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Study VVN559-CS201
Statistical Analysis Plan

A phase 2, double-masked, randomized, vehicle-controlled, dose-response study assessing the safety and ocular hypotensive efficacy of VVN539 in subjects with primary open angle glaucoma or ocular hypertension.

Dated 21 December 2022

Statistical Analysis Plan for A phase 2, double-masked, randomized, vehicle-controlled, dose-response study assessing the safety and ocular hypotensive efficacy of VVN539 in subjects with primary open angle glaucoma or ocular hypertension

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SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

LDL	Low-Density Lipoprotein
LOCF	Last observation carried forward
LogMAR	Logarithm of the Minimum Angle of Refraction
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MIGS	Minimally Invasive Glaucoma Surgery
MMRM	Mixed-model repeated measures
NCS	Non-clinically significant
OD	Oculus dexter (right eye)
OHT	Ocular Hypertension
OS	Oculus sinister (left eye)
OU	Oculus uterque (both eyes)
PI	Principal Investigator
POAG	Primary Open Angle Glaucoma
PP	Per Protocol
PRK	Photorefractive Keratectomy
PT	Preferred term
QC	Quality control
q.d.	Once a Day (Quaque Die)
RBC	Red blood cell count
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure

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

PROTOCOL SYNOPSIS

Title:	A phase 2, double-masked, randomized, vehicle-controlled, dose-response study assessing the safety and ocular hypotensive efficacy of VVN539 in subjects with primary open angle glaucoma or ocular hypertension.
Phase:	2
Design/Conduct:	Prospective, parallel-comparison, multi-center, double-masked, randomized, vehicle-controlled dose-response study assessing the safety and ocular hypotensive efficacy of VVN539 in subjects with primary open angle glaucoma (POAG) or ocular hypertension (OHT) in the United States (US).
Objective(s):	Efficacy: To evaluate the ocular hypotensive efficacy of 2 concentrations of VVN539. Safety: To evaluate the ocular and systemic safety of 2 concentrations of VVN539
Endpoint(s):	Primary Efficacy: Mean intraocular pressure (IOP) at each diurnal time point (8AM, 10AM, and 4PM) at Visit 4 (Day 7), Visit 5 (Day 14) and Visit 6 (Day 21). Secondary Efficacy: Mean change in IOP from Visit 2 (Baseline) to Visit 4 (Day 7), Visit 5 (Day 14) and visit 6 (Day 21).
Population studied:	Approximately 60 (20 per cohort) evaluable adult males or females diagnosed with OHT or POAG. Inclusion criteria: 1. 18 years of age or older. 2. Diagnosis of POAG or OHT in both eyes that are untreated, or if treated, in the opinion of the investigator are well controlled on 2 or fewer ocular hypotensive medications prior to Visit 1. • Combination medications count as 2 medications 3. Unmedicated IOP of ≥ 22 mm Hg and ≤ 36 mm Hg in the study eye, with no more than 5 mm Hg inter-eye difference at 08:00AM and 10:00AM at Visit 2. 4. Corrected visual acuity in each eye +1.0 logMAR (Snellen equivalent to 20/200) or better by ETDRS in each eye. 5. Central corneal thickness of ≥ 400 and ≤ 620 μm in each eye. 6. Able and willing to give signed informed consent and follow study instructions. 7. In the opinion of the Investigator, the subject is able to safely discontinue current ocular hypotensive medication(s), when a washout is required. Exclusion criteria: <u>Ophthalmic:</u> 1. Known hypersensitivity to any kinase inhibitors, any excipient or preservative of the formulation or to topical anesthetics or fluorescein.

	2. Unmedicated IOP of > 36 mm Hg in either eye at any time point at Visit 2. 3. History of intraocular implant for IOP treatment, glaucoma filtering surgery, placement, or removal of minimally invasive glaucoma implant (MIGS) in the study eye. 4. History of laser IOP lowering surgery within 6 months of Visit 1 in the study eye. • Note: Laser peripheral iridotomy for narrow angle is allowed if performed 3 months or more prior to Visit 1. 5. Ocular trauma within the past six months, or surgery involving the ocular surface (including cataract surgery) or non-IOP-lowering laser treatment within the past three months of Visit 1 in the study eye. 6. Refractive surgery in the study eye (including but not limited to radial keratotomy, Photorefractive Keratectomy [PRK], Laser-Assisted *in situ* Keratomileusis [LASIK], etc.). • Refractive surgery planned during study participation in either eye. 7. Have received intravitreal corticosteroid injection within 6 months or subtenon/subconjunctival steroid injection within 3 months of Visit 1 in either eye. 8. History or evidence of ocular infection, inflammation, clinically significant blepharitis, conjunctivitis, or of herpes simplex keratitis within 2 months of Visit 1 in either eye. 9. Unable or unwilling to avoid wearing of contact lenses from Visit 1 through the study. 10. Currently using 3 or more ocular hypotensive medications prior to screening in either eye (combination medications count as 2 medications). 11. Ocular medication of any kind within 28 days of Visit 2 in either eye other than: • Ocular hypotensive medications which must be washed out according to the provided schedule • Ocular Medication as part of an eye exam • Lubricating drops for dry eye 12. Clinically significant ocular disease in either eye (e.g. corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with the study. 13. Pseudoexfoliative, pigmentary, congenital, developmental or secondary glaucoma (e.g. neovascular, uveitic, pigmentary, lens-induced, steroid-induced, trauma induced or glaucoma associated with increased episcleral venous pressure) in either eye. 14. Closed angle forms of glaucoma in either eye • Shaffer grade < 3 (in 1 or more quadrants) • Gonioscopy within 3 months prior to Visit 1 is acceptable. 15. Cup-disc ratio of 0.7 or greater in either eye.

