooperation between the investigator(s) and Whitecap Biosciences personnel. Authorship will be established prior to the writing of abstracts or manuscripts, will be determined by mutual agreement, and in line with International Committee of Medical Journal Editors authorship requirements.

As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study, except as agreed with Whitecap Biosciences.

11. References

AGIS (The Advanced Glaucoma Intervention Study). The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol. 2000;130(4):429-440.

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Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120(10):1268-1279.

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Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-516.

12. Attachments

12.1. Glossary of Terms, Abbreviations and Definitions

Table 7 Glossary of Terms and Abbreviations

Term/Abbreviation	Definition
ANOVA/ANCOVA	Analysis of Variance/Analysis of Covariance
BAK	benzalkonium chloride
BCVA	best-corrected visual acuity
BID	twice daily
bpm	beats per minute
BUN	blood urea nitrogen
C/D	cup/disc
CRF/eCRF	case report form/electronic case report form
ECG	electrocardiogram
eDC	Electronic data capture
FDA	Food and Drug Administration
GAT	Goldmann Applanation Tonometer
GCP	Good Clinical Practices
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IETD	investigator emergency treatment disclosure
IOP	intraocular pressure
IP	investigation product
IRB	Institutional Review Board
IWRS	Interactive web-response system
LogMar	logarithm of the minimum angle of resolution
[redacted]	[redacted]

Term/Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mm Hg	millimeters of mercury
NOAEL	no observed adverse effect level
OHT	ocular hypertension
OU	both eyes
PGA	prostaglandin analog
POAG	primary open angle glaucoma
PP	per protocol
RGP	rigid gas permeable
SITA	Swedish Interactive Thresholding Algorithm
[redacted]	[redacted]
TCA	tricyclic antidepressant
US	United States

Table 8 Glossary of Definitions

Term	Definition
End of Study	The date of the last visit of the last subject in the study
Subject Status	Subject status is defined below:
Study entry	A subject who has signed informed consent and has undergone at least 1 screening procedure and been entered into IWRS
In screening	A subject who has is undergoing the screening process and has not yet qualified for study enrollment.
Screen failure	Subject who has signed informed consent, has undergone at least 1 screening procedure, but fails to qualify for study at any time prior to and up until the completion of the Baseline visit.
Enrolled	A subject who qualifies for study based on Inclusion and exclusion criteria (Parts 1 and 2) (see Sections 4.1 and 4.2) AND is randomized (assigned a randomization number (Part 2).
Subject completion	A subject who has completed all phases of the study including the last scheduled procedure as shown in the Schedule of Visits and Procedures.
"Should" vs "Must"	Use of the word "should" means that it is suggested or recommended, but not required, whereas the use of the word "must" means that it is required.
Concurrent Medication	A medication that the study subject is taking at the time of enrollment or after
Concurrent Treatment	A procedure or other non-medication medical treatment that the study subject is receiving at the time of enrollment or after.
eg,	for example
ie,	in other words
Prior Medication	A medication taken by the study subject within time period specified in entry criteria prior to enrolling in the study. Other prior medications within 3 months prior to enrolling into the study.
Prior Treatment	A procedure or other non-medication medical treatment received by the study subject within time period specified in entry criteria prior to enrolling in the study. Other prior treatments within 3 months prior to enrolling into the study.
Study eye	The designated eye for use in analysis of IOP effects will be based on the eye with the higher IOP at Day -1, Hour 0. If both eyes qualify, the eye with the higher IOP at Baseline (Day -1) Hour 0 will be the study eye. If both eyes have the same IOP value at this timepoint, the right eye will be the study eye.

12.2. Examination Procedures, Tests, Equipment, and Techniques

Study evaluations should be performed by the same investigator or sub-investigator throughout the study whenever possible. If it is not possible to use the same individual to follow the subject, then an attempt should be made to have visits overlap (examine the subject together and discuss findings) for at least one visit. At designated study visits, physical examinations and the comfort of eye drop subject questionnaire should be conducted prior to other assessments or invasive procedures. Data will be recorded on the appropriate eCRF.

