A Phase 2, Double-Masked, Randomized, Placebo-Controlled, Dose-Response Study Assessing the Safety and Ocular Hypotensive Efficacy of Two Concentrations of SBI-100 Ophthalmic Emulsion in Patients with Elevated Intraocular Pressure

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Sponsor:	Skye Bioscience, Inc. 11250 El Camino Real, Suite 100 San Diego, CA 92130, U.S.A.
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Prepared by:	Lexitas Pharma Services, Inc.

SIGNATURE PAGE

DocuSigned by Peter Yao
Peter Yao | I approve this document 01-Dec-2023 | 10:08:42 AM EST
C52A86AAE35642DDADE93C656C5F2346

01-Dec-2023 | 10:09:08 AM EST

Peter Yao, M.S.
Director, Biostatistics
Lexitas Pharma Services, Inc.

Date

DocuSigned by Richard Zink
Richard Zink | I approve this document 01-Dec-2023 | 9:31:08 AM EST
4DD9CA638F78400A9040A69494CA2F2A

01-Dec-2023 | 9:31:18 AM EST

Richard C. Zink, PhD
Vice President, Biostatistics and Statistical Programming
Lexitas Pharma Services, Inc.

Date

DocuSigned by Andrew Pucker
Andrew Pucker | I approve this document 01-Dec-2023 | 9:36:31 AM EST
680E4C0506DC45969874828D2CB05F24

01-Dec-2023 | 9:37:04 AM EST

Andrew Pucker, OD, PhD
Senior Director, Clinical and Medical Sciences
Lexitas Pharma Services, Inc.

Date

DocuSigned by Tu Diep
I approve this document 05-Dec-2023 | 1:27:04 PM PST
4AC18DE55A6645F28BB1DB4E4D504304

05-Dec-2023 | 1:27:29 PM PST

Tu Diep, M.S.
Chief Development Officer
Skye Bioscience, Inc.
11250 El Camino Real, Suite 100
San Diego, CA, 92130

Date

DocuSigned by Kirk Bateman
Kirk Bateman | I approve this document 01-Dec-2023 | 9:28:55 AM PST
A49D14F78AA74BAE845ADF2F51DEC8C4

01-Dec-2023 | 9:29:12 AM PST

Kirk Bateman, M.S.
Statistics Consultant
Skye Bioscience, Inc.
11250 El Camino Real, Suite 100
San Diego, CA, 92130

Date

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BCVA	Best Corrected Visual Acuity
b.i.d.	Twice a Day (Bis in Die)
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
eCRF	Electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FCS	Fully Conditional Specifications
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hct	Hematocrit
HDL	High-Density Lipoprotein
Hgb	Hemoglobin
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational product
LASIK	Laser-Assisted *in situ* Keratomileusis
LDH	Lactate Dehydrogenase

LDL	Low-Density Lipoprotein
LogMAR	Logarithm of the Minimum Angle of Refraction
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
NCS	Non-clinically significant
OD	Oculus dexter (right eye)
OE	Ophthalmic Emulsion
OHT	Ocular Hypertension
OS	Oculus sinister (left eye)
OU	Oculus uterque (both eyes)
PI	Principal Investigator
PRO	Patient Report Outcome
POAG	Primary Open Angle Glaucoma
PP	Per Protocol
PRK	Photorefractive Keratectomy
PT	Preferred term
QC	Quality control
RBC	Red blood cell count
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
SOP	Standard Operating Procedure

TEAE	Treatment emergent adverse event
UPT	Urine pregnancy test
US	United States
WBC	White blood cell count
WHODrug	World Health Organization Drug Dictionary

PROTOCOL SYNOPSIS

<table>
<tr><td colspan="3">Name of Sponsor/Company:
Skye Bioscience, Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product/Study Treatment:
SBI-100 Ophthalmic Emulsion</td></tr>
<tr><td colspan="3">Name of Active Ingredient:
SBI-100 Delta 9 Tetrahydrocannabinol an amino ester containing valine and hemisuccinate (Δ9-THC-Val-HS or THCVHS)</td></tr>
<tr><td>Protocol Number:
SBI-100-201</td><td colspan="2">Country: United States (US)</td></tr>
<tr><td>Title of Study:</td><td colspan="2">A Phase 2, Double-Masked, Randomized, Placebo-Controlled, Dose-Response Study Assessing the Safety and Ocular Hypotensive Efficacy of Two Concentrations of SBI-100 Ophthalmic Emulsion in Patients with Elevated Intraocular Pressure</td></tr>
<tr><td colspan="3">Study center(s): Multi-center, up to 6 centers</td></tr>
<tr><td colspan="2">Studied period (years):
Estimated date first patient enrolled: November 2023
Estimated date last patient completed: May 2024</td><td>Phase of development: 2</td></tr>
<tr><td colspan="3">Primary Objective:
To evaluate the diurnal ocular hypotensive efficacy of 2 dose levels of SBI-100 Ophthalmic Emulsion compared to placebo in patients with elevated Intraocular Pressure (IOP)
To evaluate the ocular and systemic safety of SBI-100 Ophthalmic Emulsion in patients with elevated IOP
Secondary:
To evaluate the ocular hypotensive efficacy at individual time points of SBI-100 Ophthalmic Emulsion in patients with elevated IOP
To evaluate the application comfort of SBI-100 Ophthalmic Emulsion
Exploratory:
• Changes in proteomic and immune biomarkers from Baseline</td></tr>
<tr><td colspan="3">Study Design: This is a multi-center, randomized, double-masked, placebo-controlled Phase 2 study to evaluate the ocular hypotensive efficacy, safety, and tolerability of SBI-100 Ophthalmic Emulsion after 14 days of binocular dosing, twice daily (BID).</td></tr>
</table>

There will be a 35-day screening period, including wash-out (if needed), followed by a visit on Day -1 to confirm eligibility. The first dose will be administered by the staff immediately after the (eligibility) 08:00 IOP measurement on Day 1, with subsequent study assessments up to 8 hours post-dose. The PM (evening) dose will be self-administered by the patient at home, approximately 12 hours after the AM (morning) dose. The patient will self-administer study treatment on Days 2 through 6 in the AM and PM. On Day 7, the patient will return to have the AM dose administered by site staff immediately after the 08:00 IOP measurement has been taken. Subsequent assessments will be performed in a similar fashion as Day 1 with study assessments up to 8 hours post dose, patient will self-administer the Day 7 PM dose and the AM and PM doses on Days 8 through 13. On Day 14, the patient will return to have the AM dose administered by site and assessments similar to that of Days 1 and 7, the patient may complete the final dose on Day 14 at the site approximately 12 hours after the AM dose and have end of study (EOS) procedures performed. Or the patient may choose to self-administer the Day 14 PM dose at home and return to the site within 2 days for EOS visit.

IOP efficacy will be evaluated by Goldmann applanation tonometry. Safety/tolerability will be evaluated by review of ocular signs and symptoms through Best Corrected Visual Acuity (BCVA), ophthalmic assessments, ocular comfort patient reported outcome (PRO), vital signs, and other standard safety measures.

Number of patients (planned): 54 in total, 18 per treatment group

Diagnosis and main criteria for inclusion: Patients with primary open angle glaucoma (POAG) or ocular hypertension (OHT)

Study Treatment, dosage, and mode of administration: A topical eye drop that is administered binocularly BID with the following treatment groups:

0.5% (5 mg/mL) SBI-100 Ophthalmic Emulsion

1.0% (10 mg/mL) SBI-100 Ophthalmic Emulsion

Placebo Ophthalmic Emulsion

Duration of study participation: 52 days in total

Screening:	Up to 35 days, including wash-out from any topical pharmacological IOP-lowering therapies (if required)
Treatment:	2 weeks (14 days)
Follow-up	Up to 2 days after the last dose on Day 14

Inclusion Criteria:

1. At least 18 years of age or greater at time of informed consent.
2. Diagnosis of either primary open angle glaucoma (POAG) or ocular hypertension (OHT) in each eye.
3. Intraocular Pressure (IOP) Criteria:

a. If currently on an IOP-lowering therapy, patient is willing to withhold therapy according to study requirements, and in the opinion of the Investigator, can do so without significant risk.
b. If treatment naïve, Screening IOP is between 21 and 36 mmHg in each eye, and in the opinion of the Investigator, is likely to be controlled on a single IOP-lowering therapy.
c. 08:00 Hour IOP is between 21 and 36 mmHg in each eye on Day -1 and Day 1.

4. Central corneal thickness between 480 and 620 µm at Screening in each eye.
5. Best correct visual acuity (BCVA) for distance equivalent to 20/100 or better in each eye at Screening and Day 1 (pre-dose).
6. Able to give signed informed consent and follow study instructions.
7. If patient and/or partner has reproductive potential, agrees to use reliable methods of contraception throughout their participation in the study and until at least 30 days after the last dose.
   a. If female of childbearing potential, has a negative pregnancy test at Screening and Day -1.