	16. Nerve fiber layer thickness assessment by Optical Coherence Tomography (OCT) documents thinning of the NFL into the abnormal range for either eye. • If, in the opinion of the investigator, the thinning of the NFL may be attributed to other ocular features (including but not limited to optic nerve drusen, myopia, chorioretinal scars), then the subject is allowed. 17. Subjects with visual fields with substantial glaucomatous loss (e.g., Bjerrum scotoma, blind spot enlargement) for whom washout and potential randomization would be unsafe. 18. In addition to the above criteria, glaucomatous damage in either eye so severe that washout of ocular hypotensive medications for up to 5 weeks and treatment for 3 weeks (for subjects randomized to vehicle control) is not judged safe in the opinion of the Investigator. • Note: Subjects may be changed to a another IOP lowering therapy with a shorter washout period as long as the appropriate washout is met prior to Visit 2. 19. Any abnormality preventing reliable applanation tonometry of either eye. <u>General/Systemic:</u> 20. Laboratory tests indicative of any clinically significant disease in the opinion of the Investigator. 21. Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, hepatic, renal, cardiovascular or endocrine disorders) which might interfere with the study in the opinion of the Investigator. 22. Participation in any study involving an investigational product within the past 30 days of Visit 1. 23. Changes of systemic beta blockers during the study that in the opinion of the Investigator could have a substantial effect on IOP within 30 days prior to Visit 1 or anticipated during the study. 24. Have received systemic corticosteroids (oral, injectable, inhaled) within 30 days of Visit 1 or planned use during the study. • Note: Topical dermatologic steroids are allowed if used for less than 3 consecutive days on no more than 3 separate areas of the body within 30 days of Visit 1 and the dosage is not expected to increase during the study. • Intranasal steroids are allowed if used less than or 4 times per week within 30 days of Visit 1 and the dosage is not expected to increase during the study. 25. History of substance abuse within 1 year of Visit 1 26. Subjects that are employees or relatives of employees at the clinical site. 27. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. • Females of childbearing potential with a positive urine pregnancy test (UPT) result at Visit 1 or Visit 2 are excluded.

	• An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization.
Investigational product(s):	VVN539 ophthalmic solution 0.02% (3mL in 5 mL bottles) VVN539 ophthalmic solution 0.04% (3mL in 5 mL bottles) VVN539 ophthalmic solution vehicle (3mL in 5 mL bottles)
Dosing regimen:	Both eyes (OU), q.d. (morning) for 7 days, then q.d. (evening) for 7 days, and then b.i.d. for 7 days.
Assessments/Evaluations:	Efficacy: • IOP for efficacy will be measured by Goldmann applanation tonometry at 8:00AM, 10:00AM and 4:00PM at Visits 2, 4, 5 and 6. Safety: • Adverse event monitoring • Best Corrected Visual Acuity (ETDRS) • IOP • Biomicroscopy of anterior segment • Central corneal thickness • Cup-disc ratio • Ophthalmoscopy (dilated) • Heart rate and blood pressure (BP) • Blood chemistry, hematology
Duration of study:	There are a total of 6 clinical visits over 8 weeks (up to 5 weeks of washout and 3 weeks of study treatment)
Statistical methods:	With a sample size in each group of 20, the study will have 80% power to detect a difference of 3.0 mm Hg between an VVN539 dose compared to vehicle at each diurnal time point assuming a common standard deviation of 3.3 mm Hg, $\alpha = 0.05$ (two-tailed). There is no correction for multiplicity for multiple time points or comparisons for high or low VVN539 doses. The primary endpoint for this study is to compare mean IOP at each diurnal time point (8AM, 10AM, and 4PM) at Visit 4 (Day 7), Visit 5 (Day 14) and Visit 6 (Day 21) for two doses of VVN539 compared to vehicle using data from the study eye. Time-matched longitudinal models adjusting for baseline and including a random effect for center will be used to test time-specific comparisons. Data from Days 7, 14, and 21 will be analyzed using mixed-model repeated measures (MMRM) with an unstructured covariance assumed for each treatment with treatment, visit, and visit by treatment interaction as a fixed effects, baseline measurement as a covariate, and a random effect for site. Sensitivity analyses include a time-matched last observation carried forward (LOCF) of the last available IOP measurement as well as analysis of covariance (ANCOVA) analyses at each visit. Additional sensitivity analyses will be performed on the PP Analysis Set as necessary.

	Analyses of change from baseline and observed and change from baseline for diurnal IOP will be performed in a manner similar to the primary efficacy analysis. Safety analyses will be performed on all subjects in the Safety Analysis Set. The assessment of safety will be based on the summary of ocular and non-ocular treatment emergent adverse events (TEAEs), Best Corrected Visual Acuity (BCVA), central corneal thickness, heart rate and blood pressure, clinical laboratory tests, and ophthalmic exams using slit-lamp biomicroscopy and dilated ophthalmoscopy. Summaries will be provided by treatment group, and for ocular assessments separately by study-eye and non-study-eye.

9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

The primary objective of this study is to evaluate the ocular hypotensive efficacy of 2 concentrations of VVN539 in subjects with ocular hypertension (OHT) or primary open angle glaucoma (POAG). The secondary objective is to evaluate the ocular and systemic safety of the 2 concentrations in this subject population.

