SBI-100 OPHTHALMIC EMULSION

SBI-100-201

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

Protocol Number:	SBI-100-201
Date of Protocol:	21 September 2023
Phase:	2
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IND Number:	158020
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GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Skye Bioscience, Inc.

Sponsor's Authorized Officer:

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INVESTIGATOR'S AGREEMENT

I have read the SBI-100-201 Protocol and agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

This study may be terminated at any time by the Sponsor, with or without cause.

I agree to personally conduct and supervise this investigation at my institution and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, and the moral, ethical, and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients.

I will ensure that the requirements relating to Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval are met. I will provide the Sponsor with any material that is provided to the IRB/IEC for ethical approval.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

I agree to promptly report to the IRB/IEC any changes in the research activity and all unanticipated problems involving risks to human patients or others. Additionally, I will not make any changes in the research without IRB/IEC and Sponsor approval, except where necessary to ensure the safety of study patients.

Investigational Site Number	Site or Institution Name

Printed Name of Principal Investigator

Signature of Principal Investigator	Date

PROTOCOL REVISION HISTORY

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
	• 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

SYNOPSIS

Name of Sponsor/Company: Skye Bioscience, Inc.	
Name of Investigational Product/Study Treatment: SBI-100 Ophthalmic Emulsion	
Name of Active Ingredient: SBI-100 Delta 9 Tetrahydrocannabinol an amino ester containing valine and hemisuccinate (Δ9-THC-Val-HS or THCVHS)	
Protocol Number: SBI-100-201	**Country:** United States (US)
Title of Study:	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
Study center(s): Multi-center, up to 6 centers	
Studied period (years): Estimated date first patient enrolled: November 2023 Estimated date last patient completed: May 2024	**Phase of development:** 2

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

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).

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 ≥ 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 (> -1.5 dB/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. In the case of >5% of patients with missing data for any time point, 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% treated patients have diurnal IOP measurement at 14 days post-dosing to assess the conditional study power.

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Table 1: Abbreviations and Specialist Terms

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
°C	Degrees in Celsius
µL	Microliters
µm	Micrometers
AE	Adverse event
AM	Ante Meridiem (before noon)
ANCOVA	Analysis of covariance
BCVA	Best Corrected Visual Acuity
BID	Twice daily
CAI	Carbonic Anhydrase Inhibitors
CB	Cannabinoid Receptor
CCT	Central Corneal Thickness
CFR	Code of Federal Regulations
CI	Confidence Interval
COVID-19	Coronavirus disease
CRF	Case Report Form
dB	Decibels
DEA	Drug Enforcement Agency
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
etc.	Et cetera
FDA	Food and Drug Administration
FIH	First-in-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
i.e.	In other words,
IB	Investigator's Brochure
ICF	Informed Consent form

Abbreviation or Specialist Term	Explanation
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LASIK	Laser Assisted in Situ Keratomileusis
logMAR	Logarithm of the Minimum Angle of Resolution
MFD	Maximum Feasible Dose
mg	Milligrams
mL	Milliliters
mmHg	Millimeters of Mercury
MR	Manifest Refraction
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OAG	Open Angle Glaucoma
OD	Oculus Dexter (right eye)
OHT	Ocular Hypertension
OS	Oculus Sinister (left eye)
PD	Pharmacodynamic
PI	Principal Investigator: the leading Investigator at clinical site.
PM	Post Meridiam (after midday)
POAG	Primary Open Angle Glaucoma
PRK	Photorefractive Keratectomy
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBI	Skye Bioscience Incorporated
SBI-100 OE	SBI-100 Ophthalmic Emulsion
SD	Standard Deviation
SLT	Selective Laser Trabeculoplasty

Abbreviation or Specialist Term	Explanation
SITA	Swedish Interactive Threshold Algorithm
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
THC-Val-HS/THCVHS	THC amino acid ester containing valine and hemisuccinate
TM	Trabecular Meshwork
TMF	Trial Master File
US	United States
VS	Vital Signs
α	Alpha
β	Beta
Δ-9-THC	Delta-nine (9)- tetrahydrocannabinol

1. INTRODUCTION

This study will be conducted according to Good Clinical Practice (GCP), as defined by the International Council for Harmonisation (ICH) and the ethical principles underlying and the United States (US) Code of Federal Regulations (CFR), Title 21, Parts 11, 50 and 312 (21 CFR 50, 21 CFR 312) and all applicable government regulations and institutional research policies and procedures.

1.1. Background

1.1.1. Disease

Glaucoma is a chronic neurodegenerative disorder characterized by progressive and irreversible vision loss due to structural and functional damage to the optic nerve head and is the third largest cause of irreversible blindness in the world (Parihar, 2016). Elevated intraocular pressure (IOP) does not result from increased aqueous humor production but rather from reduced aqueous outflow (Kwon, et al 2009).

Management guidelines from the "American Academy of Ophthalmology Preferred Practice Pattern for glaucoma treatment" recommend lowering the IOP towards a target level, which is a value or range of values at which the clinician believes that the rate of disease progression will be slowed sufficiently to avoid functional impairment from the disease (Weinreb, Aung and Medeiros, 2014).

Prostaglandin analogues and β-blockers are the first line therapies and the most commonly used medications for the management of glaucoma. Prostaglandin analogues are the most efficacious class of drops. These drugs reduce IOP by reducing outflow resistance resulting in increased aqueous humor flow through the uveoscleral pathway. β-blockers are the second most efficacious class of drops. However, despite being the best locally tolerated agent, they cause the most systemic side effects (Weinreb, Aung and Medeiros, 2014).

Cannabis is one of the most widely used drugs throughout the world. The psychoactive constituent of cannabis, Δ9-Tetrahydrocannabinol (Δ9-THC), produces a myriad of pharmacological effects in animals and humans through cannabinoid receptors (CB). Two cannabinoid receptors have been identified and characterized: CB1 and CB2 (Han et al., 2013; Abrams and Guzman, 2015). The predominance of CB1 receptors in the ocular tissues, such as the iris ciliary body and Trabecular Meshwork (TM) (Montero et al., 2005) supports the involvement of a localized IOP-reducing mechanism. Several reports can be found on the topical administration of THC formulated in various oily vehicles (Merritt et al., 1981; Elsohly et al., 1981; Jay and Green, 1983). The anatomy and physiology of the eye, however, present a formidable barrier to the intraocular delivery of drugs through the topical route. This is especially true when a drug is needed to provide neuroprotective activity at the back (posterior segment) of the eye. The combination of precorneal and corneal barriers as well as other physiological barriers results in only approximately 5% to 10% of a topically applied drug reaching the inner ocular tissues (Loftssona and Järvinen 1999; Geroski and Edelhauser, 2000). Therefore, for Δ9-THC to show both an IOP-reducing and a neuroprotective effect, it is important for it to permeate through initial layers of the eye to the target tissues (Song and Slowey, 2000; Porcella et al., 2000).