Exclusion Criteria:

Either eye:

1. Mean/Median intraocular pressure > 36 mmHg at Screening and/or any time prior to treatment administration.
2. Concurrent treatment for glaucoma requiring more than 2 topical therapies (either as 2 independent monotherapies or as fixed dose combination), oral IOP-lowering therapy and/or in the opinion of the Investigator cannot be controlled on a single IOP therapy.
3. Has planned ocular surgeries/procedures within the duration of the study.
4. In the opinion of the Investigator has clinically significant dry eye disease that requires chronic use of artificial tears, gels and/or ointments.
5. Any abnormality preventing reliable applanation tonometry.
6. History of closed angle forms of glaucoma and/or Shaffer grade <3 (in 1 or more quadrants); Laser treated narrow anatomic angle is acceptable.
7. Any occurrences of the following prior to Day 1:
   a. Ocular trauma or surgery within 6 months
   b. Ocular laser treatments within 3 months
   c. In the opinion of the Investigator history or evidence of clinically significant ocular inflammation, including but not limited to blepharitis, conjunctivitis, etc.
   d. History of recurrent ocular herpes (simplex or zoster)
   e. Previous glaucoma intraocular surgery or glaucoma laser procedure and/or refractive surgery (e.g., radial keratotomy, PRK, SLT, LASIK, etc.) within 6 months
   f. Ocular medication within 30 days prior, **except for**
      i. IOP-lowering therapies (washed-out per study requirements)
      ii. Lid scrubs
      iii. Artificial tears, gels and/or ointments to treat dry eye disease that in the opinion of the Investigator is not considered chronic use

8. Clinically significant ocular disease (e.g., corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with the study, including
    a. Glaucomatous damage so severe that wash-out of ocular hypotensive medications for at least 52 days is not judged to be safe (i.e., cup/disc ratio > 0.8)
    b. Persistent allergic conjunctivitis or allergic conjunctivitis that is likely to manifest during the study and confound the results
    c. Glaucoma: pseudoexfoliation or pigment dispersion component, congenital, developmental, or secondary (e.g., neovascular, uvetic, pigmentary, lens-induced, steroid-induced, trauma-induced, or glaucoma associated with increased episcleral venous pressure) Note: Previous laser peripheral iridotomy is acceptable.
9. Visual field loss, in the opinion of the Investigator, is functionally significant (e.g., split fixation, mean deviation greater than -20 dB or central fixation point equal to 0 dB, or field defect that is visually significant or likely to cause central visual impairment upon progression) or show evidence of fast (>-1.5dB/year) progressive visual field loss within the 12 months prior to Day 1.
10. Will require contact lenses and cannot refrain from using them at least 7 days prior to Day 1 and throughout the study.

General/Systemic:

11. Clinically significant lab abnormalities at screening and/or systemic disease which might interfere with the study as per the Investigator's discretion.
12. Participation in any investigational study within 30 days of screening.
13. Changes of systemic medication during the study that could have a substantial effect on IOP (5.1.3) within 30 days prior to screening or anticipated during the study.
14. Known hypersensitivity or allergic reaction to cannabinoids, cannabis, sesame seed/oil or any component of the SBI-100 Ophthalmic Emulsion formulation and/or topical anesthetics.
15. Females of childbearing potential (not confirmed as post-menopausal or surgically sterile within the 6 months prior to screening) who are pregnant, nursing, or planning a pregnancy during the study and not using a reliable method of contraception from screening until at least 30 days after the last dose.
16. Males with partners of childbearing potential and do not agree to use a reliable method of contraception during the study and at least 30 days after the last dose.
17. Patients with a history of substance or alcohol abuse, considered chronic tetrahydrocannabinol (THC) users and/or test positive for alcohol or illicit drug use at Screening or Day -1.

Criteria for evaluation:

Efficacy:

- IOP measured by Goldmann applanation

Safety:

- Vital signs, safety labs, and adverse events (AEs) (overall, ocular, and non-ocular)
- Ophthalmic assessments: slit lamp biomicroscopy, dilated fundus exam, BCVA, pupil diameter, visual field and pachymetry

- Ocular comfort

Statistical Considerations:

With a sample size in each group of 18 including 5% attrition (total, n=54), the study will have 80% power to detect a difference of 3.0 mmHg or greater in mean diurnal IOP between each dose of active treatment and its placebo assuming a common standard deviation of 3.0 mmHg in diurnal IOP in each group, $\alpha = 0.05$ (two-sided). All statistical summaries and analyses will be performed using SAS software as detailed in the statistical analysis plan (SAP).

The primary analysis will compare the change from baseline (Day -1) in mean diurnal IOP at Day 14 for each of the SBI-100 treatment groups to the placebo group. Analysis of covariance (ANCOVA) will be used for each comparison, at a two-sided alpha level of 0.05. The model will include adjustment for the Day -1 value. The primary efficacy analysis will be based on the Intent to Treat (ITT) population. The study eye will be defined as the eye with the highest mean diurnal IOP from the three measures on Day -1 (baseline). (In the case of a tie, the study eye will be the right eye).

For this feasibility study, the primary analysis will be based on observed data only, not imputing missing data. If the study eye is missing data for any time point on Day 14, the mean diurnal IOP will not be calculated for the primary analysis to avoid using a biased estimate. Thus, the while-on-treatment strategy for handling intercurrent events of early discontinuation will be employed.

Sensitivity analysis will be described *a priori* in the SAP and will include analyses on the Per Protocol population should there be a significant number of major protocol deviations. If there is a case where >5% of the patients have missing data for any time point, the primary analysis will be repeated on the ITT population with imputed missing data (at the visit and time point level) following other intercurrent event strategies. Other methods for defining the study eye and analyzing both eyes in a random effects model may also be considered.

Secondary efficacy endpoints will be analyzed using MMRM. Safety endpoints will be summarized descriptively.

There will be one interim analysis when at least 50% of the treated subjects have diurnal IOP measurements at 14 days post-dosing to assess the conditional study power.

9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

The primary objective of this study is 1) to evaluate the diurnal ocular hypotensive efficacy of 2 dose levels of SBI-100 Ophthalmic Emulsion compared to placebo in patients with elevated IOP and 2) to evaluate the ocular and systemic safety of SBI-100 Ophthalmic Emulsion in patients with elevated IOP.

As shown in Figure 1, this is a multi-center, randomized, double-masked, placebo-controlled Phase 2 study to evaluate the ocular hypotensive efficacy, safety, and tolerability of SBI-100 Ophthalmic Emulsion after 14 days of binocular dosing, twice daily (BID).

The study will be conducted in 54 patients with elevated intraocular pressure at approximately 6 clinical research centers in the United States.

The study includes a 35-day screening period, which encompasses a wash-out (if needed), followed by a visit on Day -1 to confirm eligibility and provide baseline diurnal IOP, followed by a 14-day double-masked treatment period entailing topical BID dosing. The end of study (EOS) assessments will be performed within 2 days of the last dose on Day 14. Dosing will occur each day in the morning and in the evening 12 hours after the morning dose.

Study visits will occur on Days -35 to Day -2 (Screening), Day -1, Day 1, Day 7, Day 14, and (if not completed on Day 14) End of Study/Early Termination (EOS/ET).

At Screening, eligible patients will be asked to wash-out of their current IOP-lowering therapy (if currently using). Patients requiring wash-out will return for Day -1 at the completion of their wash-out, in accordance with the type of IOP-lowering therapy used. Patients who are treatment naïve may return upon confirmation of screening eligibility. On Day -1, diurnal IOP will be measured at 08:00 (±30 minutes), 10:00 (±30 minutes) and 16:00 (±30 minutes) hours. If eligible, patients will be asked to return the following day to perform Day 1 procedures.

The first dose will occur in clinic on Day 1 with Investigation Product (IP) administered by the site staff in the morning immediately after the 08:00 IOP measurement and randomization via Interactive Response Technology (IRT). Subsequent study assessments up to 8 hours post-dose will be performed. The evening dose will be self-administered by the patient in the evening of Day 1 approximately 12 hours after the AM dose (~ 20:00) and continued for both mornings and evenings on Days 2 through 6.

Patients will return to the clinic on the morning of Days 7 and 14 for site administration of the morning dose with assessments up to 8 hours post-dose. The Day 7 evening dose will be self-administered by the patient in the evening approximately 12 hours after the AM dose (~ 20:00) and continue for both morning and evenings on Days 8 through 13.

When patients return to the clinic on Day 14 for site administration of the morning dose with assessments up to approximately 14 hours after the AM dose. The Day 14 evening dose (final dose) will be administered on-site with subsequent exit procedures performed. If EOS/ET procedures cannot occur on Day 14 (due to scheduling conflicts, site hours, etc.,) the Day 14 PM dose can be self-administered, with the patient returning within 2 days of Day 14 for EOS procedures (see Table 2).

IOP efficacy will be evaluated by Goldmann applanation tonometry. Safety/tolerability will be evaluated by review of ocular signs and symptoms through BCVA, ophthalmic assessments, ocular comfort PRO, vital signs, and other standard safety measures.

9.5.1.1. Visit and Procedure Schedule

See Table 2 for a complete visit and procedure schedule.

9.5.1.2. Demographics and Baseline Characteristics

9.5.1.2.1. Demographics and Disease Characteristics

Demographic characteristics such as age (years), sex, race, and ethnicity will be collected during screening. A single baseline IOP measurement will be collected at any time during screening.

9.5.1.2.2. Medical and Surgical History

Relevant medical history for the 6 months prior to the Screening Visit will be collected and any current underlying medical conditions that may have resolved before the Screening Visit will also be recorded.

In addition, social history will include smoking history (nicotine) as well as recreational alcohol and drug use for the year prior to the Screening Visit.

Ophthalmic medical history will be obtained to include any past or current ocular conditions, procedures, surgeries, and symptoms.

9.5.1.2.3. Prior and Concomitant Medications

The use of any medications, prescription or over the counter for 30 days prior to the Screening Visit and for the duration of the study, is to be recorded in the source and subsequently entered into the Electronic Data Capture (EDC) system at each visit.