Figure 1 summarizes the design of the study.

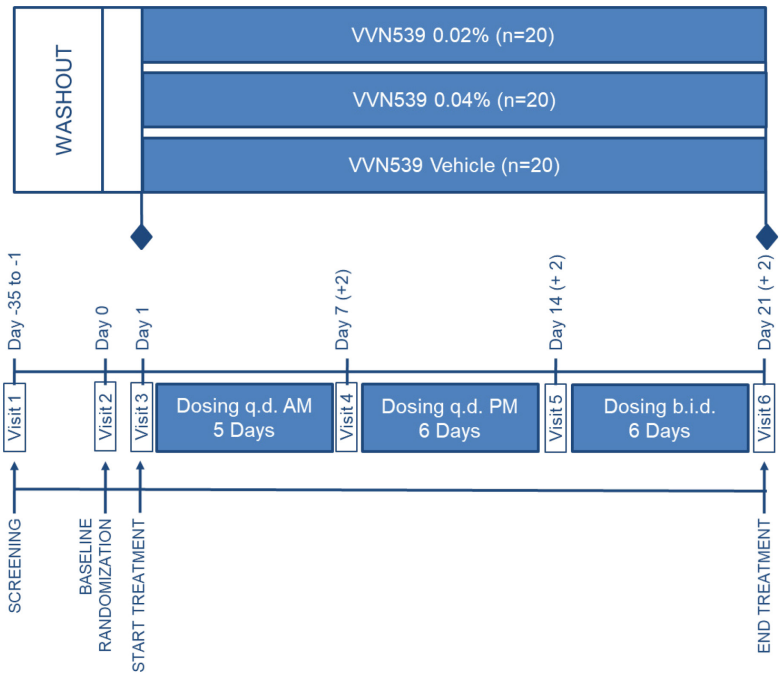

Figure 1: Study Schematic

9.5.1.1. Visit and Procedure Schedule

See Table 1 in Appendix I for a complete visit and procedure schedule.

9.5.1.2. Demographics and Baseline Characteristics

9.5.1.2.1. Demographics and Disease Characteristics

Demographic characteristics such as age (years), sex, race, and ethnicity and the normality of nerve fiber layer thickness will be collected at Visit 1. Baseline diurnal intraocular pressure (IOP) will be collected at Visit 2.

9.5.1.2.2. Medical and Surgical History

Ocular and non-ocular medical history will be collected at Visits 1 and 2.

9.5.1.2.3. Prior and Concomitant Medications

All medications that the subject has taken 2 months prior to Visit 1 and/or is taking through Visit 6 (or discontinuation from the study) will be recorded in the subject chart and the eCRF. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication and whether or not the medication was taken due to an AE will be recorded for each medication.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the case report form are concomitant prescription medications, over-the-counter medications and supplements.

9.5.1.2.4. Prohibited and Rescue Medications

Table 2 of the protocol lists medications and procedures that are exclusionary for the study and/or are prohibited during study participation.

Any subject who has an elevated IOP that the PI considers unsafe for the subject may be rescued and placed on appropriate alternate therapy. The choice of rescue medication is at the Investigator's discretion. Rescue medication should be entered into the eCRF with annotation indicating that the medication was used for rescue.

Rescued subjects will be considered as treatment failures, and the need for rescue therapy will not be considered an adverse event (AE). Rescued subjects will stop the investigational product and should not be withdrawn from the study.

The following guidance is provided to Investigators for rescue and the decision to rescue is at the discretion of the investigator's judgement:

- Ocular hypotensive medication (other than IP) is prohibited during study participation unless the subject is rescued.
- If the subject's IOP is > 36 mmHg, the Investigator may recheck the IOP within 3 day of the visit and rescue medication may be considered if the IOP remains elevated.
- Rescued subjects should discontinue the investigational product.
- Rescued subjects should continue in the study for safety follow-up after receiving the rescue medication.

9.5.1.3. Efficacy Assessments

9.5.1.3.1. Primary Efficacy Assessment(s)

The study has a single primary assessment that compares the mean IOP in the study eye at each diurnal time point (8AM, 10AM, and 4PM) at Visits 4, 5, and 6 for two doses of VVN539 compared to vehicle.

9.5.1.3.2. Secondary Efficacy Assessments

Secondary efficacy assessments will examine:

- Change from baseline (Visit 2) in IOP at each diurnal time point to Visits 4, 5, and 6;
- Change from baseline (Visit 2) in diurnal IOP to Visits 4, 5, and 6. Diurnal IOP is the average of 8AM, 10AM, and 4PM measurements at a given visit.

9.5.1.3.3. Description of Efficacy Assessments

IOP measurements will be performed utilizing a Goldmann applanation tonometer affixed to a slit lamp according to the Investigator's standard procedure (two-person reading method). Measurements will be taken with the subject seated. 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.

At Visit 1, IOP will be measured once during screening visit.

At Visit 3, IOP will be measured once at 8:00AM (±30 minutes) prior to the first q.d. AM dosing.

At Visits 2, 4, 5, and 6 diurnal IOP will be measured:

- At 8:00AM (±30 minutes), 10:00AM (±30 minutes) and 4:00PM (±30 minutes)
- At Visits 4 and 6, the 8:00AM measurement will be taken prior to the AM dosing.

9.5.1.4. Safety Assessments

The safety of VVN539 ophthalmic solution will be evaluated using the following assessments.