The development of THC as an eye drop is especially challenging because of its poor aqueous solubility and high logP. In view of the challenges in the topical delivery of THC, it is not surprising that there are discrepancies in the literature with respect to the efficacy of topically administered THC. As THC is a lipophilic molecule, it rapidly partitions into the lipophilic corneal epithelia but remains trapped there and fails to efficiently partition out into the more hydrophilic stromal layers, and thus does not reach the intraocular tissues. Therefore, a THC prodrug, SBI-100, was developed to overcome these challenges. SBI-100 is a synthetically modified THC-amino acid ester containing a valine and hemisuccinate, otherwise known as THC-Val-HS. The addition of valine and hemisuccinate to THC has demonstrated improved aqueous solubility, and enhanced ocular tissue permeation characteristics resulting in increased reduction in the IOP compared to THC (Adelli et al, 2017; Elsohly et al, 2014).

1.2. SBI-100

Skye Bioscience, Inc. (Skye) is developing SBI-100, a synthetically manufactured proprietary prodrug of Δ9-THC, as a treatment for glaucoma. THC is a naturally occurring component of *Cannabis sativa* L. (marijuana) and the primary active ingredient of the plant.

The novel ophthalmic emulsion formulation of SBI-100 (SBI-100 Ophthalmic Emulsion) has been developed to provide local therapy and to improve the ocular bioavailability of THC, reducing the potential for systemic side effects.

As a prodrug, SBI-100 is relatively more hydrophilic than the parent THC compound and achieves better tissue penetration into the different parts/tissues of the eye, including the posterior segment, as observed in nonclinical studies. Compared to the standard-of-care glaucoma treatment, SBI-100 demonstrated superior lowering of IOP in rabbits. Moreover, in an ex vivo model of the human TM, THC demonstrated a reduction of biomarkers related to fibrosis, as well as increased outflow through the TM (i.e., IOP-reducing effect).

1.3. Summary of Nonclinical Studies

1.3.1. Pharmacology

A number of in vitro and in vivo studies were conducted to establish the mechanism of action and IOP-lowering ability of THC. All nonclinical studies conducted for SBI-100 are described in detail in the Investigator's Brochure (IB).

1.3.2. Pharmacokinetics

Multiple nonclinical studies were conducted to evaluate the ocular and systemic pharmacokinetics of SBI-100. Elsohly et al. (2019) evaluated the concentration and distribution of Δ9-THC and SBI-100 in rabbits following topical delivery of SBI-100. No Δ9-THC or SBI-100 was detected in the brain tissues and plasma in this study. More detailed information is provided within the IB.

1.3.3. Toxicology

The toxicity profile of SBI-100 Ophthalmic Emulsion was characterized in Good Laboratory Practice (GLP) compliant studies including an in vitro ocular irritation study, two 14-day toxicity studies in rabbits and dogs with SBI-100 Ophthalmic Emulsion after topical ocular

administration, and 2 in vitro genotoxicity studies (Ames and micronucleus assays). Further, as SBI-100 is a prodrug of THC, toxicology data available from the published literature with THC (mainly from the National Toxicology Program [NTP] database) and from literature related to the Food and Drug Administration's (FDA) approval of Marinol provide further information on a major metabolite of SBI-100. Collectively, this information supports the clinical use of SBI-100 in clinical studies to assess the effect on IOP.

1.4. Clinical Studies

There is an ongoing SBI-100 Ophthalmic Emulsion first-in-human (FIH) study being conducted in a Phase I unit in Australia in healthy human volunteers to establish a safety profile. The FIH trial will evaluate the ocular safety and tolerability of SBI-100 Ophthalmic Emulsion. Importantly, pharmacokinetics of SBI-100 and its metabolites will be evaluated to determine systemic exposure following topical delivery of SBI-100 Ophthalmic Emulsion. These data will be important to future development of SBI-100 Ophthalmic Emulsion in patients with ocular hypertension (OHT) or primary open angle glaucoma (POAG).

1.5. Summary of Potential Risks and Benefits

SBI-100 Ophthalmic Emulsion is an investigational topical ophthalmic study drug and the safety profile in humans has not yet been established.

Although SBI-100 has not been studied in humans, cannabis and THC as IOP-reducing agents have been extensively studied in both animal and human experiments. Prior human studies showed inhalation of cannabis or ingestion of THC demonstrated marked reduction of IOP. However, the duration of IOP-reducing effect was short-lived (approximately 3 to 4 hours) and multiple side effects were noted as a result of high exposure to THC and its metabolites in the plasma (Hepler and Frank, 1971). These side effects included unwanted psychotropic effects, and decreased blood pressure (Green, 1998; Crawford and Merritt, 1979). Other human studies also evaluated topical administration of THC dissolved in mineral oil. These studies did not demonstrate any reduction of IOP, and multiple patients withdrew as a result of intolerance to the eye drops (El-Remessy et al., 2003). These poor results from topical administration are likely due to the lack of ocular bioavailability from the mineral oil formulation of THC. Nonclinical studies have demonstrated the neuroprotective benefits of THC in multiple glaucoma models (El-Remessy et al., 2003).

In nonclinical studies, SBI-100 was well tolerated across animal species at multiple dose levels. IOP was observed to be lowered with reduced systemic exposure to SBI-100, THC, or its metabolites.

Based on nonclinical study results, there is the potential that topical administration of SBI-100 Ophthalmic Emulsion in humans may cause a positive drug test (in urine) and redness around the eyes after administration.

More information about the known and expected benefits and risks and reasonably expected adverse events of SBI-100 Ophthalmic Emulsion may be found in the IB.

1.6. COVID-19 Risk Assessment

The risks of patient involvement in study SBI-100-201 will be assessed in the context of the ongoing global coronavirus disease (COVID-19) pandemic and applicable precautionary response measure in place the local or national level. Risks to patients will be assessed against the anticipated benefit of the study participation in accordance with ICH GCP E6 (Principle 2.2), and risks to quality will also be assessed in accordance with ICH GCP E6 (Section 5). Clinical trial management requirements for study SBI-100-201 will also be assessed against FDA on the management of clinical trials during the COVID-19 pandemic.

Skye Bioscience, Inc. and its Investigators will establish measures to ensure that the conduct of study SBI-100-201 prioritizes the safety of patients and the integrity of clinical data. These measures will be based on a risk assessment of the impact of COVID-19 on patient safety and on clinical trial conduct. If specific measures need to be established at the study level or at a specific site, details will be documented in the Skye Bioscience Trial Master File (TMF).

2. STUDY OBJECTIVES AND PURPOSE

Study objectives and endpoints are presented below. The primary endpoint will be assessed at Day 14. Secondary endpoints will be assessed at all time points.

2.1. Primary Objectives and Endpoints

2.1.1. Primary Objectives

- To evaluate the diurnal ocular hypotensive efficacy of 2 dose levels of SBI-100 Ophthalmic Emulsion compared to placebo in patients with elevated IOP
- To evaluate the ocular and systemic safety of SBI-100 Ophthalmic Emulsion in patients with elevated IOP

2.1.2. Efficacy Endpoints

- Change from Day-1 in mean diurnal IOP at Day 14, in the study eye (see 3.2.2) 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 (see 3.2.2) for 1.0% SBI-100 Ophthalmic Emulsion compared to placebo

2.1.3. Safety Endpoints

- Change from baseline in vital signs including heart rate and blood pressure
- Change from baseline in safety labs
- Adverse Events (overall, ocular, and non-ocular)
- Change from baseline in ophthalmic assessments – slit lamp biomicroscopy, dilated fundus exam, BCVA, pupil diameter, visual field and pachymetry

2.2. Secondary Objectives

- 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

2.2.1. Efficacy Endpoints

- Time matched change in IOP from baseline IOP at 08:00, 10:00 and 16:00 hours on Day 1, 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)

2.2.2. Safety Endpoints

- Assesses changes in Ocular Comfort Patient Reported Outcome (PRO) from Day 1 pre-dose

2.3. Exploratory Objectives

- To evaluate changes in proteomic and immune biomarkers from Baseline

3. INVESTIGATIONAL PLAN

3.1. Overall 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 7 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 (±30m), 10:00 (±30m) and 16:00 (±30m) 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 continued for both mornings 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.