12.2.1. Demographics and Baseline Characteristics

Demographic information including age, race (including limited ethnicity), gender and iris color are to be obtained at the screening visit.

12.2.1.1. Medical and Ophthalmic Histories and Procedures

Medical (relevant) and ophthalmic history (including the history of the current disease/disorder), any pertinent procedures that could potentially influence the safety of the subject and/or the outcome of the study and any information regarding underlying disease/disorders are to be obtained at Screening. Data will be recorded on the appropriate eCRF.

12.2.1.2. Physical Examination (Including Height and Weight)

The subject will be examined for any detectable abnormalities of the following body systems: general appearance; head, eyes, ears, nose and throat (HEENT); heart/cardiovascular; lungs; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic and skin.

Height will be measured (without shoes) in inches (in) or centimeters (cm). Weight (without shoes) will be measured in pounds (lb) or kilograms (kg) using a scale. Historical subject information and/or subject reports should not be used for the height and weight measurements.

12.2.1.3. Respiratory Rate and Temperature

Respiration rate will be measured after the subject has been in a resting state (seated) for at least 5 minutes. Respiration rate will be counted for 30 seconds, multiplied by 2, and recorded as breaths per minute. **Temperature** will be measured after the subject has been in a resting state (seated) for at least 5 minutes. Temperature will be measured in Celsius (°C) or Fahrenheit (°F). Oral, Skin or tympanic temperature methods of collection are acceptable.

12.2.1.4. Postural (Supine / Standing) Blood Pressure and Heart Rate

Postural Systolic/diastolic blood pressure and heart rate will be measured after the subject has been in a resting state (supine) for at least 5 minutes and then again 3 minutes after standing. Record the 2 measurements from the 2 positions (supine and standing). Pulse will be counted for 30 seconds, multiplied by 2, and recorded in bpm.

12.2.1.5. Urine Pregnancy Test

Female subjects who are of child-bearing potential (see Section 6.4 for definition) will have a urine pregnancy test performed. Pregnancy test kits will be provided by a qualified third-party vendor (see Attachment 12.4) and will be administered according to the instructions provided with the tests.

12.2.1.6. 12 lead-ECG

Sites will receive training on the use of ECG equipment provided.

[Triplicate] 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and [QTc] intervals. At each time point, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

12.2.1.7. Clinical Safety Laboratory Assessments (non-fasting)

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within [insert timeframe] after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified;
- All protocol-required laboratory assessments (see below) must be conducted in accordance with the Laboratory Manual and the Schedule of Visits and Procedures;

Laboratory assessments will include blood chemistry panel, hematology including complete blood count with differential, urinalysis and urine pregnancy test for all females who are of child-bearing potential (See Section 6.4 for definition).

The specific tests in these panels are:

Complete Blood Count (with differential): hematocrit, hemoglobin, red and white cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell morphology, reticulocyte count, platelet count, neutrophils (bands and segments), lymphocytes, monocytes, eosinophils, and basophils.

Chemistry Panel: albumin/globulin (A/G ratio), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), albumin, alkaline phosphatase, bilirubin (total, direct, and indirect), blood urea nitrogen (BUN), BUN/creatinine ratio, calcium, magnesium, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), chloride, creatinine, globulin, hemoglobin A1c (HbA1c), lactic dehydrogenase (LDH), phosphorus, potassium, serum bicarbonate, total protein, sodium, triglycerides, uric acid, and creatine phosphokinase (CPK).

Urinalysis: A urine specimen will be collected and assessed for color (appearance), specific gravity, pH, glucose, protein, ketone, urobilinogen, nitrite, leukocyte esterase, occult blood, and bilirubin. Microscopic analysis includes the following: red blood cells per high power field (RBC/HPF), white blood cells per high power field (WBC/HPF), squamous epithelial cells; additional components, abnormal and/or atypical cells will also be reported if present.