1. Adverse event (AE) monitoring
2. Best corrected visual acuity (BCVA)
3. Slit-lamp biomicroscopy
4. Central corneal thickness
5. Dilated ophthalmoscopy
6. Heart rate and blood pressure
7. Clinical laboratory tests (blood chemistry, hematology)

9.5.1.4.1. Adverse Events

AEs will be monitored throughout the study. Subjects will be encouraged to report any adverse findings during the study whether or not they are related to IP. These can be collected either in an unsolicited fashion without any prompting or in response to a general question such as: "Have you noticed anything different since you started the study; began the IP, etc?"

All AEs will be captured on the appropriate eCRF. Information to be collected at minimum includes event description, onset, assessment of severity, relationship to IP, and outcome.

The Investigator will record all AEs with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening AE,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The severity of all AEs will be assessed by the Investigator and graded as follows:

- **Mild:** requires minimal or no treatment and do not interfere with the subject's daily activities;
- **Moderate:** results in a low level of inconvenience or concern and may cause some interference with functioning;
- **Severe:** interrupts a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. The term "severe" does not necessarily equate to "serious".

All AEs must have their relationship to study intervention assessed by the Investigator who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the IP must always be suspect.

- **Unrelated:** no reasonable possibility that the administration of the IP caused the event, no temporal relationship between the IP and event onset, or an alternate etiology has been established.

- **Related:** is known to occur with the IP, is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

9.5.1.4.2. Best Corrected Visual Acuity (BCVA)

The BCVA will be measured on both eyes in LogMAR at every study visit using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. LogMAR is calculated as Baseline value + (n × 0.02); where the baseline value is the LogMAR number of the last line read (at least one letter read correctly in this line), "n" is the total number of letters missed up to and including the last line read, and "0.02" is the value for each letter.

9.5.1.4.3. Slit-Lamp Biomicroscopy

The slit-lamp biomicroscopy exam will be performed to examine eye structures for each eye at each study visit.

This procedure will be performed in the same manner for all subjects observed at the Investigator's site. The site will record all ABNORMAL findings in the source document and the Investigator will evaluate the ABNORMAL findings as Not Clinically Significant (NCS) or Clinically Significant (CS). CS and NCS ABNORMAL findings will be recorded in the source documentation. However, only ABNORMAL CS descriptions from Visits 3-6 will be captured in the eCRF as AE.

Findings for the anterior chamber (cells and flare), eyelid (hyperemia and edema), conjunctiva (hyperemia, edema (chemosis), discharge/exudate), cornea (edema), iris color, pupil, lashes, and lens will be collected.

9.5.1.4.4. Central Corneal Thickness

Corneal thickness evaluation (in microns) will be performed using a calibrated ultrasonic or optical pachymeter, provided that the same method is used for all measurements. Measurements will be taken in the central cornea after instilling topical anesthetic. A total of three readings will be obtained for each eye. Care should be taken to place the probe perpendicular to the corneal surface and to not a compress the cornea.

Pachymetry is performed at Visit 1 and Visit 6.

- At Visit 1, pachymetry within 3 months of the visit is acceptable.
- At Visit 6, Pachymetry is to be performed after the last IOP measurement.

9.5.1.4.5. Dilated Ophthalmoscopy

Dilated ophthalmoscopy will be performed at Visit 1 and Visit 6 and will include assessment of the retina for any abnormal findings and optic nerve head for pallor and cupping (cup to disc ratio). The status of the vitreous (including haze), retina (including vessels), macula, optic nerve will be determined as Normal or Abnormal. The cup-to-disc ratio will be recorded with two decimal points (e.g., 0.80).

9.5.1.4.6. Heart Rate and Blood Pressure

Heart rate and blood pressure will be measured at each study visit.

Heart rate will be measured after the subject has been seated for at least 5 minutes. The pulse rate will be measured over a 30-second period by palpitation at the wrist, and multiplied by 2. An electronic device may be used instead. The method of measurement (manual or electronic) must be documented in the subject records. Repeat measurements should be taken for out-of-range values. Confirmed heart rate readings outside the normal range must be evaluated by the Investigator for clinical significance.

Blood pressure will be measured after heart rate (while the subject is in a resting state). A sphygomomanometer with appropriate size cuff with a stethoscope will be used. A digital device may be used instead. All measurements will be obtained from the same arm using the same cuff size for all study visits. Repeat measurements should be taken for significantly high or low measurements. Confirmed BP readings outside the normal range must be evaluated by the Investigator for clinical significance.

9.5.1.4.7. Clinical Laboratory Tests (Blood Chemistry, Hematology)

Approximately 10 mL of blood will be obtained at Visit 1 and Visit 6. Fasting will not be required, therefore specific values may be out of the typical fasting range.

Abnormal laboratory values noted as clinically significant at Visit 6 that are changes from the Screening values are documented as AEs and is to be followed-up as appropriate.

The following serum chemistry and hematology parameters will be measured:

Chemistry	Hematology
Alanine aminotransferase (ALT)	Absolute/percent basophil count
Albumin	Absolute/percent eosinophil count
Alkaline phosphatase (ALP)	Absolute/percent lymphocyte count
Aspartate aminotransferase (AST)	Absolute/percent monocyte count
Bilirubin (total, direct, indirect)	Absolute/percent neutrophil count
BUN	Differential WBC
Calcium	Hematocrit (Hct)
Cholesterol (total, High-Density	Hemoglobin (Hgb)
Lipoprotein (HDL) and Low-Density	Mean corpuscular hemoglobin (MCH)
Lipoprotein (LDL))	Mean corpuscular hemoglobin conc. (MCHC)
Carbon dioxide	Mean corpuscular volume (MCV)
Chloride	Platelet count
Creatinine, serum	Red blood cells (RBC)
Glucose	White blood cells (WBC)
Lactate dehydrogenase (LDH)	
Potassium	

Sodium
Total protein
Triglycerides

9.5.2. Appropriateness of Measurements

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

9.5.3. Primary Efficacy Variable(s)

The primary efficacy endpoint for this study is to compare mean IOP at each diurnal time point (8AM, 10AM, and 4PM) at Visit 4 (Day 7), Visit 5 (Day 14), and Visit 6 (Day 21) for two doses of VVN539 compared to vehicle using data from the study eye.