3.1.1. Number of Patients

There will be 54 patients with elevated intraocular pressure.

3.2. Measures to Minimize Bias:

3.2.1. Randomization/Masking

Patients will be randomized in a 1:1:1 ratio into 1 of 3 study treatments, via IRT. The identity of treatments will be masked to all patients and clinical sites. IRT will be programmed with mask-breaking instructions in the case of an emergency (6.2).

3.2.2. Determination of Study Eye

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

3.3. Study Design Rationale

3.3.1. Design Rationale

SBI-100 is being developed for reduction of IOP in patients with POAG and OHT. It is expected to act through a novel mode of action (CB1 agonism) that leads to an increase in TM outflow, thus reducing IOP. SBI-100-201 is a proof-of-concept study for a topical ophthalmic emulsion formulation of SBI-100. Up to two different concentrations (0.5% and 1.0%) will be explored to evaluate the ocular hypotensive efficacy of SBI-100 Ophthalmic Emulsion, along with safety and tolerability. As a secondary objective, the study will also aim to characterize the pharmacodynamics of SBI-100 Ophthalmic Emulsion using IOP as a pharmacodynamic biomarker. Ocular comfort and psychotropic effects of SBI-100 will also be explored as a secondary objective.

3.3.2. Criteria for Dosing

Eligible patients will be randomized to in a 1:1:1 ratio into 1 of 3 treatment groups:

- 0.5% (5 mg/mL) SBI-100 Ophthalmic Emulsion
- 1.0% (10 mg/mL) SBI-100 Ophthalmic Emulsion
- Placebo Ophthalmic Emulsion

The proposed levels are based on the nonclinical toxicology, which demonstrated a No Observed Adverse Effect Level (NOAEL) of 1.0% BID in rabbit (binocular administration of 50 µL per drop) which represents a total dose of 1.0 mg/mL SBI-100 in each eye or 2.0 mg/mL per day. For this study, the single-unit dose dropper will deliver approximately 30 µL per drop. Therefore, the lower dose of 0.5% will deliver approximately 0.30 mg/mL SBI-100 in each eye, or 0.60 mg/mL per dose. This low dose offers 3.3 times margin of safety to doses that have shown to be relatively well tolerated in toxicological species.

3.4. End of Study Definition

The EOS is defined as the date of a patient's last procedure was performed for this study. EOS procedures are to be performed after the PM dose on Day 14. If these procedures cannot be performed on Day 14, the patient will self-administer the PM dose and return to the site within 2 days for the EOS/ET visit.

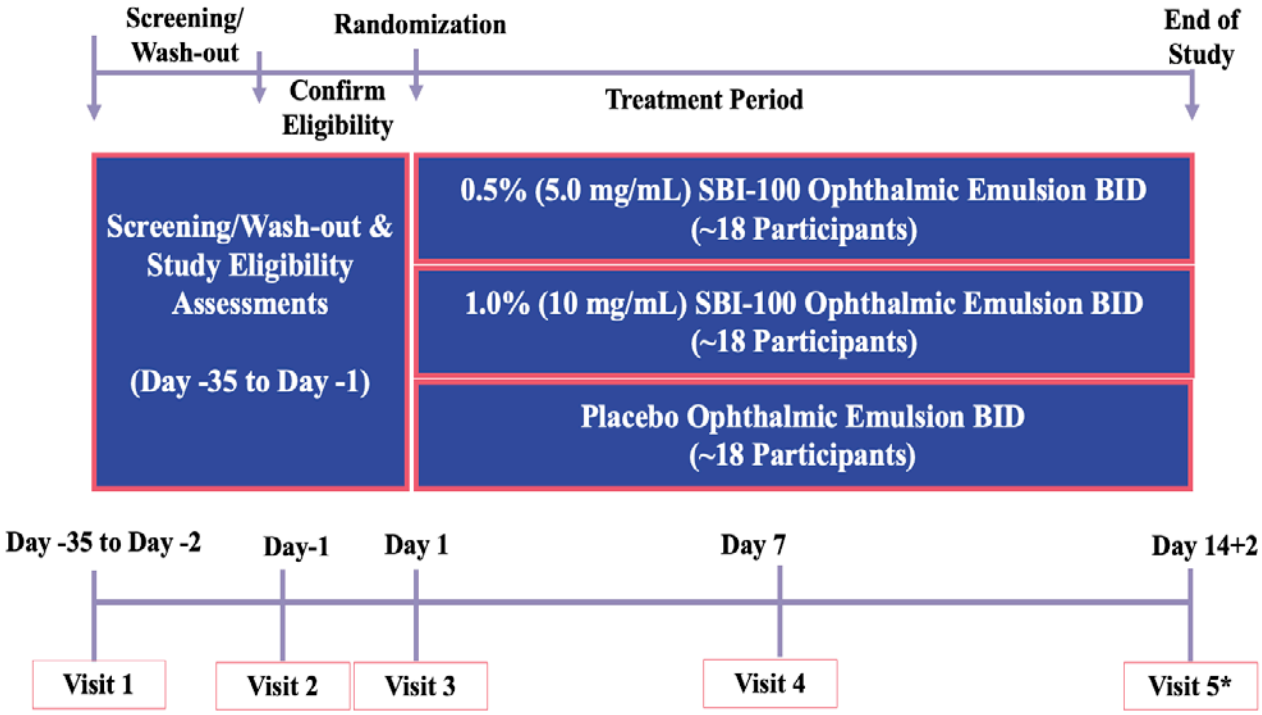
A patient is considered to have completed the study if he/she completes all the in-clinic visits (Days -1, 1, 7 and Day14) and all assessments listed in the EOS/ET visit.

If a patient withdraws from the study earlier than planned, the assessments listed within the EOS/ET visit should be performed.

3.5. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

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

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Patients must meet all the following inclusion criteria to participate in this study:

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 ≥ 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.

4.2. Exclusion Criteria

A patient who meets any of the following exclusion criteria cannot participate in this study:

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 (> -1.5 dB/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 (see 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.

4.3. Withdrawal Criteria

4.3.1. Screen Failures

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

If a patient is a screen failure due to wash-out from ocular procedures listed in exclusion criteria #7, the Investigator may contact the Medical Monitor and discuss the potential for re-screening in advance of wash-out completion. If the Medical Monitor agrees, the Investigator may schedule a re-screening upon completion of wash-out and file documentation of discussion within their site files.

All other individuals who do not meet the criteria for participation in this study (screen failure) will not be re-screened.

4.3.2. Early Termination of Patients

Patients have the right to withdraw from the study at any time for any reason. An early termination will occur if a patient who signed the informed consent form (ICF) and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol defined study procedures.

The Investigator can also withdraw a patient if it is deemed by the Investigator or the Sponsor that it is unsafe for the patient to continue the study. The Sponsor should be notified of early patient discontinuation. Whenever possible, the decision to withdraw a patient should be discussed with the Sponsor.