From Screening Visit to the EOS/ET visit, site staff will question each patient specifically on the use of concomitant medications. Site staff must notify the Sponsor immediately if the patient consumes any protocol prohibited medications. Patients who used prohibited medications may be discontinued from the study at the discretion of the Investigator or Sponsor in collaboration with advisement from study's Medical Monitor.

For this protocol, permitted medication and procedures are as follows:

- Highly effective contraceptive medication
- Vitamin administration
- Acetaminophen up to 2,000 mg/day (if confirmed as acceptable with Investigator)
- Ocular treatments (noted below) are permitted on Days 2 through 6 and Days 8 through 13. These treatments should **NOT** be used on in-office treatment days or within ±15 minutes of drop instillation
    - Lid Scrubs

- Artificial tears, gels and/or ointment to treat dry eye disease

Therapy considered necessary for the patient's welfare may be given at the discretion of the Investigator.

If permissibility of a specific medication/intervention is in question, or if there are any questions regarding concomitant or prior therapy, the Medical Monitor should be contacted.

9.5.1.2.4. Prohibited and Rescue Medications

Use of ocular medications other than the study treatment or medications administered to conduct study procedures are prohibited from the screening visit until the EOS/ET visit, to include:

- Investigational treatments
- Concurrent IOP-lowering therapy
- Current or anticipated use of topical ocular medication and/or steroids.
- Planned invasive ocular procedures and/or surgeries
- Changes in beta blocker, diuretics and/or any other medication changes that impact IOP as per Investigator discretion.

The decision to administer a prohibited medication/treatment will be made with the safety of the study patient as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/procedure is administered.

Any patient who has an elevated IOP that the Investigator considers unsafe may be rescued and placed on an alternative therapy. The choice of therapy is the Investigator's discretion.

The following guidance may assist Investigators for rescue therapy; however, the decision to rescue is at the discretion of the Investigator's judgement:

- Outside of study treatment, ocular hypotensive medications are prohibited for the duration of the study unless rescue therapy is required for a specific patient.
- If the patient's IOP is > 36 mmHg, the Investigator may re-check the IOP within 1 day of the visit and rescue therapy may be considered if the IOP remains elevated.
- The reason a patient requires rescue medication/therapy (i.e., elevated IOP) can be considered an AE and should be documented as a treatment failure. However, the act of a patient requiring rescue is not considered an AE.
- The choice of rescue medication prescribed will be entered in the concomitant medications page of the CRF, noting that it was used as a rescue therapy.
- Patients who require the use of rescue medication should discontinue use of the study treatment but will continue to be followed for safety purposes and should not be withdrawn from the study.

9.5.1.3. Efficacy Assessments

9.5.1.3.1. Primary Efficacy Assessment(s)

Primary efficacy endpoints are as follows:

- Change from Day -1 in mean diurnal IOP at Day 14, in the study eye for 0.5% SBI-100 Ophthalmic Emulsion compared to placebo
- Change from Day -1 in mean diurnal IOP at Day 14, in the study eye for 1.0% SBI-100 Ophthalmic Emulsion compared to placebo

9.5.1.3.2. Secondary Efficacy Assessments

Secondary efficacy assessments will examine:

- Time matched change in IOP from Day -1 IOP at 08:00, 10:00, and 16:00 hours on Day 1 (10:00 and 16:00 only), Day 7, and Day 14
- Difference in change from 8:00 in IOP (mmHg) at 10:00 and 16:00 between Pre-dose (Day -1) and Post-dose visits (Day 1, Day 7, and Day 14)

9.5.1.3.3. Description of Efficacy Assessments

IOP measurements should be conducted after the biomicroscopy exam is completed and prior to pupil dilation, as applicable. IOP will be measured using a Goldmann applanation tonometer, using a masked-examiner method. A 2-person reading method will be used for all IOP measures wherein 1 person adjusts the dial in the masked fashion and a second person reads and records the reading. All pressure will be recorded in mmHg. Two consecutive measurements are taken in each eye and recorded as the mean of the two measurements. If the two measurements differ by >1.0 mmHg, a third measurement is performed, and the median is recorded.

As IOP measurements vary throughout the day, Day-1 will provide a baseline diurnal IOP for patients. Serial IOP measurements must be performed within time windows.

During screening, IOP will be measured once.

At Day -1, Day 1, Day 7, and Day 14 diurnal IOP will be measured:

- At 8:00AM (±30 minutes), 10:00AM (±30 minutes) and 4:00PM (±30 minutes)

9.5.1.4. Safety Assessments

The safety of SBI-100 ophthalmic solution will be evaluated using the following assessments. Ophthalmic assessment

a. Best Corrected Visual Acuity (BCVA)
b. Pupil Diameter
c. Central Corneal Thickness
d. Slit Lamp Biomicroscopy
e. Dilated (Fundus) Exam

f. Visual Fields
g. Ocular Comfortable Assessment PRO

2. Adverse event (AE) monitoring
3. Vital Signs
4. Clinical laboratory tests (chemistry, hematology, and urinalysis)

9.5.1.4.1. Ophthalmic Assessment

9.5.1.4.1.1. Best Corrected Visual Acuity (BCVA)

BCVA will be measured at time points noted in Table 2. It is recommended that the ETDRS Chart 1 be used for testing the right eye and the Chart 2 be used for testing the left eye. BCVA testing should precede slit lamp examination, intraocular pressure measurement, the administration of topical anesthetic agents or any examination requiring contact with the eye.

Visual acuity will be assessed monocularly in both eyes, testing the right eye first and then the left eye. The patient should be positioned according to the elevation of the chart (either seated or standing) so that the chart is at a comfortable viewing angle. The patient should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The patient should be told that the chart has letters only, no numbers. If the patient reads a number, they should be reminded that the chart contains no numbers, and the examiner should then request a letter instead of the number. The patient should be asked to read slowly, about 1 letter per second, to achieve the best identification of each letter. The patient is not to proceed to the next letter until they have given a definite response. If the patient changes a response before he has read aloud the next letter, then the change must be accepted.

Maximum effort should be made to identify each letter on the chart; the patient should be encouraged to guess. When it becomes evident that no further meaningful readings can be made, the examiner should stop the test. The number of letters missed or read incorrectly should be noted.

In order to provide standardized and well-controlled assessments of visual acuity during the study, the same lighting conditions must be used consistently throughout the study.

Calculations: LogMAR VA = Baseline value + (n x 0.02)

- where: the baseline value is the LogMAR number of the last line read (at least 1 letter read correctly in this line), and “n” is the total number of letters missed up to and including the last line read, and “0.02” is the value for each letter.

9.5.1.4.1.2. Pupil Diameter

Pupil diameter will be assessed by pupilometer following BCVA assessment as per time points delineated in Table2. Pupil diameter will be conducted using the same logMAR chart as the distant target for the uncovered eye not being tested.

9.5.1.4.1.3. Central Corneal Thickness

Central corneal thickness measurements of each eye will be made using an ultrasonic pachymeter. Contact pachymetry will be performed after IOP measurement.

9.5.1.4.1.4. Slit Lamp Biomicroscopy

A biomicroscopy examination will be performed without pupil dilation using a slit lamp and magnification consistent with standard clinical practice. The exam will include evaluation of patients' lids, cornea, conjunctiva, anterior chamber, and iris/pupils.

Screening will include a gonioscope to assess the angle closure. At the Screening Visit and EOS/ET, a lens assessment will be collected through a dilated pupil using the slit lamp biomicroscope. Findings will be evaluated for the presence and severity of nuclear, cortical, and posterior subcapsular lens opacities.

9.5.1.4.1.5. Dilated (Fundus) Exam

Stereoscopic fundus examination will be performed through a dilated pupil. The examinations will include evaluation of the macula, vitreous, and retina. The cup/disc ratio and presence of optic disc pathology will be determined using stereoscopic evaluation.

9.5.1.4.1.6.Visual Fields

Visual field examinations will be assessed using automated threshold visual filed (using either 24-2 Swedish Interactive Thresholding Algorithm [SITA] standard, or Octopus G1 or 24-2 and dynamic or normal strategy). The same test methodology must be used throughout the entire study for a given patient. Visual fields must be reliable, defined as:

- Fixation losses ≤ 33%
- False positives ≤ 33%
- False negatives ≤ 33%

The gaze track and blind spot should be turned on in order to calculate the fixation losses. Visual fields should be performed with a non-dilated pupil, unless, in the opinion of the Investigator, the pupil is so miotic that dilation is required.

If a patient has prior results (within 3 months of Screening), these results can be used for entry if it meets the automated threshold visual field and considered reliable, otherwise it should be performed at screening to determine eligibility.

Testing can be performed at any point during a visit but *must be* performed prior to assessments requiring dilation.

9.5.1.4.1.7. Ocular Comfortable Assessment PRO

Interviewer administered Ocular Comfort Assessment in the form of a PRO is a snapshot of patient's ocular comfort (in both eyes) at the moment of administration. Patients should be educated on how to appropriately rate their level of ocular comfort on the scale at the Day 1 visit prior to the first administration of the PRO. This education should be repeated as needed at the

investigators / PRO interviewers' discretion. However, great care must be taken to not unduly influence the outcome.

Prior to study treatment instillation (pre-dose), the PRO should be administered to assess the patient's current ocular comfort level.

Post-dose the PRO is to assess the ocular comfort in relation to drop instillation.