To claim superiority, the two-sided 95% confidence interval estimates of the treatment differences in mean IOP between VVN539 and vehicle must exclude zero for all 9 time points.

9.5.4. Drug Concentration Measurements

No drug concentration measurements will be made for this study.

9.6. DATA QUALITY ASSURANCE

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

9.6.1. Training and Education of Investigators and Study Site Personnel

An Investigator Meeting will be held before study initiation and attended by the Investigators and/or Sub-Investigators from each study site, study coordinators from each study site, if possible, and personnel from the sponsor and the Contract Research Organization (CRO), Lexitas Pharma Services, Inc. (hereafter referred to as Lexitas). The purpose of this meeting is to ensure the Investigators and study coordinators are trained and instructed on the proper conduct of the clinical trial and ensure that all participants are aware of their obligations set out by the protocol, ICH guidelines, GCP guidelines, and other applicable regulatory requirements.

9.6.2. Monitoring of Study Sites

Lexitas Pharma Services, Inc. will conduct the clinical monitoring for this study. A clinical Monitoring Plan is to be used, which will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed and the distribution of monitoring reports.

9.6.3. Data Entry and Verification of Database Used for Analysis and Reporting

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site's Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to insure accurate interpretation of data. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into IBM Clinical Development, a 21 CFR Part 11-compliant data capture system provided by Lexitas Pharma Services, Inc. The data system includes password protection and

internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

9.6.4. Clinical Study Report

The final clinical study report will be reviewed, audited, and approved by medical, clinical, statistical, and regulatory staff from the sponsor, and key study contributors from Lexitas.

9.6.5. Inter-Laboratory Standardization Methods

Not applicable. A single, qualified, and certified central clinical laboratory will be used to analyze and report clinical laboratory data.

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

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

9.7.1. Statistical and Analytical Plans

General Conventions

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

Number of subjects, minimums, and maximums will be calculated to the same number of decimal places as the source data. Means, medians, standard deviations, standard errors, and quartiles will be calculated to one more decimal place than the source data. Percentages will be calculated to the nearest one decimal place and will use the number of non-missing responses as the denominator, unless otherwise noted. Zero count cells will be displayed as “0” with percentage of (0%). Unless otherwise noted, summaries will be performed by the treatment group and presented in the order of: VVN539, 0.04%; VVN539, 0.02%; Vehicle.

Statistical tests will be presented as two-sided p-values rounded to four decimal places; p-values less than 0.0001 will be presented as '<0.0001' and p-values = 1 will be presented as '>0.9999' in all tables. Unless otherwise indicated, statistical testing will be carried out at the $\alpha = 0.05$ significance level.

Baseline values will be defined as the last scheduled or unscheduled measurement prior through Visit 2. Ocular measurements will use the most recent measurement for each eye.

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

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

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

Strata and Covariates

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

Subgroups

Not applicable.

Multiplicity

Time-matched longitudinal models adjusting for baseline and including a random effect for center will be used to test time-specific superiority comparisons as well as the overall superiority hypothesis using 95% confidence intervals. To claim study success for the primary endpoint based on the model, the two-sided 95% confidence interval estimates of the treatment differences in mean IOP between VVN539 and vehicle must exclude zero for all 9 time points (8AM, 10AM, and 4PM at Visits 4, 5, and 6). No adjustment to the individual confidence intervals is required since all criteria need to be met to claim superiority.

Comparisons will be made first between VVN539, 0.04% versus vehicle. If the treatment differences for all 9 time points are statistically significant, testing will proceed to VVN539, 0.02% versus vehicle.

Missing Data and Outliers

Every attempt will be made to capture all study data. The primary analysis will be analyzed using observed data assuming missing at random (MAR) using a longitudinal model (mixed model repeated measures, MMRM). Sensitivity analyses of the primary endpoint will be performed utilizing time-matched last observation carried forward (LOCF) of the last available IOP measurement.

Safety analyses will use observed data only.

Visit Windows

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

Missing Dates

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

- For start dates, if the given year (or year-month) is the same as study drug administration, the start date will be imputed as study drug administration date; otherwise, missing month-day (or day) will be imputed as ’01-01’ (or ’01’).

- For stop dates, missing months will be imputed as '12' and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used.

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

Interim Analysis

There is no unmasked efficacy or futility interim analysis for this study.

9.7.1.1. Analysis Populations

9.7.1.1.1. Populations

The Full Analysis Set (FAS) consists of all subjects who were randomized. Subjects will be analyzed in the group to which they were randomized. This set will be used for the analysis of all efficacy endpoints as the primary analysis.

The Per Protocol (PP) Analysis Set will include all subjects who completed study-required treatment and who followed the protocol without significant deviations. The determination of significant protocol violations, including the use of prohibited medications, will be made prior to locking the final database and unmasking. Subjects will be analyzed in the group to which they were treated.