Patients who require use of rescue medicine should *not be* withdrawn from the trial (5.1.4).

If a patient 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 patient 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.

4.3.3. Procedures for Early Termination

Early patient discontinuation will be clearly documented with date and the reason for discontinuation recorded in the appropriate case report form (CRF).

Reasons for discontinuation:

- Protocol deviation
- Patient non-compliance
- Adverse Event (AE)
- Pregnancy (9.5)
- Investigator decision
- Sponsor decision (if study is canceled)
- Death
- Lost to follow-up
- Withdrawal of consent

If a patient discontinues during the study, all efforts should be made to have the EOS/ET visit procedures completed.

When a patient fails to return for scheduled assessments, efforts should be made to contact them to determine a reason for the failure to return. The site will attempt to contact the patients and reschedule the missed visit within 1-2 days and counsel the patients on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study. Patients should continue the current dosing regimen until the rescheduled visit.

Before a patient is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the patient (3 telephone calls and, if unsuccessful, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts must be documented in the patient's medical record or study file.

Should the patient continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up. Site procedures should follow internal procedures to document attempted contact with the patient. All attempts at contact should be documented in the patient's medical records. If a patient cannot be contacted, they will be considered as lost to follow-up.

All attempts should be made to retrieve the used and un-used study treatment for reconciliation regardless if an EOS/ET visit must be performed with associated documentation.

5. STUDY REQUIREMENTS

5.1. Prior and Concomitant Medications/Procedures

The use of any medications, prescription or over the counter for 30 days prior to screening 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 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.

5.1.1. Permitted Medications/Procedures

The following medications/procedures are permitted during the study:

- 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 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.

5.1.2. Prohibited Medications/Procedures

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
- concurrent 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.

5.1.1 notes medications that are permitted. 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.

5.1.3. Wash-out of IOP-Lowering Therapies

Treatment naïve patients that meet eligibility criteria may be scheduled for Day-1.

If the patient is currently being treated with an IOP-lowering therapy, it is to be withheld prior to Day-1 based on type of treatment in accordance with the following schedule:

~28 days (additional days can be added as per Investigator discretion)	β-adrenoceptor antagonists, prostaglandins, rho-kinase inhibitors.
14 days	adrenergic agonist, sympathomimetics
5 days	Muscarinic agonist, carbonic anhydrase inhibitors (CAI)

5.1.4. Rescue Medication/Therapy

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.

5.2. Study Restrictions

5.2.1. Contact Lens Use

The use of contact lenses is not permitted during the study. Patients who wear contact lenses must cease use of contact lenses at least 7 days prior to Day 1 and for the duration of the trial.

5.2.2. Prevention of Pregnancy

5.2.2.1. Females of Non-Childbearing Potential

All females are considered of childbearing potential unless they are naturally amenorrheic for at least 12 months (post-menopausal) prior to screening and/or are considered surgically sterile. If surgically sterile, medical history within at least 3 months prior to Day 1 of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

5.2.2.2. Females of Childbearing Potential

If of childbearing potential, female patients must not be pregnant, breastfeeding and/or intend to become pregnant during the study. All female patients of childbearing potential must have a negative pregnancy test at Screening and Day-1 and be willing to undergo additional pregnancy test as required throughout the study.

Females of childbearing potential must also agree to use a reliable form of contraception throughout the study until (at least) 30 days after the last dose of study treatment.

5.2.2.3. Contraceptive Methods (Males & Females)

The following methods of contraception are considered reliable, if used properly:

- Established hormonal contraception (oral contraceptive pill, long-acting implantable hormones, injectable hormones).
- A vaginal ring or an intrauterine device
- Tubal ligation
- If patient is female and male (sole) partner has had a vasectomy with follow-up confirming the absence of sperm noted in the medical history
- If male, vasectomy with follow-up confirming the absence of sperm noted in medical history

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered highly effective methods of birth control.

Patients with same-sex partners (abstinence from penile-vaginal intercourse) are not required to use contraception when this is their preferred and usual lifestyle.

5.2.3. Cannabis

Patients will be expected to refrain from the use of cannabis and other cannabinoid compounds (other than study treatment) from Screening and throughout the study (from time of Screening until the EOS/ET visit).

6. INVESTIGATIONAL PRODUCT/STUDY TREATMENT

6.1. Description of Investigation Product/Study Treatment

Table 3: Study Treatment/Investigational Product

Investigational Product/Study Treatment*			
Product Name:	0.5% (5 mg/mL) SBI-100	1.0% (10 mg/mL) SBI-100	Placebo **
Dosage Form:	Sterile Ophthalmic Emulsion for Topical Administration		
Unit Dose	0.3 mL single use vial (1 vial per dose, applied binocularly)		
Route of Administration	A single drop (approximately 30 µL) applied in each eye (binocularly) BID		
Physical Description	White/opaque sterile emulsion containing SBI-100 (THC-valine- hemisuccinate with emulsion carbomer) at pH 3.5 to 4.5		Matching sterile emulsion without active drug
Manufacturer	NextPharma-Tampere Oy, Tampere, Finland (manufacturing and testing), with QA and release by Skye		

*Throughout this document investigational product will be referred to as "Study Treatment". The term study treatment is a generalized reference to any IP for this study, encompasses all dose levels and the matching placebo.
**Placebo has a matching formulation to the active treatment but does not include active drug.

6.2. Randomization and Treatment Assignment

A Randomization list will be generated by the Sponsor/designee and will be transmitted to the assigned clinical packaging organization for labeling. The labels of the treatment materials identify only the kit number.

Only patients enrolled in the study may receive study treatment, and only authorized site staff may dispense, administer and/or retrieve study treatment from a patient.

Treatment will be allocated using the IRT system according to a randomization schedule. On Day 1, upon the confirmation of all eligibility measurements and immediately after the IOP measurements, sites will contact IRT to be assigned a kit number. Three (3) treatment groups are defined as follows:

- 0.5% (5.0 mg/mL) SBI-100 Ophthalmic Emulsion BID
- 1.0% (10 mg/mL) SBI-100 Ophthalmic Emulsion BID
- Placebo Ophthalmic Emulsion BID

6.2.1. Masking

This study is considered double-masked; therefore, the identity of study treatment will be masked to the patients and study centers. The IRT system will be programmed with unmasking instructions.

IP will be provided in masked study kits that are identical in appearance and packaging. The single use vials contained within the carton have no visible formulation differences.

In the case of an emergency the Investigator has the sole responsibility for determining if unmasking of a specific patient is warranted.

Masking of the study team will be maintained during the interim analysis by having the unmasked portions of the analysis performed by an unmasked biostatistician that is not affiliated with the study. Masking will be maintained at all investigational sites and for the study team executing and monitoring the trial. Any designated unmasked personnel will be clearly identified in an unmasking plan, and those individuals will not be involved in the ongoing conduct of the trial.

6.2.2. Unmasking

Emergency unmasking during the trial may be required for therapeutic or for regulatory reasons (for expedited safety reporting). Patient safety must always be the first consideration in determining if unmasking a patient's treatment assignment is warranted.

At a clinical site, the identification of the assigned treatment is programmed into the IRT system and can be revealed in emergency situations. In such situations, the Investigator will only break the mask for the involved patient.