The PRO will only be administered during the AM dosing on Days 1, 7 and 14.

Trained site staff will administer the PRO pre-dose, immediately after drop instillation up to 2 minutes after instillation, 5 minutes (±2 minute) and 10 minutes (±5 minutes). If at the 10-minute time point the patient's comfort has not returned to that day's pre-dose value, the PRO should be administered every 30 minutes until the pre-dose value is achieved. The same trained interviewer should administer the PRO for a patient throughout a visit.

Investigator may use their discretion to perform ophthalmic assessments in addition to the PRO should the discomfort be persistent. Investigators should assess for adverse events if a patient's PRO values represent a grade change of 2 or more from that day's pre-dose values.

9.5.1.4.2. Adverse Events

An AE is any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the medicinal product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or wash-out periods, even if no study treatment has been administered.

Adverse events may be reported, spontaneously by the patient and/or,

- In response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site.
- Lab abnormalities or changes from baseline that the Investigator deems as clinically significant
- Changes from baseline in study assessments that the Investigator deems clinically significant (i.e., blood pressure, pulse, etc.,)
- Abnormal values that constitute an SAE or lead to discontinuation of administration of Study treatment

The Investigator will assess the severity, causality (relationship to study drug), and seriousness of each AE.

Severity of Adverse Events

The Investigator will assess the severity of all AEs as mild, moderate, or severe, based on the following definitions, developed from the Clinical Data Interchange Standards Consortium Study Data Tabulation Model standard terminology v3.1.1.

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research patient.
- **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

An Investigator who is qualified in medicine must make the determination of relationship to the study treatment for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study treatment. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study treatment and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the study treatment is determined to be "possible" or "probable" the event will be related to the study treatment for the purposes of expedited regulatory reporting.

Serious Adverse Events (SAE)

A SAE is an AE occurring during any study phase (i.e., wash-out, treatment, or follow-up) that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

9.5.1.4.3. Vital Signs

Vital signs measurements will include blood pressure, heart rate and respiratory rate. These measurements will be performed after at least 5 minutes of rest at the time points delineated in Table 2. Repeat measurements should be taken for out-of-range values. Confirmed vital sign readings outside the normal range must be evaluated by the Investigator for clinical significance.

9.5.1.4.4. Clinical Laboratory Tests

Safety laboratory tests (chemistry, hematology, and urinalysis) will be performed at the time points noted in Table 2 with additional testing performed at the discretion of the Investigator.

The clinical laboratory results must be reviewed by the Investigator to assess inclusion/exclusion criteria prior to randomization. Patients with any clinically significant abnormal values that the Investigator determines can affect the patient's safety and/or affect the results of the study will not be eligible.

Refer to the laboratory manual for further details regarding the collection, processing, and storage of clinical laboratory samples. Specific testing and ranges will also be included in the laboratory manual.

9.5.1.4.4.1. Pregnancy Testing

Females of childbearing potential must have a negative pregnancy test at Screening (serum) and Day -1 (urine) to qualify for randomization. Urine pregnancy test will be performed for the EOS/ET visit.

9.5.1.4.4.2. Drug and Alcohol Screening

Testing will be performed using on-site testing kits for the following substances:

- Alcohol
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Methamphetamines
- Methadone
- Opiates
- Phencyclidine
- Tetrahydrocannabinol
- Tricyclic Antidepressants

At Screening a positive test will be repeated once prior to Day -1 to confirm the result. At Day-1 a positive test will be repeated once prior to Day 1. If the second test is positive, the patient must be screen failed and not allowed to re-screen.

Should there be any questions regarding the validity of positive results for any test during the course of the study, the Medical Monitor/Sponsor should be contacted.

9.5.1.4.4.3. Biomarker Testing

Samples for biomarker testing will be collected at some or all sites participating in the study. Blood samples for biomarker testing will be drawn on the Day-1 and Day 14 visits. Proteomic biomarker testing and immunological testing will be performed on serum samples and samples containing peripheral blood mononuclear cells, respectively. Blood samples may be drawn anytime during the Day-1 visit, any time after dosing during the Day 14 visit. Please refer to the laboratory manual for specifics of the preparation of the blood samples. No genetic biomarker testing will be performed.

Tear samples must be drawn at 10:00 (±30m) AND at least 10 minutes prior to IOP measurement within that time window. Please refer to the study procedures manual for details of the tear collection and preparation of samples.

9.5.2. Appropriateness of Measurements

All assessments used in this study are widely used and generally recognized as reliable, accurate, and relevant.

9.5.3. Primary Efficacy Variable(s)

The primary efficacy variable is the mean diurnal IOP based on three measurements (8AM, 10AM, and 4PM) during the Day 14.

9.5.4. Drug Concentration Measurements

No drug concentration measurements will be made for this study.

9.6. DATA QUALITY ASSURANCE

Please refer to the study protocol for the details.

9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

This section of the analysis plan describes the analyses explicitly mentioned in the protocol as well as additional analyses not explicitly mentioned in the protocol but planned prior to breaking the treatment mask. Section 9.8 describes any changes to analyses that were explicitly mentioned in the protocol or statistical analysis plan.

9.7.1. Statistical and Analytical Plans

General Conventions

Summary statistics for the data collected during this study will be presented to give a general description of the patients studied. Data from all sites will be combined in the computation of these descriptive summaries. Categorical variables will be summarized by the frequency and percentage of patients in each category. Continuous variables will be summarized using N, mean, standard deviation (SD), median, minimum, and maximum values and where appropriate and two-sided 95% confidence interval (CI).

Minimums, and maximums will be calculated to the same number of decimal places as the source data. Means, medians, and quartiles will be calculated to one more decimal place than the source data; Standard deviations, and standard errors will be calculated to two more decimal place than the source data. Percentages will be calculated to the nearest one decimal place and will use the number of non-missing responses as the denominator, unless otherwise noted. Zero count cells will be displayed as “0” with percentage of (0%). Unless otherwise noted, summaries will be performed by the treatment group and presented in the order of the following: 1.0% SBI-100 OE, 0.5% SBI-100 OE, and Placebo.

Statistical tests will be presented as two-sided p-values rounded to four decimal places; p-values less than 0.0001 will be presented as '<0.0001' and p-values = 1.0000 will be presented as '>0.9999' in all tables. Unless otherwise indicated, statistical testing will be carried out at the $\alpha = 0.05$ significance level.

Baseline is defined as the last measure prior to the initiation of study treatment. For endpoints measured multiple times per day (e.g., IOP), there may be multiple, time-specific baseline measures. Changes from baseline will use the time-specific baseline where applicable.

Numeric laboratory data may be recorded at limits of detection (with a ‘<’ or ‘>’ sign, i.e. < 0.1 or > 0.1). To summarize the data, the original value will be converted to one unit less or more at the level of measured precision (e.g. 0.4 in the case of < 0.5 and to 0.6 in the case of > 0.5). The actual values will be presented in the data listings.

All data collected in this study will be presented in individual patient data listings for all patients.

Computations for all results will be performed using SAS (Version 9.4, SAS/STAT 15.2) computer software package (SAS Institute, Inc, 2013, 2020), unless otherwise specified.

Strata and Covariates

For analysis of efficacy endpoints, analysis of covariance (ANCOVA) at Visit 5 (Day 14) or longitudinal models across all Post-dose visits will model the observed value or change from baseline of each endpoint as the dependent variable with the baseline measurement of the corresponding endpoint as a covariate and treatment group as a main effect. Longitudinal models will include a covariate for visit as well as an interaction term for visit and treatment.

Subgroups

Not applicable.

Multiplicity

For this feasibility study, the primary analysis is hypothesis-generating for future registration studies. As such, there will be no adjustments for multiple comparisons.

Missing Data and Outliers

Every attempt will be made to capture all study data.

For this feasibility study, in general, the analysis will be based on observed data only, not imputing missing data. If an eye is missing data for any time point, the mean diurnal IOP will not be calculated for the primary analysis to avoid using a biased estimate.

However, in the case of >5% of patients with missing IOP data for any time point, imputation will be conducted for sensitivity analysis as described in Section 9.7.1.5.1.

Visit Windows

The nominal visits listed in the CRF will be used in the summaries. In general, unscheduled visits will not be summarized in tables unless otherwise noted.

Missing Dates

Missing dates that occur for prior or concomitant medications or adverse events will be queried for a date. If no date is obtained, the following imputation rules will apply:

- For start dates, if the given year (or year-month) is the same as study drug administration, the start date will be imputed as study drug administration date; otherwise, missing month-day (or day) will be imputed as ’01-01’ (or ’01’).
- For stop dates, missing months will be imputed as ‘12’ and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used.

Imputed dates will only be used to classify events or medications, such as occurring before or after the start of treatment. Imputed dates will only be used in tables. Listings will display the collected date data.

Interim Analysis

There will be one interim analysis conducted when at least 50% treated patients have diurnal IOP measurement at 14 days post-dosing to assess the conditional study power of each active dose to placebo.

During this interim analysis, blinding to treatment assignment will be maintained at all investigational sites, and for the whole study team. Subject level treatment assignment unblinding will be restricted to an unblinded statistician who will have no other responsibilities associated with the study, and who will been given validated SAS programs for the SDTM, ADaM, and tables, and generate final tables with actual randomization assignment.

The results of interim analyses will not be shared with the investigators prior to the completion of the study. The extent to which individuals are unblinded with respect to results of interim analysis will be documented.

This interim analysis is not to stop the study for either efficacy or futility.