The Safety Analysis Set will include all subjects who took at least one dose of investigational product as indicated on the dosing record. Subjects will be analyzed in the group according to the treatment received. All safety variables will be analyzed using the Safety Analysis Set and only observed data will be included (i.e., missing data will remain missing for the safety analysis).

A listing of subjects excluded from the analysis sets will be provided.

9.7.1.1.2. Analysis Eyes

The study eye is defined as meeting all inclusion criteria and no exclusion criteria, and with the higher IOP at 8:00AM at Visit 2. Should both eyes have the same IOP and meet all inclusion criteria and no exclusion criteria, then the right eye will be the study eye.

Efficacy analyses will focus on the study eye only, though supportive analyses will also be presented by the non-study eye, irrespective of qualification. Ophthalmic safety analyses will be presented by the study eye and non-study eye.

9.7.1.2. Analysis of Subject Disposition

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

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

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

- Number of patients screened;
- Number and percentage of subjects randomized;
- Number and percentage of subjects randomized with any protocol deviation;
- Number and percentage of subjects treated;
- Number and percentage of subjects treated with any protocol deviation;
- Number and percentage of subjects treated who completed the study through Visit 6 (Day 21);
- Number and percentage of subjects treated who discontinued from the study;
- The reasons for study discontinuation;
- Number and percentage of subjects withdrawn from study drug due to elevated IOP and subsequent rescue treatment;
- Number and percentage of subjects attending each visit.

A listing of subjects who do not meet all inclusion criteria or meet exclusion criteria will be provided. A table of major protocol deviations will be presented using the FAS.

9.7.1.3. Analysis of Demographic and Baseline Characteristics

9.7.1.3.1. Demographics and Disease Characteristics

Demographic and baseline disease characteristics including age (years), age group (18-<45, ≥45), sex, race, ethnicity, iris color, study eye (OD/OS), normality of nerve fiber layer thickness, baseline diurnal IOP of the study eye, and baseline IOP at 8:00 AM, 10:00 AM, and 4:00 PM will be summarized descriptively by treatment group and overall using the FAS, Per Protocol, and Safety Analysis Sets. For categorical parameters, the percentages will be calculated overall and based on the number of subjects in each treatment group based on non-missing observations.

Ocular baseline characteristics for central corneal thickness (average of three measurements), gonioscopy, and visual field will be summarized by study eye and non-study eye.

9.7.1.3.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 24.1, Mozzicato, 2009). The frequency and percentage of subjects with any medical history will be summarized by treatment group using the FAS. System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within VVN539, 0.04%;
2. Descending frequency within VVN539, 0.02%;
3. Descending frequency within Vehicle;
4. PT in alphabetical order.

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

9.7.1.3.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) (Version 2021-09, Lagerlund et al., 2020) for anatomical therapeutic chemical (ATC) classification and preferred drug name.

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

1. Descending frequency within VVN539, 0.04%;
2. Descending frequency within VVN539, 0.02%;
3. Descending frequency within Vehicle;
4. PT in alphabetical order.

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

Prior medications are defined as any medications that started and stopped prior to the date of first dose of double-masked study drug. Concomitant medications are defined as any medications that (1) start prior to the date of first dose of double-masked study drug and stop or are ongoing at or after the date of first dose of double-masked study drug; or (2) start at or after the date of first dose of double-masked study drug. Medications started after Visit 6 or withdrawal from the study are not considered concomitant.

9.7.1.4. Analysis of Study Medication Adherence and Exposure

Treatment adherence and exposure will be assessed by the data from the Study Drug Administration and Treatment Adherence eCRFs and will be summarized by treatment group using the Safety Analysis Set.

Treatment adherence was assessed by 3 questions: Did subject return (clinic staff), and two subject reported measures: Did subject miss any doses, and if so, how many doses missed. Descriptive statistics will be presented for these measures by visit by treatment group.

Duration of exposure of double-masked study drug will be calculated as the total number of days from the first double-masked dose date to the last double-masked dose date plus 1 (one) regardless of temporary dose interruptions. Other dosing durations are calculated as follows:

- For q.d. morning dosing, duration of exposure is calculated as Visit 4 date - Visit 3 date + 1. If the date of last dose is between Visit 3 and Visit 4 date (inclusive), the Visit 4 date is replaced with the date of last dose.
- For q.d. evening dosing, duration of exposure will be calculated as Visit 5 date - Visit 4 date. If the date of last dose is between Visit 4 + 1 date and Visit 5 date (inclusive), the Visit 5 date is replaced with the date of last dose.
- For b.i.d. dosing, duration of exposure will be calculated as Visit 6 - Visit 5 date. If the date of last dose is between Visit 5 + 1 date and Visit 6 date (inclusive), the Visit 6 date is replaced with the date of last dose.

9.7.1.5. Analysis of Efficacy

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

In general, efficacy analyses will be performed using the FAS and the observed data at each Visit for the study eye. Only data prior to rescue therapy will be summarized and imputation strategies for missing data will only consider data prior to rescue therapy. The primary and secondary endpoint analysis will also be performed using the Per Protocol Analysis Set.

For subjects who discontinue the study prior to the Visit 6, data collected using Early Termination eCRFs will not be summarized separately unless the termination occurred on a scheduled visit (within the visit windows of a particular visit).

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

9.7.1.5.1. Primary Efficacy Analysis

Primary Estimands: The primary estimands are the treatment differences between VVN539 and vehicle at 8:00 AM, 10:00 AM, and 4:00 PM at each of Days 7, 14, and 21 in the study eye using the FAS. The primary estimands treat subjects as if they do not receive rescue therapy.