If the Investigator decides that unmasking is warranted, the Investigator should make every effort to contact the Medical Monitor/Sponsor prior to unmasking, unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unmasked the Sponsor must be notified within 24 hours after breaking the mask. The date and reason the mask was broken must be recorded in the source documentation.

6.3. Investigational Product Materials & Management

The Sponsor will supply the study treatment to the investigational site's designated pharmacy. The study treatment provided for this study was manufactured under current Good Manufacturing Practices and will be suitable for human use. Any treatment intended to be administered to a study patient is referred to as study treatment, regardless of if it is considered the active drug or placebo (IP without any active ingredient) according to the study protocol.

The IP/study treatment is a controlled substance and should be transported, labelled, and stored in accordance with FDA, Drug Enforcement Agency (DEA), Good Manufacturing Practice, and local regulatory requirements.

6.3.1. Drug Enforcement Agency (DEA) Considerations

IP must only be maintained by Investigator/designee that have been approved by the DEA in accordance with the site's diversion plan. The approved Investigator/designee will be fully responsible for the security, accessibility, documentation, and storage of IP, as well as the DEA Form 222, while at the investigational facility. Investigator/designee must ensure that all forms are properly completed, filed and readily accessible.

6.3.2. Investigational Product Packaging and Labeling

Study treatment will be provided as masked kits comprised of an outer carton containing 2 pouches. The outer carton label will be comprised of an affixed and tear-off portion. Each pouch will have an affixed label and contain 10 sterile, single use ampules. The pouches and carton will

have labels, labels will contain information requested by Good Manufacturing Practice, local regulations, and DEA requirements (if applicable). Labels will also contain a kit number.

The affixed portion of the label will remain on the carton and the tear-off will be removed from the carton at the time of dispensation and attached to the IRT confirmation sheet per dispensation. The Investigator/designee will be responsible for ensuring accurate records of the corresponding patient identification number (per kit), date of dispensation and confirm/document vials dispense per kit.

6.3.3. Investigational Product Shipping and Storage

IP will be shipped at a temperature of 2ºC to 8ºC. Upon receipt, the Investigator/designee must follow instructions to confirm the shipment details within the IRT, noting temperature conditions during transit and report any discrepancies. The appropriate elements of the DEA Form 222 must also be completed and properly filed. Any discrepancy reported must be resolved prior to the kit being assigned to a patient.

The IP must be stored at 2ºC to 8°C, secured and maintained in accordance with the diversion plan. The Investigator/designee must provide instructions on the handling, secure access, diversion prevention, and storage of IP to the patient during kit dispensation. The Principal Investigator must ensure that any tasks involving handling or management of IP are performed by site staff noted within the diversion plan. The Principal Investigator must also ensure that all site staff involved with dispensation and/or return of IP are appropriately trained on assessing abuse potential and discussing diversion strategies with the patients.

6.3.4. Investigational Product Accountability

Only patients randomized to treatment may receive study treatment. DEA-approved Investigators/designees may dispense, administer, or return study kits. It is the responsibility of the Investigator/designee to maintain accurate records of the inventory at the site, details of dispensation per patient and returns.

6.3.5. Investigational Product Handling and Disposal

All used and un-used vials of study treatment, along with the corresponding packaging (cartons and pouches) must be returned to the Sponsor at the conclusion of the study. Due to IP being a controlled substance, no destruction will occur at any of the clinical sites.

6.4. Administration of Investigational Product

6.4.1. Study Treatment Administration

Upon treatment assignment the clinic staff will instill 1 drop of study treatment in each eye, immediately after the pre-dose IOP to be performed at 08:00.

One vial of study treatment should be enough to administer 1 drop of study treatment to each eye with about 4 to 6 drops remaining in the vial (see Table 4). After administration, the remaining should be wasted but the VIAL MUST BE KEPT for accountability/reconciliation at the vial level.

Following administration patients should keep their eyes closed for 30 to 45 seconds without blinking. In addition, punctal occlusion may be performed by pressing a finger on the lacrimal puncta after the drop is instilled.

Table 4: SBI-100 Ophthalmic Emulsion Administered Dose/Drop

Assumed Drop Volume (mL)	SBI-100 Administered Dose/Drop			
	0.5% (5 mg/mL) SBI-100		1.0% (10 mg/mL) SBI-100	
	Dose/Drop	Daily Dose*	Dose/Drop	Daily Dose
0.030 (mean)	0.150	0.600 mcg	0.300	1.200 mcg
0.040 (maximum)	0.200	0.800 mcg	0.400	1.600 mcg

*1 drop per eye BID (AM and PM)

6.4.2. Patient Instructions for Use

On Day 1, prior to leaving the clinical site, staff will demonstrate drop instillation and provide instructions on the proper use, storage, and handling of the study treatment. Patients will be instructed to:

- Use a vial for each dose period (AM or PM) dose.
- Shake vial well before using.
- Instill 1 drop in each eye for the Day 1 PM dose at 12 hours after the AM dose (should occur approximately 8PM).
- After administration, the product remaining in the vial should be discarded but the VIAL must be kept with the original kit to be returned to the clinic.
- Store treatment in a refrigerator and protect it from freezing. Secure the IP to keep out of the reach of children.
- During transport, the vials should be protected from extreme temperatures and placed into the refrigerator immediately.
- Do Not instill AM treatment prior to the Day 7 or Day 14 visit.
- Keep all vials (used and un-used) together to be returned to the clinical site for the Day 7 and 14 visit.

Site staff will discuss methods to help the patient comply with these instructions. Staff will provide reminders prior to Days 7 and 14 to ensure instructions are followed for the on-site visit.

6.4.3. Kit Dispensation and Return

During the Day 1 visit, the Investigator/designee will dispense the initial IP kit to the patient after the AM dose. The initial kit contains enough vials for dosing until the Day 7 visit, all used and un-used vials, along with the original packaging (carton and pouches) will be returned by the patient on the Day 7 visit. After the AM dose on Day 7, the Investigator/designee will dispense another IP kit as assigned by the IRT system and should be returned on Day 14 in the same fashion as Day 7.

Prior to each dispensation the Investigator/designee must confirm and document the vials dispensed.

Vial counts will be performed by the Investigator/designee upon each return by the patient and all vials must be accounted for. The Investigator/designee must review use of each with the patient to assess for administration compliance, potential AEs, losses and/other reasons for diversions. The Investigator/designee must ensure vial level accountability of IP received, used and un-used, with detailed documentation.

If a patient has not returned all IP vials by the last visit, the site staff must make all attempts to retrieve all used and un-used study treatment for reconciliation. The site must document all attempts to retrieve IP within the patient's medical records

7. STUDY VISITS

Where possible, assessments should be conducted in order of least invasive to most invasive.

All ophthalmic assessments will be performed in each eye. Assessments within a visit should occur in the order noted below. Additional instructions on study assessments will be provided within the study procedure manual.

7.1. Visit 1: Screening (Day -35 to Day -2)

Patients will be provided with an ICF and given time to review study information and ask any questions prior to signing. As part of the consent discussion, investigator/designee should discuss diversion prevention and expectations regarding IP accountability processes.