Conditional power will be calculated based on Brownian Motion Method illustrated by Proschan, Lan and Wittes (2006).

As mentioned above, there will be an interim analysis after at least 50% of the planned subjects (n=18) in each arm have been evaluated for the primary endpoint. The Null distribution of test Statistics over time, Z_N, are summed across the two independent components, defined as follows:

$$Z_N = \frac{S_n + S_N - S_n}{\sqrt{V_N}} = \frac{S_n}{\sqrt{V_N}} + \frac{S_N - S_n}{\sqrt{V_N}} \quad (9.1)$$

The first term in equation (9.1), $\frac{S_n}{\sqrt{V_N}}$ is called the B-value due to its connection to Brownian Motion. We define the following ratio as information fraction:

$$t = \frac{V_n}{V_N} = \frac{var(S_n)}{var(V_N)} \quad (9.2)$$

This ratio measures the proportion that the trial is complete. Note *t* can be simplified to *n/N*, the fraction of subjects in the whole study who have been evaluated so far. While *t*=0 and *t*=1 correspond to the beginning and the end of the trial.

Let us define the interim Z-score $\left(\frac{S_n}{\sqrt{V_n}}\right)$ at the trial fraction t by *Z(t)*, B-value, i.e. *B(t)* at trial fraction t, is related to the Z-score with the following feature:

$$B(t) = \frac{S_n}{\sqrt{V_N}} = \frac{\sum_{i=1}^{n} Di}{\sqrt{var(SN)}} = \sqrt{\frac{var(Sn)}{var(SN)}} \frac{\sum_{i=1}^{n} Di}{\sqrt{var(sn)}} = \sqrt{t} * \mathrm{Z(t)} \quad (9.3)$$

The B value is used instead of a z-score in this equation (9.3) to utilized monitored data and to calculate the conditional power. The reason is that $E\{B(t)\} = \theta t$, and it follows that $B(t)/t$ estimates the drift parameter, θ, a simple transformation of the treatment effect estimate ($B(t) = \sqrt{t}$ *Z(t)). Geometrically, $B(t)/t$ is the slope of the line joining the origin to $(t, B(t))$.

We can easily determine whether the treatment effect estimate increases from one interim analysis to the next one by verifying whether the slope of the line increases.

At the end of the trial, the B-value is equal to be the Z-score, i.e., $B(1) = Z(1) = \frac{S_N}{\sqrt{V_N}}$, then the equation (9.1) becomes

$$B(1) = B(t) + \{B(1) - B(t)\} \quad (9.4)$$

Term $B(t)$, interim *B* value at trial fraction of *t*, represents the past cumulative data by the time of interim analysis, $B(1) - B(t)$ is the remaining data in the study.

Let us illustrate the procedure to compute conditional power using B-value formula in (9.4). Conditional power is the conditional probability that $B(1) > Z_{\alpha/2}$ given that $B(t) = b$. $B(1)$ can be presented as $B(t) + B(1) - B(t)$. The increment $B(1) - B(t)$ is independent of $B(t)$ with following mean and variance:

$$E\{B(1) - B(t)\} = \theta * 1 - \theta * t = \theta * (1 - t) \quad (9.5)$$

$$var\{B(1) - B(t)\} = var\{B(1)\} + var\{B(t)\} - 2cov\{B(1), B(t)\} = 1 + t - 2t = 1 - t$$

Given that $B(t) = b$, the term $B(1) = b + \{B(1) - B(t)\}$ is normally distributed with variance $(1 - t)$ and the following mean

$$E_\theta\{B(1)|B(t) = b\} = b + \theta * (1 - t) \quad (9.6)$$

where the drift parameter θ is the expected Z-score at the end of the study.

The conditional power for a two-sided test at level α (or one-sided test at level α/2) under empirical treatment effect and standard deviation is defined as follows:

$$CP_\theta(t) = 1 - \phi\left(\frac{Z_{\alpha/2} - E_\theta\{B(1)|B(t)=b\}}{\sqrt{1-t}}\right) \quad (9.7)$$

Where θ and *t* represent the drift parameter and the information fraction, respectively, $E_\theta\{B(1)|B(t) = b\}$ denotes expected *B* value given *B(t)* =b, the expected *B* value is the drift parameter θ under empirical condition. The *b* value is the expected *B* value under the null hypothesis in which the drift parameter $\theta = 0$.

9.7.1.1. Analysis Populations

9.7.1.1.1. Populations

The Intent-to-Treat (ITT) population is defined as all patients who are randomized. The ITT population will be used for efficacy endpoints. Patients will be analyzed based on the treatment to which they were randomized.

The Per Protocol (PP) population is a subset of the ITT Population and will include all subjects in the ITT population who completed study-required treatment and who followed the protocol without significant deviations. The determination of significant protocol violations will be made

prior to locking the final database and unmasking. Reasons for exclusion will include but are not limited to:

- Inclusion and exclusion criteria
- Informed consent form
- Investigational product
- Missed procedure
- Prohibited medication or procedure
- Study assessments
- Study visit schedule
- Other

The safety population includes all patients randomized who received at least one dose of investigational product. Patients will be analyzed according to their actual treatment received. The safety population will be used for all safety analyses. Only observed data will be included (i.e., missing data will remain missing for the safety analysis). A listing of subjects excluded from the analysis populations will be provided.

For the efficacy analysis, subjects will be analyzed in the treatment group to which they were randomized; for the safety analysis, the subject will be analyzed by the treatment group to which they were treated.

9.7.1.1.2. Analysis Eyes

The study eye will be determined for efficacy analysis purposes. Both the study eye and the non-study eye will be analyzed for safety. The study eye will be determined through statistical programming to select the eye with the highest mean IOP from the three measures taken on Day -1 (baseline). In the case of a tie, the study eye will be the right eye.

9.7.1.2. Analysis of Subject Disposition

The number of subjects randomized at each site will be summarized by treatment group and overall.

Subjects' enrollment and disposition during the study will be summarized by treatment group and overall based on Randomized Subjects. The reasons for discontinuation will be displayed in the order as they appear on the eCRF.

Summary tables will include the following. The percentages will be calculated based on the number of subjects randomized (with reasons for discontinuation based on the number of subjects discontinued).

- Number of patients screened;
- Number and percentage of subjects treated;
- Number and percentage of subjects in ITT, PP, and Safety Populations;

- Number and percentage of subjects who completed the study through Day 14;
- Number and percentage of subjects who discontinued from the study;
- The reasons for study discontinuation;
- Number and percentage of subjects withdrawn from study drug due to elevated IOP and subsequent rescue treatment;
- Number and percentage of subjects attending each visit.

A listing of subjects who do not meet all inclusion criteria or meet exclusion criteria will be provided. A table of major protocol deviations, including any deviation, minor, major, and critical deviation, will be presented using the ITT Population. Subjects in each analysis population will be presented in a listing.

9.7.1.3. Analysis of Demographic and Baseline Characteristics

9.7.1.3.1. Demographics and Disease Characteristics

Demographic and baseline disease characteristics including age (years), age group (18-39, 40-59, ≥=60+), sex, race, ethnicity, ocular hypertension (OHT), primary open angle glaucoma (POAG), and study eye (OD/OS will be summarized descriptively by treatment group and overall using the ITT, PP, and Safety Populations. For categorical parameters, the percentages will be calculated overall and based on the number of subjects in each treatment group based on non-missing observations.

9.7.1.3.2. Medical and Surgical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 25.1 or later). The frequency and percentage of subjects with any medical history will be summarized by treatment group using the ITT. System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within SBI-100, 1.0% SBI-100 OE;
2. Descending frequency within SBI-100, 0.5% SBI-100 OE;
3. Descending frequency within Placebo;
4. PT in alphabetical order.

The medical history will include both the ocular and the general (non-ocular) history. Ocular medical history and general (non-ocular) medical history will be summarized separately. Ocular and non-ocular medical histories are identified according to which CRF the event is recorded. Ocular medical history will be summarized separately for study eye, non-study eye, and either eye.

9.7.1.3.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) (B3 WHO Drug Global, Version Sep 2022 or later) for anatomical therapeutic chemical (ATC) classification and preferred drug name.

The frequency and percentage of subjects with coded medications will be summarized by treatment group using the ITT. A subject who used multiple medications will be counted only once for each ATC and preferred drug name. Therapeutic Subgroup is sorted alphabetically, and preferred term is sorted by descending frequency overall within each Level 3 term according to:

1. Descending frequency within SBI-100, 1.0% SBI-100 OE;
2. Descending frequency within SBI-100, 0.5% SBI-100 OE;
3. Descending frequency within Placebo;
4. PT in alphabetical order.

Prior and concomitant medications will be summarized separately. Ocular medications are defined as those medications for which an eye has been specified (OD, OS, or OU). Ocular and non-ocular medications will be summarized separately. Ocular medications will be summarized separately for study eye, non-study eye, and either eye.

Prior medications are defined as any medications that started 30 days prior to screening and stopped prior to the date of first dose of double-masked study drug. Concomitant medications are defined as any medications that (1) start prior to the date of first dose of double-masked study drug and stop or are ongoing at or after the date of first dose of double-masked study drug; or (2) start at or after the date of first dose of double-masked study drug. Medications started after Day 14 or withdrawal from the study are not considered concomitant.

9.7.1.4. Analysis of Study Medication Adherence and Exposure

The overall treatment compliance will be assessed by the investigational products returned, the daily dosing diary is only secondary evidence. Subject drug dosing and compliance will be summarized by treatment group on the Safety Population.