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

Endpoint: Observed IOP measurements at each time point in the study eye.

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

Population-level Summaries: The difference in the mean IOP at the nine time points of interest and their corresponding p-values and 95% confidence intervals.

Intercurrent Events and Strategies to Address Intercurrent Events

- Discontinuation of study therapy with continued participation in the study without receipt of rescue therapy
    - Treatment Policy – no imputation; use observed data
- Receipt of rescue therapy in the study eye
    - Hypothetical Approach – data for visits after the receipt of rescue therapy will be set to missing and will be analyzed assuming missing at random (MAR) using a longitudinal model (mixed model repeated measures, MMRM)
- Missing data without withdrawal or with withdrawal regardless of reason
    - Hypothetical Approach: visits that are missing data will be analyzed assuming MAR using MMRM

Time-matched longitudinal models adjusting for baseline and including a random effect for center will be used to test time-specific superiority comparisons as well as the overall superiority hypothesis using 95% confidence intervals. To claim study success for the primary endpoint based on the model, the two-sided 95% confidence interval estimates of the treatment differences in mean IOP between VVN539 and vehicle must exclude zero for all 9 time points (8AM, 10AM, and 4PM at Visits 4, 5, and 6). Comparisons will be made first between VVN539, 0.04% versus vehicle. If the treatment differences for all 9 time points are statistically significant, testing will proceed to VVN539, 0.02% versus vehicle.

Data from Days 7, 14, and 21 will be analyzed using MMRM with an unstructured covariance assumed for each treatment with treatment, visit, and visit by treatment interaction as a fixed effects, baseline measurement as a covariate, and a random effect for site. If the model fails to converge using this covariance structure, heterogenous Toeplitz, or compound symmetry will be implemented in this order until convergence is reached.

Sample code for the model run separately for 8AM, 10 AM, and 4 PM:

```
PROC MIXED DATA=indata;
       CLASS subject site visit treatment;
       MODEL IOP = baseline visit treatment visit*treatment / solution DDFM=KR;
       REPEATED visit / SUBJECT=subject TYPE=UN group = treatment;
       RANDOM site;
       LSMEANS visit*treatment / slice = visit CL diff;
RUN;
```

Sensitivity analyses include a time-matched last observation carried forward (LOCF) of the last available IOP measurement as well as analysis of covariance (ANCOVA) analyses at each visit with baseline measurement as a covariate. Percent of baseline and percent change from baseline

will also be performed as a sensitivity of the primary analysis. Additional sensitivity analyses will be performed on the PP Analysis Set as necessary.

9.7.1.5.2. Secondary Efficacy Analyses

Analyses of change from baseline in IOP at each time point and of observed and change from baseline in diurnal IOP will be performed in a manner similar to the primary efficacy analysis. Percent of baseline and percent change from baseline of diurnal IOP will also be performed.

9.7.1.6. Analysis of Safety

Safety will be evaluated by AEs, BCVA, slit-lamp biomicroscopy, central corneal thickness, dilated ophthalmoscopy, heart rate and blood pressure, and clinical laboratory tests (blood chemistry, hematology).

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

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

All visits will be included in listings.

9.7.1.6.1. Adverse Events

AEs are coded using MedDRA Version 24.1. Treatment-emergent adverse events (TEAE) are defined as events that start on or after the date of first dose of double-masked study drug up to and including the last dose of double-masked study medication. Ocular AEs are defined as those events for which an eye has been specified (OD, OS, or OU).

Ocular and non-ocular AEs will be summarized separately. Ocular AEs will be presented by study eye and non-study eye and overall (OU) if an event occurs in either eye.

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

Overall summaries of AEs by treatment will include:

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

The overall summaries of TEAEs will also include:

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

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

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

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

1. Descending frequency within VVN539, 0.04%
2. Descending frequency within VVN539, 0.02%
3. Descending frequency within Vehicle;
4. PT in alphabetical order.

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

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

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

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

9.7.1.6.2. Best Corrected Visual Acuity (BCVA)

Descriptive summaries of the observed values of logMAR at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes. A categorical analysis of subjects who lose 0.3 lines ETDRS in either eye at each visit or final visit will be conducted.

9.7.1.6.3. Slit-Lamp Biomicroscopy

The frequency and percentage of subjects with observed values of each category as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for both eyes for the following measures of interest: anterior chamber cell, anterior chamber flare,

and conjunctive hyperemia. The percentages are calculated based on the number of subjects at each visit in each treatment group of the Safety Analysis Set.

9.7.1.6.4. Dilated Ophthalmoscopy

The frequency and percentage of subjects with observed values of each categorical response at Visits 1 and 6 as well as the categorical shift from baseline at Visit 6 will be tabulated for both eyes. The percentages are calculated based on the number of subjects at each visit in each treatment group of the Safety Analysis Set.

Descriptive summaries of the observed cup-to-disc ratio at Visits 1 and 6 as well as the change from baseline at Visit 6 will be presented for both eyes.

9.7.1.6.5. Heart Rate and Blood Pressure

Descriptive summaries of the observed values for heart rate and blood pressure at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented.

Repeat measurements of cardiovascular outcomes will be taken for out-of-range measurements. The most recent (latest measurement) at each visit will be summarized in tables.