Urine pregnancy test: All females who are of child-bearing potential are required to have urine pregnancy tests.

Handling of Biological Specimens: Samples of blood and urine for evaluation of hematology, chemistries and urinalysis will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology [CAP] or Clinical Laboratory Improvement Amendments [CLIA] certification).

12.2.2. Ophthalmic Examination Procedures, Tests, Equipment, and Techniques

Visits for ophthalmic examinations should be scheduled at approximately the same time of the day. A gross general examination of the external eye and adnexa should be performed, and pathology described. See the Schedule of Visits and Procedures (Tables 1, 2 and 3) for the order in which the procedures should be performed.

12.2.2.1. Subject Comfort of Eye Drops Evaluation (Questionnaire) (Part 2 only)

Subjects will be asked questions by a designated clinical staff member at the site to assess the study medications by responding to a series of questions regarding their comfort of their IOP-lowering medications. Conduct these interviews in a quiet place with only the study participant and the interviewer present. Please instruct each subject that his/her input is important. Subjects should report on their experiences and impressions (ie, there are no "right" or "wrong" answers). Begin with asking the subject about all of the symptoms s/he may be experiencing or overall comfort in the right eye and then when complete, ask about the symptoms of the left eye.

Subjects will be asked questions by a clinical staff member at the site to assess the comfort of their eye drop medication(s) (for each eye):

- (if applicable) the IOP-lowering medication they are taking prior to entry into the study (at Screening);
- the study medication (at post-Baseline visits).

Leading Question at Screening: Thinking about your <appropriate> eye, how would you rate the overall comfort of your current glaucoma eye drops?

Leading Question at Study Visits: Thinking about your <appropriate> eye, how would you rate the overall comfort of the study eye drops?

Using the Subject Comfort of Eye Drops Questionnaire on a 6-point scale, read to the subject each of the responses for the selection that best matches their experience: Very comfortable, Comfortable, Slightly uncomfortable, Uncomfortable, Very Uncomfortable, Intolerable.

12.2.2.2. Macroscopic Bulbar Conjunctival Hyperemia

The macroscopic (gross) hyperemia grading should be completed prior to any other eye examinations. Bulbar hyperemia will be graded by the Investigator upon gross inspection under consistent illumination by comparing the appearance of the bulbar conjunctiva to standard photographs.

0	(None)	=	[redacted]
+0.5	(Trace)	=	[redacted]
+1	(Mild)	=	[redacted]
+2	(Moderate)	=	[redacted]
+3	(Severe)	=	[redacted]

The gross macroscopic hyperemia evaluation should be performed by the same evaluator in the same facility with consistent lighting throughout the entire study, whenever possible.

12.2.2.3. Visual Acuity

Manifest refraction will be performed at specified study visits (See the Schedule of Visits and Procedures Tables 1, 2, and 3 in the protocol synopsis and see Section 8) to obtain a correction for all visual acuity evaluations. Visual acuity (in Snellen equivalents) will be measured for each eye using a logarithmic (LogMar) visual acuity chart for testing at 4 meters. [redacted]

12.2.2.4. [redacted]

[redacted]

12.2.2.5. [redacted]

[redacted]

12.2.2.6. Biomicroscopic Examinations

Findings other than those listed below should be recorded under "other" for the appropriate location of the finding. Required dilated examinations are designated on the Schedule of Visits and Procedures.