Treatment compliance is defined as the proportion of doses taken out of the number of doses that should have been taken during the double-masked treatment period per study protocol. The overall compliance (%) will be calculated as (the actual total number of doses taken / the expected number of doses that should have been taken) × 100. The expected number of doses that should be taken is defined in the protocol. Actual total number of doses taken will be based on IP accountability. The expected number of doses is defined as:

> [2 × (last double-masked dose date - first double-masked dose date + 1)] if the subject takes 2 doses per day.
>
> The duration of exposure to double-masked study drug is calculated in days as last dose date - first dose date + 1.

Compliance will be adjusted for the early withdrawals. If a subject's last dosing date is same as the date of discontinuation, at least one dose is assumed to be taken on the day of early withdrawal. If data are collected on the unscheduled visits, it will be included in the calculation.

The number and percentage of subjects in the following study drug compliance categories: (<80%, >=80%) will be summarized by treatment group. The percentages will be calculated based on the number of subjects in each treatment group of the Safety Population.

9.7.1.5. Analysis of Efficacy

Summary descriptive statistics will be presented for all study visits at which efficacy data are collected. Efficacy analyses will be presented for the study eye.

In general, efficacy analyses will be performed using the ITT and the observed data at each Visit for the study eye. Only data prior to rescue therapy will be summarized; however, missing data imputation will be conducted for sensitivity analysis for the primary efficacy endpoint. The primary and secondary endpoint analysis will also be performed using the PP Analysis Set.

For subjects who discontinue the study prior to the Visit 5, data collected using Early Termination eCRFs will not be summarized separately unless the termination occurred on a scheduled visit (within the visit windows of a particular visit).

ANCOVA and longitudinal models for continuous outcomes will be fit using the MIXED procedure. Categorical analyses will be conducted using the FREQ procedure.

9.7.1.5.1. Primary Efficacy Analysis

Primary Estimand: The primary estimand is the treatment differences between SBI-100 Ophthalmic Emulsion (either 1.0% or 0.5%) and Placebo for the mean diurnal IOP change from baseline (Day -1) in the study eye at Day 14 (Visit 5) using the ITT population.

Target Population: Subjects with open-angle glaucoma or ocular hypertension that meet the study entry criteria.

Endpoint: Change from Day -1 in mean diurnal IOP at Day 14, in the study eye for either 1.0% or 0.5% SBI-100 Ophthalmic Emulsion compared to placebo

Treatment Condition(s): Treatment condition is based on the randomized treatment group.

Population-level Summaries: The difference in change from baseline (Day -1) in the mean diurnal IOP at Day 14 and their corresponding p-values and 95% confidence intervals.

Intercurrent Events and Strategies to Address Intercurrent Events

- Discontinuation of study therapy with continued participation in the study without receipt of rescue therapy
    - Treatment Policy – no imputation; use observed data
- Receipt of rescue therapy in the study eye
    - Hypothetical Approach – data for visits after the receipt of rescue therapy will be set to missing and will be analyzed assuming missing at random (MAR) using a ANCOVA model

- Missing data without withdrawal or with withdrawal regardless of reason
    - Hypothetical Approach: visits that are missing data will be analyzed assuming MAR using a ANCOVA model

The principal analysis for the primary efficacy endpoint will utilize observed data up until the first time of an intercurrent events, such as taking any rescue medications or therapies, based on the ITT population. ANCOVA will be used for each comparison at a two-sided alpha level of 0.05 without any multiplicity adjustments. The model will include the mean diurnal change from baseline value in IOP as the response variable and will include the categorical covariates of treatment group, , and baseline IOP value as a continuous variable.

The null and alternative hypotheses for the primary endpoint are defined respectively, as follows:

$$H0: CHG1 = CHG0$$

$$Ha: CHG1 \neq CHG0$$

Where $CHG0$ and $CHG1$ represents the change from baseline (Day -1) in mean diurnal IOP at Day 14 for Placebo and SBI-100 Ophthalmic Emulsion [1.0% SBI-100 OE or 0.5% SBI-100 OE], respectively.

To reject the null hypothesis for the primary efficacy endpoint, the two-sided 95% confidence interval estimates of the treatment differences in Change from Day -1 in mean diurnal IOP between SBI-100 and Placebo must exclude zero at Day 14. Comparisons will be made between SBI-100 OE, 1.0% versus vehicle, and between SBI-100 OE, 0.5% versus vehicle simultaneously, regardless of significance of either comparison.

In addition, changes from Day -1 in mean diurnal IOP at Day 7 between dose groups (0.5% SBI-100 OE, 1.0% SBI-100 OE) and Placebo will be estimated with least square mean differences, its associated two-sided 95% CIs, and two-sided p values. Sensitivity analysis for the primary endpoint will be conducted by imputing missing in the case either more than 5% of patients with missing data at any time points or following other intercurrent event strategies such as receiving rescue therapies.

Missing values for scheduled visits over 14-day post-treatment diurnal IOP will be imputed using the fully conditional specification (FCS) method that assumes the data are missing at random with the following four steps:

1. Identify missing data pattern: Based on the data, either monotone or arbitrary pattern, will be determined. Normally, arbitrary pattern is assumed. It should be monotone in this case.
2. Imputation: Multiple imputed values for diurnal IOP will be created (100 imputations). Imputations in each dataset will be generated for subjects who are missing 14-day post-treatment IOP values. The range of IOP at 14 days is between 10 and 36 mmHg. If an imputed value is above 36 or below 10 mmHg, it will be truncated to 36 or round up to 10 mmHg. The minimum of 10 mmHg and maximum of 36 mmHg for imputed IOP values will be specified in Option statement in Proc MI statement. The main goal is to impute missing IOP values at Day 14 as accurately as possible. Therefore, all observed

and imputed IOP data from Day -1 through Day 14 will be utilized during this imputation process. The change from baseline to 14-day post-treatment will be calculated for each subject at each time, in each dataset.

```
PROC MI DATA=xx OUT=midi_mi SEED=76673 NIMPUTE=100 ROUND = . . . 1 1 1 1;
  CLASS treatment;
  FCS REG (iop_d_1 iop_d1 iop_d7 iop_d14);
  VAR treatment  iop_d_1 iop_d1 iop_d7 iop_d14;
RUN;
```

3. Analysis: For each imputed dataset, the change from baseline to Day 14 post-treatment in mean diurnal IOP will be analyzed using ANCOVA with treatment, and baseline IOP as independent variables.

4. Pooling: The results of the analysis of each imputed dataset will be combined using Rubin's method (Little and Rubin, 2002). The adjusted mean change from baseline and its standard error (SE) will be provided for treatment groups, along with the Placebo-adjusted mean change, i.e. difference in IOP change from baseline between active and placebo groups, its 95% confidence interval (CI), and the associated two-sided p-values. The sample code is as follows:

```
PROC MIANALYZE DATA=xxx;
      BY arm;
      MODELEFFECTS estimate;
      STDERR stderr;
RUN;
```

9.7.1.5.2. Secondary Efficacy Analyses

Time matched change in IOP from baseline IOP (Day -1) at 8:00AM, 10:00 AM and 16:00 PM on Day 1, Day 7, and Day 14 will be analyzed using MMRM with an unstructured covariance assumed for each treatment with treatment, visit, and visit by treatment interaction as a fixed effects. If the model fails to converge using this covariance structure, heterogeneous Toeplitz, or compound symmetry will be implemented in this order until convergence is reached. The following model is repeated for each time-point (8:00AM, 10:00AM, and 16:00PM) except that IOP comparison at 8:00 am won't be made between Day -1 and Day 1.

```
PROC MIXED DATA=indata;
      CLASS subject visit treatment;
      MODEL IOPCHG = baseiop visit treatment visit*treatment / solution
      DDFM=KR;
      REPEATED visit / SUBJECT=subject TYPE=UN;
      LSMEANS treatment visit*treatment / slice = visit CL diff;
      SLICE treatment × visit / SLICEBY=visit PDIFF CL;
RUN;
```

In this model, baseline is defined as the last IOP measure before the first dose of the study drug at each specific time-point. For 8:00AM at Day 7 and 14, baseline is defined as the 8:00AM on Day 1. For 10:00AM and 16:00PM across all Post-dose visits, baseline is defined as the measure at 10:00AM and 16:00PM on Day -1, respectively. IOPCHG is the change of IOP at Day 1, 7, and 14 from baseline at each specific time-point (8:00AM, 10:00AM, or 16:00PM).

In addition, the difference in change from 8:00 AM in IOP (mmHg) at 10:00 AM or 16:00 PM during the day between Pre-dose (day -1) and Post-dose (day 1, 7, and 14) visits will be analyzed using the same MMRM model with the following steps:

1) The baseline changes in IOP from pre-dose, i.e. 8:00 AM, to 10:00 AM and 16:00 PM will be calculated at Day -1 by each treatment groups.

2) Similarly, the change from pre-dose to 10:00 AM and 16:00 PM will be computed at post-dose visits (Day 1, 7, and 14) by each treatment group, respectively.

3) Then, the mean differences between baseline changes in IOP from pre-dose at Day -1 in Step (1) and the change from pre-dose to 10:00 AM and 16:00 PM at each post-dose visit in Step (2) will be estimated by each treatment group, respectively.

4) Finally, those least mean square differences in IOP in Step (3) will be compared by hours (10:00 AM and 16:00 PM) between dose groups [1.0% SBI-100 or 0.5% SBI-100] and Placebo with two-sided 95% confidence intervals, and 2-sided p values by each post-dose visit.