9.7.1.6.6. Clinical Laboratory Tests (Blood Chemistry, Hematology)

Descriptive summaries of the observed test results at Visits 1 and 6 as well as the change from baseline at Visit 6 will be presented for blood chemistry and hematology labs. The frequency and percentage of subjects with observed values of Low, Normal, High at baseline and Visit 6 will be tabulated. The percentages are calculated based on the number of subjects at each visit in each treatment group of the Safety Analysis Set.

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

The results of pregnancy tests for women of childbearing potential will be presented in a listing.

9.7.2. Determination of Sample Size

With a sample size in each group of 20, the study will have 80% power to detect a difference of 3.0 mmHg between an VVN539 dose compared to vehicle at each diurnal time point assuming a common standard deviation of 3.3 mmHg, $\alpha = 0.05$ (two-tailed).

There is no correction for multiplicity for multiple time points or comparisons for high or low VVN539 doses.

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

9.8.1. Protocol Amendments

Amendment 1 of protocol made the following notable changes:

- Revised exclusion criteria to minimize the risk of study subjects randomized to vehicle for potential glaucomatous loss;
- Allowed investigators to switch subjects who were previously treated with an ocular hypotensive medication with a 4 week washout period to a ocular hypotensive medication with a shorter washout period provided the appropriate washout is met prior to Visit 2.

9.8.2. Changes from Protocol-Specified Analyses

Version 2 of the statistical analysis plan clarifies the inconsistent presentation of analyses with regards to rescue and prohibited medications. This version clarifies that data prior to rescue treatment will be used for efficacy analyses. Minor corrections to sample proc mixed code were made as well.

REFERENCES

1. Mozzicato P. (2009). MedDRA: An overview of the medical dictionary for regulatory activities. Pharmaceutical Medicine 23: 65-75.
2. Lagerlund O, Strese S, Fladvad M & Lindquist M. (2020). WHODrug: A global, validated and updated dictionary for medicinal information. Therapeutic Innovation & Regulatory Science 54: 1116–1122.
3. SAS Institute Inc. What's New in Base SAS® 9.4 and SAS® Viya®. (2013). SAS Institute Inc., Cary, NC, USA.
4. SAS Institute Inc. (2020). SAS/STAT User's Guide. SAS Institute Inc., Cary, NC, USA.

APPENDIX I: SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Study Period	Screening	Washout[1]	Baseline	Treatment Period			End of Treatment
Visit No.	**1**		**2**	**3**	**4**	**5**	**6**
Visit Window	**Day-35 to -1**		**Day 0**	**Day 1**	**Day 7 (+2)**	**Day 14 (+2)**	**Day 21 (+2)**
Informed consent[2]	**X**						
Ocular and medical history	**X**		**X**				
Demographics	**X**						
Inclusion/Exclusion criteria	**X**		**X**				
BCVA	**X**		**X**	**X**	**X**	**X**	**X**
Biomicroscopy[3]	**X**		**X**	**X**	**X**	**X**	**X**
IOP	**X**			**X**[4,]			
Diurnal IOP[5]			**X**		**X**	**X**	**X**
Cup-to-disc ratio	**X**						**X**
Dilated ophthalmoscopy	**X**						**X**[6]
Pachymetry[7]	**X**						**X**
Gonioscopy[8]	**X**						

[1] Washout period: Prostaglandins, β-adrenoceptor antagonists, kinase inhibitors (4 weeks), adrenergic agonists (2 weeks), muscarinic agonists and carbonic anhydrase inhibitors (5 days)
[2] Informed consent will be obtained prior to the conduct of any study specified or associated procedures or evaluations.
[3] Biomicroscopy of anterior segment includes corneal epithelium, bulbar and lower conjunctiva, and lens.
[4] Measured at 8:00AM
[5] Measured at 8:00AM, 10:00AM and 4:00PM
[6] After the last IOP measurement
[7] Central corneal thickness will be measured at entry for IOP interpretation. Pachymetry performed within 3 months of screening is acceptable. Ultrasound and optical pachymetry is permissible provided that the same methodology is used at Visits 1 and 6.
[8] Gonioscopy performed within 3 months of Visit 1 is acceptable.

Study Period	Screening	Washout[1]	Baseline	Treatment Period			End of Treatment
Visit No.	**1**		**2**	**3**	**4**	**5**	**6**
Visit Window	**Day-35 to -1**		**Day 0**	**Day 1**	**Day 7 (+2)**	**Day 14 (+2)**	**Day 21 (+2)**
Visual field[9]	**X**						
Optical Coherence Tomography	**X**[10]						
Blood chemistry, hematology	**X**						**X**
BP, HR	**X**		**X**	**X**	**X**	**X**	**X**
Pregnancy test[11]	**X**		**X**				**X**
Randomization			**X**				
Study drug administration in clinic				**X**[12]	**X**[13]		**X**[13]
Dispense investigational product				**X**	**X**	**X**	
Collect study drug					**X**	**X**	**X**
Prior/Concomitant medications	**X**		**X**	**X**	**X**	**X**	**X**
Adverse event assessment				**X**	**X**	**X**	**X**
Abbreviation key: BCVA=best corrected visual acuity; BP=blood pressure; HR=heart rate; IOP=intraocular pressure							

[9] Visual field within 3 months of Visit 1 is acceptable, provided that it is reliable and meets the requirement for automated threshold visual field (e.g., 30-2 or 24-2 Humphrey). Unreliable entry fields must be repeated prior to study drug dispensation.

[10] Optical Coherence Tomography within 3 months of Visit 1 is acceptable.

[11] Women of childbearing potential only

[12] After 8:00AM IOP measurement

[13] After 8:00AM and prior to 10:00AM IOP measurement