Eyelid/Eyelid Margins/Lashes

Edema

0	(None)	=	[redacted]
+0.5	(Trace)	=	[redacted]
+1	(Mild)	=	[redacted]
+2	(Moderate)	=	[redacted]
+3	(Severe)	=	[redacted]

Erythema

0	(None)	=	[redacted]
+0.5	(Trace)	=	[redacted]

+1	(Mild)	=	[redacted]
+2	(Moderate)	=	[redacted]
+3	(Severe)	=	[redacted]

Conjunctiva (Bulbar)

Hyperemia

0	(None)	=	[redacted]
+0.5	(Trace)	=	[redacted]
+1	(Mild)	=	[redacted]
+2	(Moderate)	=	[redacted]
+3	(Severe)	=	[redacted]

Edema

0	(None)	=	[redacted]
+0.5	(Trace)	=	[redacted]
+1	(Mild)	=	[redacted]
+2	(Moderate)	=	[redacted]
+3	(Severe)	=	[redacted]

Cornea

Edema

0	(None)	=	[redacted]
+0.5	(Trace)	=	[redacted]
+1	(Mild)	=	[redacted]
+2	(Moderate)	=	[redacted]
+3	(Severe)	=	[redacted]

Superficial Punctate Keratopathy

0	No superficial punctate keratopathy
+0.5	(Trace)
+1	(Mild)
+2	(Moderate)
+3	(Severe)

Anterior Chamber

For the measurements of cells and flare based on standardized uveitis nomenclature (SUN Working Group, 2005), the following settings should be used:

1 x 1 mm slit			High magnification
Highest slit lamp voltage			Low ambient lighting
Illumination angle of 45 degrees			Same grader and slit lamp whenever possible
Cells			
0	=	0 cells	
+0.5	=	1-5 cells (trace)	
+1	=	6-15 cells	
+2	=	16-25 cells	
+3	=	26-50 cells	
+4	=	>50 cells	
Flare			
0	=	None:	No flare seen
+1	=	Faint:	Faint flare seen
+2	=	Moderate:	Iris and lens details clear
+3	=	Marked:	Iris and lens details hazy
+4	=	Intense:	Fibrin or plastic aqueous

Iris/Pupil

The iris/pupil will be evaluated for pathology. If pathology is present, it will be described.

Iris Color (Screening only)

Iris color will be recorded at Screening using the following classification: blue, blue-gray, blue/gray-brown, gray, green, green-brown, hazel, brown, dark brown, or other (specify).

12.2.2.7. Intraocular Pressure (IOP) (mm Hg)

IOP should be measured only after the biomicroscopic exam is completed and must be measured prior to pupil dilation. IOP measurements will be taken by two qualified

independent study site personnel using a Goldmann applanation tonometer (GAT) affixed to a slit lamp with the subject seated. One person will adjust the dial in masked fashion while a second person will read and record the value. The subject and slit lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight fitting neckwear should be loosened. Both eyes will be tested, with the right eye preceding the left eye. Each IOP measurement is to be recorded.

One person ("the measurer") looks through the binocular viewer of the slit lamp at low power. The tension knob is pre-set at a low-pressure value (4 to 6 mm Hg). The measurer follows the image of the fluorescein-stained semicircles while he/she slowly rotates the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle. When this image is reached, the measurer takes his/her fingers off the tension knob and the second person ("the reader") records the IOP reading along with the date and time of day in the source document, thus maintaining a masked IOP reading. For a given subject, the reader should not also be the person to dispense/administer/discuss study medications with the subject.

At least two, and if necessary, three consecutive measurements will be taken to determine IOP in the manner described above. If the first two measurements differ by 2 mm Hg or less, a third measurement is not required, and the two measurements will be recorded. If the first two measurements differ by more than 2 mm Hg, a third measurement should be made, and all three measurements will be recorded.