9.7.1.6. Analysis of Safety

Safety will be evaluated by ophthalmic data, AEs, vital signs, and clinical laboratory tests (blood chemistry, hematology, and urinalysis).

The Safety Analysis Set will be used for all safety analyses. All data, including data after rescue, will be summarized as observed and no data imputation will be performed. No statistical treatment group comparisons will be performed, unless otherwise specified. Analyses will be presented by study eye, non-study eye, and either eye if applicable.

For by visit summaries, data collected using Early Termination eCRFs will not be summarized unless the termination occurred within the visit windows of a particular visit.

Data in all visits will be included in listings.

9.7.1.6.1. Analysis of Ophthalmic data

Ophthalmic data will be evaluated by BCVA, pupil diameter, central corneal thickness, slit lamp biomicroscopy, dilated fundus exam, visual fields, and ocular comfort assessment patient reported outcomes.

9.7.1.6.1.1. Best Corrected Visual Acuity (BCVA)

Descriptive summaries of the observed values of logMAR at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented. A categorical analysis of subjects who loses ≥ 2 lines (defined as 10 or more letters) in BCVA at each visit will be conducted in the Safety Population.

9.7.1.6.1.2. Pupil Diameter

Descriptive summaries of the observed values of pupil diameter at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented in the Safety Population.

9.7.1.6.1.3. Central Corneal Thickness

Similarly, descriptive summaries of the observed values of central corneal thickness at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented in the Safety Population.

9.7.1.6.1.4. Slit Lamp Biomicroscopy

The frequency and percentage of subjects with observed values (normal, abnormal CS, and abnormal NCS) of each category as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for the following measures of interest: patients' lids, cornea, conjunctiva, anterior chamber, iris/pupils, and lens.

9.7.1.6.1.5. Dilated Fundus Exam

The frequency and percentage of subjects with observed values of each categorical response, i.e. normal, abnormal CS, and abnormal NCS, at each scheduled visit as well as the categorical shift from baseline to each post-dos visit will be tabulated. The Parameters are retina, vitreous, macula, choroid, and cup-disc ratio.

Descriptive summaries of the observed cup-to-disc ratio at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented.

9.7.1.6.1.6. Visual Fields

The frequency and percentage of subjects with observed values of each categorical response (normal or abnormal) at each scheduled visit from baseline to each post-dose visit will be tabulated. The percentages are calculated based on the number of subjects at each visit in each treatment group of the Safety Population. Reliability of visual fields will be presented at each scheduled visit as well.

Descriptive summaries of the Mean Deviation at each scheduled visit will be presented.

9.7.1.6.1.7.Ocular Comfort Assessment Patient Reported Outcome

The frequency and distribution of ocular Comfort Patient Reported Outcome (PRO) will be presented at Pre-dose, Immediately Post-dose, 5- and 10-minutes post-dose across Day 1, 7, and

14. In addition, changes from Day 1 Pre-dose in PRO will be shown at Immediately Post-dose, 5- and 10-minutes Post-dose at Day 1, 7, and 14 for either eye by treatment groups. Furthermore, the comparison in the localized ocular TEAEs between subjects with discomfort PRO and those without will be presented by each treatment group. Among three assessments in discomfort PRO after dosing, the worse one will be utilized.

9.7.1.6.2. Adverse Events

AEs are coded using MedDRA Version 25.1. Treatment-emergent adverse events (TEAE) are defined as events that start on or after the date of first dose of double-masked study drug up to and including the last dose of double-masked study medication. Ocular AEs are defined as those events for which an eye has been specified (OD, OS, or OU).

Ocular and non-ocular AEs will be summarized separately. Ocular AEs will be presented by study eye, non-study eye, and either eye because both eyes are treated .

In all summaries of AEs, percentages are calculated based on the number of subjects in each treatment group of the Safety Population.

Overall summaries of AEs by treatment will include:

- the number of AEs and SAEs reported;
- the number and percentage of subjects who experienced any AE;
- the number and percentage of subjects who experienced any serious adverse event (SAE) and the reason for seriousness;
- the number and percentage of subjects with any AE by worst severity and worst relationship.

The overall summaries of TEAEs will also include:

- the number and percentage of subjects with any TEAEs leading to discontinuation of double-masked study drug;
- the number and percentage of subjects with any TEAEs leading to study termination.

Summaries of the frequency and percentage of subjects with AEs by SOC and preferred term by treatment group will include:

- All AEs by SOC and preferred term;
- All AEs by SOC, preferred term, and maximum severity;
- All AEs by SOC, preferred term, and maximum relationship.

System organ class (SOC) will be sorted alphabetically, and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within SBI-100 OE, 1.0%
2. Descending frequency within SBI-100 OE, 0.50%
3. Descending frequency within Placebo;

4. PT in alphabetical order.

Subjects are counted only once for each SOC and PT. In summaries of maximum severity and maximum relationship, subjects with multiple occurrences of events will only be counted once at the maximum severity/relationship per SOC and PT.

Any treatment-emergent AEs that have a missing severity will be presented as severe in the summary table but will be presented with a missing severity in the data listing. Any treatment-emergent AEs that have a missing relationship will be presented as "Related" in the summary table but will be presented with a missing relationship in the data listing.

All AEs are displayed in listings. In addition, separate listings will be provided for:

- Subjects with any treatment-emergent adverse event leading to study drug discontinuation or study termination;
- Subjects with any serious adverse event (treatment-emergent or otherwise);
- Subject deaths.

9.7.1.6.3. Vital Signs

Descriptive summaries of the observed values for vital signs at each scheduled visit will be presented. In case of duplicate measurements in vital sign, the most recent (latest measurement) at each visit will be summarized in tables. Vital signs include heart rate (bpm), respiratory rate (bpm), and systolic and diastolic blood pressure (BP).

9.7.1.6.4. Clinical Laboratory Tests (Chemistry, Hematology, and Urinalysis)

Descriptive summaries of the observed test results at Screening and Visit 5a (End of Study) will be presented for blood chemistry and hematology labs. The frequency and percentage of subjects with observed values of Low, Normal, High at scheduled visits will be tabulated. The percentages are calculated based on the number of subjects at each visit in each treatment group of the Safety Population.

It is expected that all samples will be analyzed by a central laboratory. If a local laboratory is used (such as for an unscheduled visit), the results will be included in the listings of laboratory data, but the data will not be included in descriptive summaries.

The results of pregnancy tests for women of childbearing potential will be presented in a listing. In addition, the results of drug and alcohol test will be shown in a listing.

9.7.2. Determination of Sample Size

From prior studies, the expected standard deviation (SD) of diurnal IOP in each treatment group ranges from 2.0 to 3.0 mmHg, with an average of 2.7 mmHg. The following estimates rely on a conservative SD of 3.0 mmHg for all visits and time points.

Analyses will be performed using a 2-sided alpha level of 0.05 for each test. For this feasibility study, no adjustments will be made for multiple comparisons across the multiple treatment groups versus the control group, or across tests for multiple visits and time points.

Sample sizes for both 80% and 90% power, and assuming a pooled SD of 3.0, are shown below. In addition, the table below summarizes the sample size requirements for various expected differences in mean diurnal IOP between the active treatments and placebo. Sample sizes are shown prior to considering dropouts or non-compliance for the various endpoints and assumptions.

Table 1. Sample Size Requirement

Endpoint: Superiority of treatment over placebo for change from baseline (Day-1) at Day 14; SD = 3.0		
	Power	
	80%	90%
Difference (SBI-100 – Placebo) = 3.0	17	23
Difference (SBI-100 – Placebo) = 3.5	13	17
Difference (SBI-100 – Placebo) = 4.0	10	13

For this feasibility study, a difference of 3.0 mmHg in mean diurnal IOP between treatment and placebo is assumed with 80% study power.

Accounting for up to 5% dropout over a short-term study, an additional ~5% will need to be enrolled in each treatment group. For an expected difference of 3.0 mmHg at 80% power, 17/95% = 18 patients per treatment group will need to be enrolled, for a total of 54 patients in this 3-treatment group study.

There is no correction for multiplicity for multiple time points or comparisons for high or low SBI-100 doses.

9.8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1. Protocol Amendments

The protocol revision history is as follows:

Protocol Version/Date	Protocol Section (s)	Description of Change
Version 1.0 dated, 13 December 2023	Original protocol.	
Version 1.1 dated, 09 June 2023	Synopsis	Updated study period
	Synopsis Table 2 Figure 1 Protocol Sections: 2.0, 3.0, 4.0, 6.0, 7.0 and 10	Modified dosing regimen from 7 days to 14 days. Changes made to reflect associated protocol areas such as study design, participant eligibility, study procedures/execution, study treatment and analysis of data.
	Protocol Section 6 Table 4 added	Modification for clarity and consistency of study treatment dosing and strength of SBI-100 per drop/dose.
Version 1.2 dated, 17 July 2023	Header, Table 2, Protocol Sections: 7.1, 7.2 and 8.2.2	Version changed to 1.2. Modified to indicate any failed alcohol or drug test will be repeated.
Version 2.0 dated, 21 September 2023	• Synopsis • Protocol Sections: 6.2.1, 10.2,	Addition of interim analysis
	Synopsis Table 2 Protocol Sections: 2.3, 7.2, 7.5, 8.2.3, 10.4.4, 12.4,	Addition of biomarker testing
	Synopsis Table 2 Protocol Sections: 2.2.1, 3.1; 7.1, 7.3, 7.4, 7.5	Removal of 8:15 assessments on Day 1, Day 7 and Day 14 and serial assessments of best corrected visual acuity, pupil diameter, slit lamp, vital signs
	Table 2 Protocol Sections: 7.1, 7.2, 7.6, 8.2.2, 8.2.2.1 (previous, removed),	Clarification of drug and alcohol screening and removal of End of Study / Early Termination Tetrahydrocannabinol screening

Protocol Version/Date	Protocol Section (s)	Description of Change
	Table 2 Protocol Sections: 6.3.3, 6.4.3, 7.1, 7.3, 7.4, 8.1.4,	Clarification of investigational product diversion and patient education procedures
	Table 2 Protocol Sections: 7.3, 7.4, 7.5, 8.3.9	Clarification of Ocular Comfort Patient Reported Outcomes procedure
	Throughout the document	Editorial changes, minor changes for consistency and clarity, updated dates and version change

9.8.2. Changes from Protocol-Specified Analyses

Analysis in changes in proteomic and immune biomarkers from Baseline won't be described in this SAP.