After the consent form is signed, with a copy of the signed ICF provided to the patient, the following assessments will be carried out as follows:

- Perform drug and alcohol testing (if positive, will be repeated once prior to Day -1). Patients with a confirmed positive test must be screen-failed and are not eligible for re-screening.
- Review/documentation of
  - Demographic information
  - Medical, ophthalmic, and surgical history
  - Prior and concurrent medications/therapies, planned ocular procedures
  - Childbearing potential, methods of birth control if of childbearing potential
- Baseline Manifest Refraction, BCVA and Pupil Diameter
- Slit lamp biomicroscopy, includes gonioscope to assess angle closure and lens assessment
- IOP
- Pachymeter to measure central corneal thickness
- Vital signs
- Visual field (if no results within 3 months of screening, meeting testing requirements)
- Dilated Fundus exam
- Labs
  - Chemistry, hematology, and urinalysis
  - Serum pregnancy tests for females of childbearing potential
- Review/documentation of AEs, assess eligibility
- If treatment naïve, upon confirmation of eligibility (i.e., assessment of screening labs) schedule Day-1. Otherwise begin wash-out as detailed in 5.1.3.

7.2. Visit 2: Day-1

- Perform drug and alcohol testing (if positive, will be repeated once prior to Day 1). Patients with a confirmed positive test must be screen-failed and are not eligible for re-screening.
- Review and documentation of AEs and concomitant medication
- 08:00 (±30m) IOP, confirm eligibility prior to performing remaining assessments
- Urine pregnancy testing for females of childbearing potential
- Blood draw and tear collection for biomarkers; blood draw may occur anytime during the visit. Tear collection must occur at 10:00 (±30m) AND at least 10 minutes prior to IOP measurement within that time window.
- IOP at 10:00 (±30m) and 16:00 (±30m)
- Confirm changes from screening in medications, procedures, and medical history

7.3. Visit 3: Day 1

IOP measurements must be performed at the same time as the Day-1 time points, when possible.

- Review and documentation of AEs and concomitant medication
- Pre-dose (confirm changes from last visit)
  - BCVA & Pupil Diameter
  - Vital signs
  - Ocular Comfort PRO
  - Slit lamp
  - IOP at 08:00 (±30m)
  - Confirmation of eligibility and randomization via IRT
- Site administration of study treatment should occur **immediately** after 08:00 IOP and IRT randomization.
- Post-dose
  - Ocular Comfort PRO: administered immediately after drop instillation up to 2 mins, 5m (±2m), and 10m (±5m). *If at 10 minutes, PRO rating has not returned to the visit day pre-dose value, administer every 30 minutes until pre-dose value is achieved.*
  - IOP: 10:00 (±30m) and 16:00 (±30m)
- Prior to the patient's departure from the clinical site the staff shall:
  - Discuss diversion prevention and IP expectations.
  - Demonstration of drop instillation provided to patient.

- Dispense study treatment kit to the patient for at home, self-administration starting with the PM dose
- AM dose should occur at 08:00, the PM dose to occur approximately 12 hours after AM dose

7.4. Visit 4: Day 7

Assessments for Day 7 are similar to Day 1. However, eligibility/randomization is not required.

- Review and documentation of AEs and concomitant medication
- Pre-dose
  - BCVA & Pupil Diameter
  - Vital signs
  - Ocular Comfort PRO
  - Slit Lamp Biomicroscopy
  - IOP at 08:00 (±30m)
- Site administration of study treatment should occur **immediately** after 08:00 IOP
- Post-dose
  - Ocular Comfort PRO: administered immediately after drop instillation up to 2 mins, 5m (±2m), and 10m (±5m). *If at 10 minutes, PRO rating has not returned to the visit day pre-dose value, administer every 30 minutes until pre-dose value is achieved.*
  - IOP: 10:00 (±30m) and16:00 (±30m)
- All vials and cartons of study treatment will be returned, staff will perform vial level accountability
  - Staff will determine if doses were missed and discuss with the patient reason for missing doses (i.e., AE occurred)
- Dispense another kit of study treatment through the IRT system.
  - Discuss diversion prevention and IP expectations.
- Patient will self-administer PM dose
  - The PM dose to occur within 12 hours of AM dose

7.5. Visit 5: Day 14

Assessments for Day 14 are similar to Day 7. The visit will be longer as the last dose should be performed on-site (PM dose) with EOS procedures following. Patients will return their used and un-used IP since the Day 7 dispensation.

- Review and documentation of AEs and concomitant medication
- Pre-dose
  - BCVA& Pupil Diameter
  - Vital signs
  - Ocular Comfort PRO
  - Slit Lamp Biomicroscopy
  - IOP at 08:00 (±30m)
- Site administration of study treatment should occur **immediately** after 08:00 IOP
- Post-dose
  - Ocular Comfort PRO: administered immediately after drop instillation up to 2 mins, 5m (±2m), and 10m (±5m). *If at 10 minutes, PRO rating has not returned to the visit day pre-dose value, administer every 30 minutes until pre-dose value is achieved.*
  - Blood draw and tear collection for biomarkers; blood draw may occur anytime during the visit after dosing. Tear collection must occur at 10:00 (±30m) AND at least 10 minutes prior to IOP measurement within that time window.
  - IOP: 10:00 (±30m) and16:00 (±30m)
- All vials and cartons of study treatment will be returned, staff will perform vial level accountability
  - Staff will determine if doses were missed and discuss with the patient reason for missing doses (i.e., AE occurred)
- If possible, PM dose will be administered by site staff 12 hours after the AM dose. No Ocular Comfort PRO is required.
  - Procedures for EOS will be performed after the PM dose.
- If administration of the PM dose and EOS procedures cannot be performed at the end of this visit, the patient will self-administer PM dose and will be instructed to return to the site within 2 days after this visit. The patient will be given an additional vial of investigational product, if needed.
  - The PM dose to occur within 12 hours of AM dose.

7.6. Visit 5a: EOS/ET (Day 14+ 2 Days)

EOS procedures will be performed after the final dose of IP has been administered. If the EOS procedures cannot occur after the last dose, the Day 14 PM dose can be self-administered with the patient returning within 2 days for the EOS procedures.

- Review and documentation of AEs and concomitant medication
- BCVA and Pupil Diameter
- Slit lamp biomicroscopy and lens assessment
- IOP
- Pachymeter for central corneal thickness measurement
- Vital signs
- Dilated Fundus exam
- Visual field
- Labs
  - Chemistry, hematology, and urinalysis
  - Urine pregnancy tests for females of childbearing potential
- *All vials and cartons of study treatment will be returned, staff will perform vial level accountability*
  - *Staff will determine if doses were missed and discuss with the patient reason for missing doses (i.e., AE occurred). Required if visit is not occurring on Day 14.*

Procedures listed within this visit should be performed if a patient early terminates from the study.

8. STUDY ASSESSMENTS

The methods for collecting safety data are described below.

8.1. General Assessments

8.1.1. Demographics

Demographic information will be collected at screening: age at time of informed consent, gender, race, and ethnicity.

8.1.2. Medical/Ophthalmic/Surgical History

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

In addition, social history to include smoking history (nicotine), recreational alcohol and drug use will be obtained for the year prior to screening.

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

8.1.3. Vital Signs

Blood pressure, heart rate and respiratory rate will be measured 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.

8.1.4. IP Expectations and Diversion Prevention

As part of the consent discussion, site staff should discuss diversion prevention and expectations regarding IP. . Discussions should include instructions for use, storage, and handling of IP as well as expectations for return of used and unused IP. Patients should be reminded of this when IP is dispensed on Day 1 and Day 7. Site staff must review all used and un-used vials with the patient to determine if a diversion occurred as part of the IP return process.