12.2.2.8. Visual Field

Measure the subject's pupils (to the nearest 0.5 mm). If they are less than 3 mm in diameter, dilate them with 2.5% phenylephrine drops, unless contraindicated. If the brow is heavy or the upper lid is drooping, tape accordingly. Visual field results must be reliable (ie, ≤ 33% fixation losses, false positive or false negative errors) or the field should be repeated within two weeks. Visual field examinations will be performed using a Humphrey automated perimetry test (24-2) using the full threshold or SITA standard testing method). The same test method (eg, SITA Standard 24-2) should be used for all visual fields for a given subject, including the historical visual field, if applicable. Preferred equipment is the Humphrey 700 Humphrey Field Analyzer (HFA) 2 series machines (eg, 740 or 750). Visual fields will be reported as normal or abnormal and the mean deviation will also be recorded in decibels (dB).

Begin by testing the right eye. Adjust the chin rest and the table height as needed to achieve proper alignment as well as to maintain the subject in a comfortable seated position throughout the test. It is permissible to encourage the subject occasionally if the subject seems to be fatigued or losing concentration, and to allow the subject to pause and rest if necessary. The subject should also be informed that a good time to blink is when the response button is pushed so as not to affect the results of the test.

12.2.2.9. Other Ophthalmic Examinations

Use biomicroscopic examination, indirect lenses, direct/indirect ophthalmoscopy, etc. as appropriate to visualize.

Lens

Lens Status

Lens status will be assessed as phakic, pseudophakic, or aphakic. The lens (including the posterior capsule for subjects who have undergone lens extraction) will also be evaluated for pathology. If pathology is present, it will be described.

Cataract Assessment (phakic eyes only)

Under dilated examination, the presence and severity of nuclear, cortical and posterior subcapsular cataract lens opacities will be evaluated. At the first dilated examination, each type of cataract, if present, will be graded using the scale below. At the last follow-up dilated examination, each type of cataract will be assessed for change from baseline and if changed, the current severity will be graded using the scale below:

0	=	None
+1	=	Mild
+2	=	Moderate
+3	=	Severe

Vitreous

The vitreous will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

Fundus

The fundus (posterior pole; periphery, when dilated) will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

Optic Nerve

The optic nerve will be evaluated for pathology. If pathology is present, it will be described. Note if the condition is not evaluable.

Cup/disc ratio will be reported using a 0.0 to 1.0 scale. The Armaly chart provided by Whitecap Biosciences provides a pictorial scale of cup/disc ratio of 0.0 to 0.8. Note if the condition is not evaluable.

12.3. Other Study Supplies

As needed, Whitecap Biosciences will provide logarithmic visual acuity charts as necessary, the Armaly chart (for measurement of cup/disc ratio), and the bulbar hyperemia grading guide (standard photographs). In addition, ECG equipment will be provided to each site as needed. [redacted] Study sites are to use their own equipment for all other examinations and measures.

The kits for collection of non-fasting clinical laboratory analysis, as well as urine pregnancy test kits will be provided a qualified third-party vendor (see Attachment 12.4):

- Laboratory kits (including pregnancy tests) for the collection and shipment of blood and urine samples.
- Shipping materials for shipment of laboratory samples to the central laboratory.

12.4. List of Computerized Systems

Electronic Data Capture (EDC)

This protocol will use eCRFs using remote eDC through a qualified third-party vendor. The data will be entered on the eCRFs in a timely manner on an ongoing basis. Data will be located in a study-specific clinical database. [redacted]

Interactive Web-Based Response System (IWRS)

The IWRS, a module of the eDC, will be used to confirm Baseline IOP eligibility and in Part 2 only, stratification, randomization and medication kit numbers assignment. The IWRS will also be used to manage study medication inventory. [redacted]

Clinical Laboratory Sample Analysis

Analysis of laboratory samples: blood chemistry panel, hematology including complete blood count with differential, urinalysis, and urine pregnancy tests for all females who are of

child-bearing potential will be performed by a qualified third-party vendor. [redacted]

12.5. Protocol Amendments

12.5.1. Amendment 1 Summary

Study Title: A Phase 1/2a Assessment of WB007 Ophthalmic Solution in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension

Protocol WB007-001_01 (Amendment 1); **Date of Amendment**: July 2019

Section	Revision	Rationale
Synopsis	**Study Population:** Adult (at least 18 years of age) male or female subjects with primary open-angle glaucoma or ocular hypertension in each eye who are otherwise in generally good health. Only one eye must meet all ocular entry criteria.	Clarified that only one eye must meet all ocular entry criteria to participate in the study.
	Dosage/Dose Regimen (Part 2): added "Site personnel will administer the morning dose at study visits."	Added emphasis here that site personnel will administer doses at study visits.
	Randomization/Stratification: added "When both eyes qualify, the study eye will be defined using the Interactive Web Response System (IWRS), a module within the electronic data capture (eDC) system."	Clarified use of IWRS during randomization
Synopsis, Sections 9.3.1.1 and 9.4	[redacted]	[redacted]
Sections 3.2, 5.1.1, 7.5, 8.3.2, 12.4	[redacted]	[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
Tables 1, 2, 3; Section 7.3, 8.2, 8.3, 8.4, 10.4.1, 12.2.1.3, 12.2.1.4	"Vital Signs" has been removed. Respiration rate and temperature have been separated from "Postural blood pressure and heart rate".	Clarify seated vs. supine and standing measurements. The use of the term "vital signs" became superfluous.
Table 1	Removed footnote d: "At Day 1 Hour 0, if IOP has changed by more than 3 mm Hg from Baseline (Day -1) Hour 0, the subject is not eligible."	Decision to simplify entry criteria and alignment between Parts 1 and 2.
Table 3, Section 8.4.2	Subject Comfort of Eye Drops Evaluation (administered by designated site personnel) (Day 14/Exit only)	Clarified that evaluation will be performed at Day 14 only (not Days 7 AND 14)
Table 3, Section 8.4.2	Added footnote e to table: "Give study medication to subject at the end of the visit" and clarified language in Section 8.4.2	Clarify in Part 2 that subject will be given the study medication at the end of the Day 1 visit.
4.2	• Removed exclusion criterion #9 • Removed exclusion criterion #10	Original criteria 10, 11 and 12 were sub-bullets of Criterion #9. A formatting issue occurred which elevated criteria 10, 11 and 12 to same level as 9, rendering 9 unnecessary. Criterion #10 was a duplicate of criterion #2.
4.2	Exclusion #33 was modified to allow subjects with up to +1 (mild) conjunctival hyperemia (rather than up to +0.5 (trace) to screen for this study.	Loosened the criterion to ensure efficient enrollment of this study population without jeopardizing the outcome of the study.
[redacted]	[redacted]	[redacted]
8.4.1	Part 1 – Day 1 (Hour 0): added a bullet for study medication assignment	
8.4.2	Added bullet to Part 2 – Evening before Day 7 and Day 14 (Exit): "Contact from site to remind subject to dose study medication approximately 12 hours prior to Hour 0 appointment time."	Clarified in this section to align with Table 3 and Sections 5.2.1, 8 and 8.6
8.4.2 and 8.6	Added bullet to Part 2 - Days 7 and 14/Exit (Hour 0) (±10 minutes): "Site to collect study medication following final dose (Day 14/Exit only)"	Clarified when study medications will be collected from the subject in Part 2.

Section	Revision	Rationale
8.6	Added to Subject Instructions: "To avoid discussing side effects (if any experienced) with other subjects in the study" and in Part 2: "The study medications should be kept in their unit carton (box). Do not show the bottles to other subjects or study staff (except the individual who dispenses the study medication to the subject."	To minimize bias
9.3.1.2	Moved analysis of variance to secondary efficacy endpoint	To accommodate updated primary analysis.
10.1.3	Rephrased the 4th bullet: If the ICF is modified during the subject's participation in the study, subjects must be re-consented to the most current version of the ICF(s).	Previous wording was confusing.
[redacted]	[redacted]	[redacted]
12.2.2.7	For a given subject, the reader should not also be the person to dispense/administer/discuss study medications with the subject.	To minimize bias