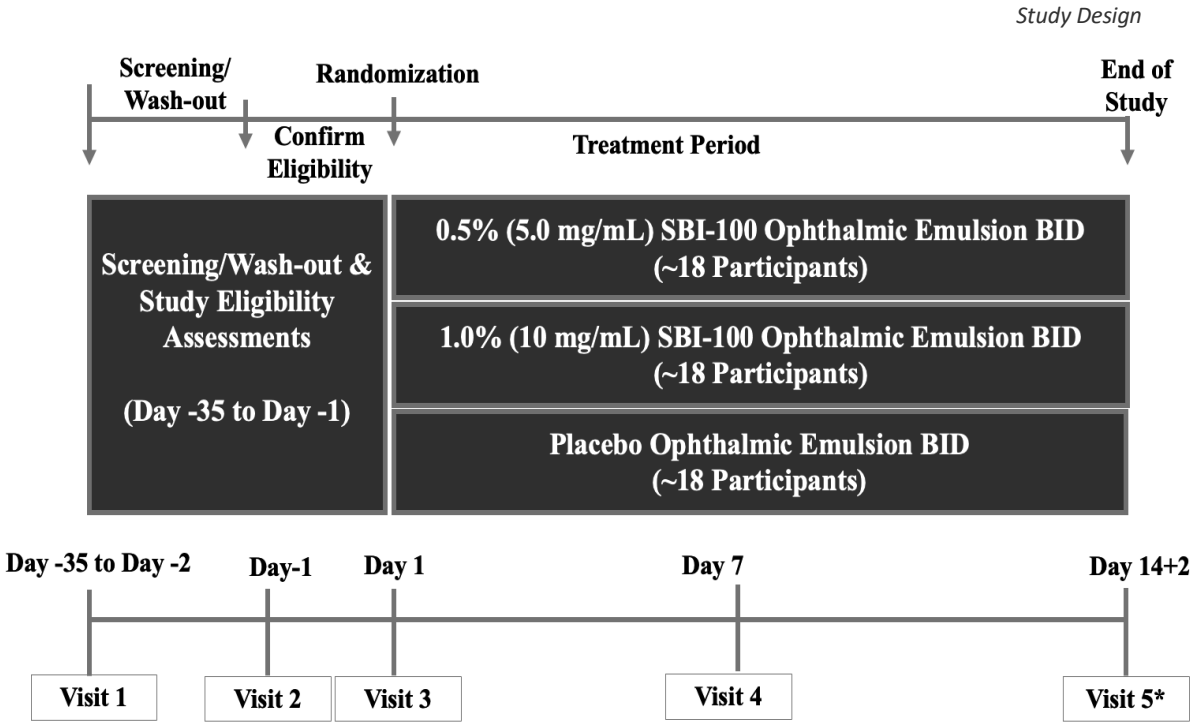
9.8.3. SAP Amendments

There is no amendments.

REFERENCES

1. Little, Roderick J.A., and Donald B. Rubin. 2002. Statistical Analysis with Missing Data. Second Edition. John Wiley & Sons, Inc., Hoboken, New Jersey.
2. Proschan M.A., K. K. Gordon Lan K.K.G., & Wittes J.T. Statistical monitoring of clinical trials: A unified approach., *Springer*, New York, 2006
3. SAS Institute Inc. What's New in Base SAS® 9.4 and SAS® Viya®. (2013). SAS Institute Inc., Cary, NC, USA.
4. SAS Institute Inc. (2020). SAS/STAT User's Guide. SAS Institute Inc., Cary, NC, USA.

Figure 1: Study Design



*Day 14 (PM dose) to occur on-site with EOS procedures following. If EOS procedures cannot occur post-PM dose on Day 14 (PM dose), the patient may self-administer at home and will return for EOS/ET within 2 days.

Table 2. Schedule of Assessments

	Visit 1	Visit 2	Visit 3		Visit 4		Visit 5	Visit 5a	
If not treatment naïve must wash-out of IOP-lowering therapy prior to Day-1.	Screening / Wash-out (D-35 to -2)	Day -1	Day 1		Day 7		Day 14	EOS/ ET (D 14+2)	**Day 14 – PM dose to occur on-site with EOS procedures following. Patient to self-administer PM dose if EOS procedures to occur on separate day.** Procedures listed in EOS/ET are to be performed for any early terminations
Informed Consent	X								
Demographics	X								
Medical/Ophthalmic/Surgical Hx	X	X							Confirm changes from screening at Day-1
Inclusion/Exclusion	X	X	X						Specific criteria must be confirmed at Day-1 and Day 1 (pre-dose)
BCVA & Pupil Diameter	X		X		X		X	X	Screening: baseline manifest refraction included with VA Post-dose BCVA with ≥ 2 log line drop requires further assessment (repeat MR, assessment of AE, etc.)
Slit Lamp Biomicroscopy	X		X		X		X	X	*Screening: includes gonioscope*
Biomarker Collection - Blood		X					X		May be performed anytime during the Day -1 visit, anytime after dosing during the Day 14 visit.
Biomarker Collection - Tears		X					X		Performed at 10:00 (±30m) and must be performed at least 10 minutes prior to IOP measurement within time window
Intraocular Pressure (IOP)	X	S	S		S		S	X	Serial: 08:00 (±30m),10:00 (±30m) and 16:00 (±30m). IOP is to be measured at the same time on visit days as Day-1.
Central Corneal Thickness	X							X	
Vital Signs	X		X		X		X	X	Performed after 5 mins of rest. Blood pressure, heart rate and respiratory rate.
Dilated Fundoscopy	X							X	
Visual Field	X							X	Results within 3 months of screening used for entry if using automated threshold visual field (24-2 or SITA Fast) and considered reliable
Safety Labs	X							X	Includes – chemistry, hematology, and urinalysis.
Pregnancy Test	X	X						X	For females of childbearing potential. Serum at Screening, urine at visits 2 and 5a.
Drug/Alcohol Screen	X	X							Testing will be repeated once prior to randomization to confirm a positive test at screening or day -1.
Randomization			X						Via IRT after 08:00 IOP confirms eligibility
On-site Dosing			X		X		X		AM dose administered following 08:00 IOP. Treatment provided as a single use vial for binocular instillation BID. AM around 08:00 and PM around 20:00. Dose should be separated by 12 hours. Patient may self-administer PM dose on days 1 and 7.

Days 2 to 6 Patient Administered (Home) Dosing

Days 8 to 13 Patient Administered (Home) Dosing

	Visit 1	Visit 2	Visit 3		Visit 4		Visit 5	Visit 5a	
If not treatment naïve must wash-out of IOP-lowering therapy prior to Day-1.	Screening / Wash-out (D-35 to -2)	Day -1	Day 1		Day 7		Day 14	EOS/ ET (D 14+2)	**Day 14 – PM dose to occur on-site with EOS procedures following. Patient to self-administer PM dose if EOS procedures to occur on separate day.** Procedures listed in EOS/ET are to be performed for any early terminations
Ocular Comfort PRO			S		S		S		Applies to AM dose occurring on-site. Pre-dose and immediately after drop instillation up to 2 mins, 5m ±2m and 10m±5m post-dose. If at 10 min, PRO rating has not returned to the visit day pre-dose value, administer every 30 minutes until pre-dose value is achieved.
Kit Dispensing /Return			D		D/R		R	R	Day 1: patient education on drop instillation, handling, and storage. Return: used and un-used vials must be returned. Dispensing: discuss with the patient IP expectations and diversion prevention. Return: Staff must review with the patient vial level use and determine reasons for missed doses.
Prior/Concomitant Medications	X	X	X		X		X	X	
Adverse Events	X	X	X		X		X	X	Assessments performed outside of scheduled visits due to an adverse event should be captured as unscheduled visits.

H = hour (s), m = minute(s), S = serial procedures, D = Dispense, R = Return

H = hour (s), m = minute(s), S = serial procedures, D = Dispense, R = Return *Day -1*Day -1Day -1Day -1

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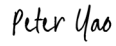
Peter Yao peter.yao@lexitas.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: C52A86AA-E356-42DD-ADE9-3C656C5F2346 Using IP Address: 96.227.143.28 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/1/2023 9:26:57 AM Viewed: 12/1/2023 10:08:32 AM Signed: 12/1/2023 10:09:08 AM
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Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Completed	Security Checked	12/5/2023 4:27:29 PM

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