8.2. Laboratory Assessments

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.

8.2.1. 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.

8.2.2. 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.

8.2.3. 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, anytime 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.

8.3. Ophthalmic Assessments

When applicable, assessments requiring dilation should occur at the end of the visit. Detailed instructions can be found within the study procedure manual.

8.3.1. Manifest Refraction

Conducted at the screening visit for distance at 4M using the clinic's standard practices for the right (OD) and left (OS). The manifest refraction measurements from screening will be used for subsequent BCVAs.

8.3.2. Visual Acuity

Best Correct Visual Acuity (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.

8.3.2.1. Losses in Visual Acuity

If a patient loses ≥ 2 lines (defined as 10 or more letters) in BCVA in comparison to the Day 1 (pre-dose) BCVA measurement, this will warrant further assessment to determine the reason for the loss (i.e., repeat manifest refraction and/or other ophthalmic assessments). If a repeat manifest refraction is performed, it should be conducted in the corresponding eye and assessed for safety by the Investigator. It is the Investigator's discretion to perform the repeat manifest refraction in each eye.

The assessment(s) performed to assess the safety and reason for visual acuity losses must have corresponding documentation of actions taken, noted in the source.

8.3.3. Pupil Diameter

Pupil diameter will be assessed by pupilometer following BCVA assessment as per time points delineated in Table 2. Pupil Diameter will be conducted using the same logMAR chart as the distant target for the uncovered eye not being tested.

8.3.4. Intraocular Pressure

IOP measurement 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 a 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.

8.3.5. 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.

8.3.6. 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 Screening 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.

8.3.7. 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.

8.3.8. 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.

8.3.9. Ocular Comfort Assessment PRO

Interviewer administered Ocular Comfort Assessment in the form of a PRO (see Section 15) 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. SAFETY

The methods for collecting safety data are described below.

9.1. Adverse Event (AE)

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.

9.1.1. Severity

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.

9.1.2. 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.

9.2. Recording/Reporting of Adverse Events

At each visit, the Investigator will elicit information on AEs. Any information on AEs should be recorded in the source documentation and in the electronic Case Report Form (eCRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded under one diagnosis.

The AE term should be reported in standard medical terminology. All AEs will be recorded by the date when the AE started and stopped, the severity, causality, seriousness, the action taken regarding SBI-100 Ophthalmic Emulsion, outcome and whether or not it caused the patient to discontinue the study.

For new ocular AEs, the Investigator must perform the appropriate ophthalmic procedures as needed to assess the affected eye. The Investigator will complete the associated eCRF page.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under 9.3. An AE of severe intensity may not be considered serious.

9.2.1. Reporting Period

The study period during which AEs must be reported is defined as the period from randomization to treatment until the EOS/ET visit, whether or not they are related to the study or study procedures, and they must be recorded in source document and EDC.

AEs that occur from the time of informed consent up until randomization to treatment will be assessed in accordance with the site processes and will be considered changes in patient health status. These events will be captured in the patients’ medical histories.

9.2.2. Timing, Treatment and Follow-up of AEs

During the study, AEs will be followed up until they have returned to baseline status, resolved and/or considered stabilized.

If an AE is not resolved at the time of the last visit, efforts will be made to follow up until resolution or stabilization of the event, unless the Investigator and Sponsor agree that follow-up is no longer necessary. Associated documentation of the follow-up and discussions on the handling of the AE should be available within the site files.

Treatment of AEs is at the discretion of the Investigator and should follow the standards of medical care at the Investigator’s institution.

9.3. Serious Adverse Events (SAE)

A serious adverse event 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.

9.3.1. Recording Serious Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of the ICF until the EOS/ET visit. Any SAEs considered possibly or probably related to the study treatment and discovered by the Investigator at any time after the study should be reported.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported as SAEs as well as elective abortions without complications.

Note: Pre-planned surgeries or procedures for pre-existing known medical conditions for which the patient requires hospitalizations is not considered a SAE, if this was known at the time of screening.

9.3.2. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction (SUSAR) is the term used to refer to an AE that occurs in a clinical trial patient, which is assessed by the Sponsor and/or Investigator as being unexpected, serious, and having reasonable possibility of causal relationship with the study treatment.

Should an Investigator become aware of a patient experiencing a SUSAR during the study and at any time after the study, the Investigator/designee must report this to the Sponsor in the same manner as an SAE.

9.4. Reporting and Handling of Safety Events

9.4.1. Investigator Reporting: SAEs/SUSARs

All SAEs must be reported to the Sponsor/designee within 24 hours of the Investigator's first awareness of the event. The Investigator/designee must:

- Enter all details into the AE CRF page ensuring that "serious" is noted

- Update any corresponding CRF pages with relevant information such as concomitant medications or procedures
- Compile all available and relevant medical records in support of the SAE, ensuring all personal health information has been redacted
- Complete an SAE Cover Letter with the Investigator's signature
- Email the entire packet to: PVG@DrugSafetyNavigator.com

The Investigator will keep a copy of the SAE cover letter on file at the study site.

The Investigator will provide any additional information regarding the event to PVG@DrugSafetyNavigator.com as soon as possible.

9.4.2. Investigator Reporting: Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Notification

The Investigator is responsible for notifying the IRB/IEC of all SAEs that have occurred. All AEs that are study treatment related, serious, and unexpected (not listed in the IB) must be reported to the governing IRB/IEC as required by local regulations.

Copies of each report and documentation of IRB/IEC notification and receipt will be kept in the Investigator's study file.

9.4.3. Sponsor Reporting: Notifying Regulatory Authorities

The Sponsor is required to report certain study events in an expedited manner to the applicable Regulatory Agency as required by local regulations and/or governing health authorities. The following describes the safety reporting requirements of the FDA by timeline for reporting and associated type of event:

- Immediately and within 7 calendar days
  - Any suspected adverse reaction that is: associated with the use of the study treatment, unexpected, and fatal or life-threatening
  - Follow-up information must be reported in the following 8 calendar days
- Immediately and within 15 calendar days
  - Any suspected adverse reaction that is: associated with the use of the study treatment, unexpected, and serious, but not fatal or life-threatening
  - Any finding from tests in laboratory animals that suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity
  - Any event in connection with the conduct of the study or the development of the investigational medicinal product that may affect the safety of the study patients
  - Follow-up information must be reported within 15 calendar days

For the purposes of expedited reporting, the determination of causality will be the responsibility of the Sponsor with consideration of the Investigator's assessment of causality.

The Sponsor will comply with all additional local safety reporting requirements, as applicable.

9.4.4. Sponsor Reporting: Notifying Participating Investigators

It is the responsibility of the Sponsor or designee to immediately notify all participating Investigators of any AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human patients.

9.5. Pregnancy

The definition of childbearing potential and approved methods of contraception are noted in 5.2.2.

Female patients must be advised to immediately inform the Investigator if she becomes pregnant during the study and must not receive further study treatment. Pregnancies occurring through the EOS/ET must be reported to the Investigator and recorded on a Pregnancy Report Form.