12.5.2. Amendment 2 Summary

Study Title: A Phase 1/2a Assessment of WB007 Ophthalmic Solution in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension

Protocol WB007-001_02 (Amendment 2); **Date of Amendment**: Sept 2019

Section	Revision	Rationale
4.1	IOP in fellow eye at Baseline $\leq$ 34 mm Hg at Hour 4 added.	Inadvertently omitted Hour 4.
4.1, 7.3 and 12.2.2.3, 12.3	Visual Acuity (VA): replaced testing distance of 3 meters to 4 meters; removed distance from entry criterion; visual acuity charts will be provided to sites as necessary.	Testing distance of 4 meters is a standard practice with logarithmic VA charts. Distance for VA testing is redundant in inclusion criterion. Logarithmic VA charts will be provided as necessary.
8.2	Clinical laboratory evaluation (non-fasting), "including CBC with differential, Blood Chemistries, Urinalysis" added.	Clarified that both blood and urine specimens will be collected.
8.4.2	Part 2, Day 1, 30 minutes Subject Comfort of Eye Drop Evaluation was added	Examination inadvertently omitted in the text.
8.4.2	Part 2, Days 7 and 14/Exit Hour 2 Visual Field examination is to be performed at Day 14/Exit only. Part 2, Days 7 and 14/Exit Hour 8 Fundus examination is to be performed at Day 14/Exit only.	Clarified that these 2 examinations are to be performed at Day 14/Exit only.

12.5.3. Amendment 3 Summary

Study Title: A Phase 1/2a Assessment of WB007 Ophthalmic Solution in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension

Protocol WB007-001_03 (Amendment 3); **Date of Amendment**: January 2020

Section(s)	Revision	Rationale
Synopsis, Table 3, Figure 3; Sections 8, 8.4.2, 8.6, and 9.3.2	Moved Day 7 to Day 4	Assess potential to observe early steady state
Synopsis, Table 3, Figure 3; Sections 8 and 8.4.2	Removed Day 2-3 required phone call	Phone call now optional.
Synopsis	Schematic of study design for Part 2 modified duration of diurnal days from 12 to 8 hours	Align with protocol text.
8.3.2.	Removed "Hour 0" from IOP required to enter into IWRS. All Baseline IOP needs to be entered prior to randomization.	Align with inclusion criteria 3e and 3f
Table 3; Sections 5.1.1 and 8.4.2	IP kits for Part 2 will include 2 bottles, each in a unit carton. Secondary packaging to group the bottles for each subject will also be used. Only 1 bottle at a time is to be dispensed to a subject.	If necessary (eg, lost or damaged bottle), a second bottle will be available to dispense.
Table 8	Updated definition of Concurrent medication and concurrent procedure to include during the study	Clarified to include post-enrollment additions

12.5.4. Amendment 4 Summary

Study Title: A Phase 1/2a Assessment of WB007 Ophthalmic Solution in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension

Protocol WB007-001_04 (Amendment 4); **Date of Amendment**: September 2020

Section(s)	Revision	Rationale
4.1	Exclusion 15: removed "evidence of unilateral cataract surgery" from the criterion. The criterion now is: "Evidence of cataract surgery resulting in complications (eg, capsular rupture) in the study eye."	Loosened the criterion to ensure efficient enrollment of the study population without jeopardizing the outcome of the study.
4.1 and 8.4.1	Modified exclusion 27: "Previous participation in this study" to "Previous randomization in Part 2 of this study". Part 1 Day 2 (Hour 0): removed statement not allowing participation in Part 2 for subjects who participated in Part 1.	Allow for subjects who participated in Part 1of the study to participate in Part 2. A subject who participates in both Parts 1 and 2 will be counted only once in the total number of participants of the study.

12.5.5. [redacted]

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