The Investigator must report all pregnancies to the Sponsor within 24 hours of notification. The Investigator should counsel the patient on the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

If a female partner of a male patient becomes pregnant during the study, the Investigator will notify the Sponsor once the pregnancy is confirmed. The Investigator will obtain consent from the female partner to conduct safety follow-up assessments until the pregnancy has come to term. The outcome of the pregnancy should be documented.

Pregnancy is not considered an AE, unless there are pregnancy complications that may or may not be related to the study treatment.

At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

10. STATISTICS

10.1. 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. 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 5: Sample Size Requirements

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.

10.2. 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. 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).

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:

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

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 expected B value under the null hypothesis

the drift parameter $\theta = 0$. The process to calculate conditional power will be described in the SAP.

10.3. Analysis Populations

10.3.1. Intent-to-Treat Population (ITT)

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.

10.3.2. Per Protocol Population

The Per Protocol population is a subset of the ITT population, defined as all patients who are randomized and do not have any major protocol deviations that could have an impact on study outcomes. Major protocol deviations will be defined in a masked review prior to study unmasking. Patients will be analyzed according to their actual treatment received. The Per Protocol population will be used for sensitivity analysis of the primary efficacy endpoints in the case of a significant number of major protocol deviations.

10.3.3. Safety Population

The safety population includes all patients randomized who received at least one treatment. Patients will be analyzed according to their actual treatment received. The safety population will be used for all safety analysis.

Additional analysis populations may be specified in the Statistical Analysis Plan (SAP).

10.4. Statistical Analyses

This section provides a broad outline of planned statistical summaries and analyses. Full details will be provided in a separate SAP for this study. Any changes to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP.

10.4.1. General Considerations

Descriptive summary statistics will be provided for demographics and other baseline characteristics, disposition, and dose exposure. The number and percentage of patients who discontinued from the study, along with reasons for discontinuations, will be tabulated and described in listings.

Continuous data will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and, where appropriate, graphic representation, and two-sided 95% confidence interval (CI); categorical data will be summarized by sample size and proportions.

Data summaries will be provided for the values at each scheduled visit, as well as changes from baseline at each scheduled visit. 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. For safety endpoints, data from unscheduled visits will be included in summaries of the worst-case post-baseline measure within each eye (for ocular data) or patient. Unscheduled visits will not be analyzed for efficacy endpoints.

The study eye will be determined for efficacy analysis purposes. The study eye will be defined as the eye with the highest mean diurnal IOP from the three measures taken on Day-1 (baseline). In the case of a tie, the study eye will be the right eye.

Unless otherwise specified, continuous variables will be analyzed using analysis of covariance (ANCOVA) at the two-sided 0.05 level at a visit. If data consists of multiple visits , mixed model with repeated measurement (MMRM) will be utilized. Categorical variables will be analyzed using the chi-square tests at the two-sided 0.05 level. Additional statistical methodology, sensitivity analyses accounting for missing data, and adjustments for covariates, if any, will be described in the SAP.

10.4.2. Primary Endpoint

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. ANCOVA will be used for each comparison at a two-sided alpha level of 0.05 without any adjustment as described in 10.4.6. The model will include adjustment for the baseline value. The primary efficacy analysis will be based on the ITT population.

The null hypothesis for the primary endpoint is as follows:

The change from baseline (Day-1) in mean diurnal IOP of each dose level of SBI-100 Ophthalmic Emulsion will not be different from that of its placebo after 14 days of BID dosing.

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 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.

The actual mean diurnal IOP values at each visit will be analyzed with MMRM.

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. In the case of >5% of patients with missing data for any time point, the primary analyses 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.

10.4.3. Secondary Endpoints

Other secondary endpoints will be analyzed using the method described in 10.4.1. Full details of the analyses will be provided in the SAP.

Changes from time-specific baseline in IOP measure and differences in change from 8:00 IOP measure at 10:00 and 16:00 between Pre-dose (Day -1) and Post-dose visits (Day 1, Day 7, and Day 14) will be analyzed using MMRM. Medication comfort responses will be analyzed on a

continuous scale and categorically in a similar fashion. Full details of the analyses will be provided in the SAP.

10.4.4. Exploratory Endpoint

Proteomic and immune biomarker testing will be conducted on Visit 2 (Day -1) and Visit 5 (Day 14). Summary statistics as well as change from baseline of proteomic and immune biomarkers will be provided.

10.4.5. Safety Analyses

Safety analyses will be performed using the safety population defined in 10.3.3.

All analyses of safety data will be presented using descriptive summary statistics. For AEs, an overall summary will be provided for ocular, non-ocular, and all events, including the number and percentage of patients with any AEs, related AEs, SAEs, related SAEs, AEs leading to treatment discontinuation or interruption, and maximum severity of AEs. The percentage of patients reporting an event will be calculated based on the number of patients in the corresponding treatment group. AE analyses by coded terms will include (but not be limited to) summaries of Treatment Emergent Adverse Events (TEAEs), ocular TEAEs, study treatment related TEAEs, SAEs, ocular SAEs, TEAEs leading to treatment discontinuation or interruption, and ocular and non-ocular AEs by maximum severity.

The observed and change from baseline in BCVA, pupil diameter, central corneal thickness (CCT), ophthalmic examination findings, and vital signs will be summarized descriptively by treatment groups. The appropriate shift tables will also be provided showing the shift from baseline to post-treatment assessments.

More details will be outlined in the SAP.

10.4.6. Adjustment for 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.

10.5. Summaries of Data Prior to Study Completion

Data will be analyzed, and the results will be presented in tables and listings.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor/designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that study treatment accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Skye Bioscience, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

11.2. Audits and Inspections

Authorized representatives of Skye Bioscience, Inc., a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Skye Bioscience, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Council for Harmonisation, and any applicable regulatory requirements. The Investigator should contact Skye Bioscience, Inc. immediately if contacted by a regulatory agency about an inspection.

11.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study, including the patient ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

12. ETHICS

12.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Skye Bioscience, Inc. before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Skye Bioscience, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

12.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and Skye Bioscience, Inc.'s policy on Bioethics.

12.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study-specific procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed and dated Informed Consent Form must be given to the patient.

12.4. Future Use of Stored Specimens

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the biomarker testing lab. These samples may be used for future biomarker research in patients with glaucoma or ocular hypertension. Future research will only involve proteomic and immune biomarkers, not genetic biomarkers. The biomarker lab will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biological sample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the biomarker testing lab.

13. DATA HANDLING AND RECORDKEEPING

13.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

13.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

13.3. Publications

After completion of the study, the data may be considered for reporting at scientific meetings or for publication in scientific journals. The Sponsor will be responsible for these activities and has final approval authority over decisions related to data publication, including, without limitation, the publication to which it will be submitted and other related issues.

Data are the property of the Sponsor and cannot be published without their prior authorization.

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15. APPENDICES

Appendix 1: Ocular Comfort – Patient Reported Outcome

Ocular Comfort – PRO

PARTICIPANT ID: _____ **VISIT DAY:** _____

DATE: _____
DD/MON/YYYY

TIMEPOINT:

Predose: ☐ Immediately Post-Dose: ☐ 5 minutes: ☐ 10 minutes: ☐

Additional: ☐

PLEASE RATE THE CURRENT LEVEL OF COMFORT IN YOUR EYES

0	1	2	3
NO DISCOMFORT	MILD DISCOMFORT	MODERATE DISCOMFORT	SEVERE DISCOMFORT

Time Administered: ____:____ Administered by: _____