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Clinical Study VVN461-CS201
Statistical Analysis Plan
19 January 2024

Statistical Analysis Plan for a phase 2, double-masked, randomized, vehicle-controlled study of VVN461 Ophthalmic Solution in treating post-operative ocular inflammation in subjects undergoing routine unilateral cataract surgery

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SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACC	Anterior Chamber Cell
ACF	Anterior Chamber Flare
AE	Adverse Event
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical Classification
BCVA	Best Corrected Visual Acuity
CELR	Cataract Extraction And Lens Replacement
CFB	Change From Baseline
CRF	Case Report Form
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
IOP	Intraocular Pressure
IP	Investigational Product
MMRM	Mixed-Effect Repeated Measures
NPRS	Numeric Pain Rating Scale
OD	Right Eye
OS	Left Eye
OU	Both Eyes
PP	Per Protocol
PT	Preferred Term
QID	Four Times A Day
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan

SD	Standard Deviation
SOC	System Organ Class
SUN	Standardization Of Uveitis Nomenclature
TEAE	Treatment-Emergent Adverse Events
US	United States
WHODRUG	World Health Organization Drug Dictionary
WOCBP	Women Of Childbearing Potential

PROTOCOL SYNOPSIS

Title:	A phase 2, double-masked, randomized, vehicle-controlled study of VVN461 Ophthalmic Solution in treating post-operative ocular inflammation in subjects undergoing routine unilateral cataract surgery
Phase:	2
Design/Conduct:	This is a multicenter, double-masked, randomized, vehicle-controlled, parallel comparison study conducted at sites in the United States (US) in subjects undergoing routine unilateral cataract extraction and lens replacement (CELR) surgery via phacoemulsification
Objectives:	**Primary:** Evaluate the ocular efficacy of 2 different doses of VVN461 Ophthalmic Solution in treating post-operative ocular inflammation associated with cataract surgery compared with the ocular efficacy of a matching Vehicle **Secondary:** Evaluate the safety of VVN461
Endpoints:	**Primary Endpoint:** • Proportion of subjects with anterior chamber cell (ACC) Grade 0 in the study eye at Visit 6 (Day 14) **Secondary Endpoints:** • Proportion of subjects with ACC Grade 0 in the study eye at Visit 5 (Day 7) • Proportion of subjects with anterior chamber flare (ACF) Grade 0 in the study eye at Visit 6 (Day 14) • Proportion of subjects with ACF Grade 0 in the study eye at Visit 5 (Day 7) • Proportion of subjects requiring rescue medication before Visit 6 (Day 14) **Exploratory Endpoints:** • Mean change from baseline (CFB) in ACC Grade in the study eye at each visit • Mean CFB in ACF Grade in the study eye at each visit • Proportion of subjects with no post-operative ocular pain in the study eye at Visit 6 (Day 14) • Proportion of subjects with no post-operative ocular pain in the study eye at Visit 5 (Day 7)
Population Studied:	Approximately 90 completed subjects (30 per group) who have undergone routine unilateral CELR surgery via phacoemulsification without surgical complication. Subjects who meet all inclusion criteria will be eligible for study participation.

	Inclusion Criteria: 1. ≥21 years of age and in good general health at Visit 1 (Screening) 2. Willing and able to provide informed consent and provide relevant privacy authorization(s) 3. Willing and able to comply with study requirements and visit schedule 4. Clear ocular media (other than cataract) in the study eye 5. Planning to undergo routine unilateral CELR surgery via phacoemulsification extraction and implantation of an intraocular lens. **Allowed** in the study eye at Visit 2 (Day of Surgery): a. Limbal relaxing incisions (laser-assisted and non-laser) b. Intracameral injections and intracameral medications, excluding those identified in Exclusion Criterion #2 6. At Visit 1 (Screening), has pinhole best corrected visual acuity (BCVA) ≤0.2 Logarithm of the Minimum Angle of Resolution (LogMAR) (i.e., 20/32 Snellen) in the study eye as assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) 7. At Visit 1 (Screening), has BCVA ≤1.0 LogMAR (i.e., 20/200 Snellen) in the non-study eye due to pathology other than cataract as assessed using ETDRS 8. Able to self-administer eye drops 9. At Visit 3 (Baseline/Randomization; Day 1), has ACC Grade ≥2 in the study eye Subjects who meet any of the following exclusion criteria will not be eligible for study participation. **Exclusion Criteria:** **Ophthalmic (Either Eye)** 1. Any ocular pain at Visit 1 (Screening) 2. Used within 1 week before Visit 1 (Screening), or be planning to use during the study, corticosteroids, oral or topical non-steroidal antiinflammatory drugs (NSAIDs), or Omidria® (i.e., phenylephrine and ketorolac injection) 3. Moderate to severe lid, conjunctival, or corneal findings at Visit 1 (Screening) 4. Corneal abnormality (e.g., stromal, epithelial, or endothelial dystrophies, including epithelial basement membrane dystrophy) 5. History of chronic/recurrent inflammatory eye disease (e.g., scleritis, any uveitis, herpes keratitis) 6. Any signs of intraocular inflammation (cell/flare) at Visit 1 (Screening) 7. Intraocular pressure (IOP) ≥24 mmHg at Visit 1 (Screening)

	Ophthalmic (Study Eye) 8. Using or unwilling to forgo contact lens use within defined windows before Visit 2 (Day of Surgery) and for the duration of the study a. Polymethyl methacrylate contact lenses (6 months before surgery and throughout study) b. Gas permeable rigid lenses (1 month before surgery and throughout study) c. Extended wear or daily soft lenses (7 days before surgery and throughout study) 9. Known pathology that may affect visual acuity, particularly retinal changes that affect vision (e.g., macular degeneration, cystoid macular edema, proliferative diabetic retinopathy) 10. Capsule or zonular abnormalities with pre-operative crystalline lens tilt or decentration (e.g., Marfan's syndrome) or abnormalities that may affect post-operative centration or tilt of the crystalline lens (e.g., pseudoexfoliation syndrome) 11. History of moderate to severe ocular trauma with the possibility of previous zonule dehiscence 12. Ocular or periocular surgical interventions within defined windows before Visit 1 (Screening) a. Microinvasive glaucoma surgery, any incisional ocular surgery, or intracameral drug depot to lower IOP (any history) b. Intraocular surgery (6 months) c. Laser surgery, limbal relaxing incision procedure, eyelid surgery (3 months) 13. Pupil abnormalities (e.g., non-reactive, tonic pupils, abnormally shaped pupils, pupils that do not dilate at least 3.5 mm under mesopic/scotopic conditions) 14. Keratoconus or significant irregular astigmatism on pre-operative ocular topography 15. Have a condition, or be in a situation, that may put the subject at significant risk of complex surgery and surgical complications that would lead to withdrawal from the study **Ophthalmic (Non-study Eye)** 16. Underwent cataract surgery <14 days before Visit 1 (Screening) or, during the study, will require cataract surgery <1 day after Visit 2 (Day of Surgery) **General** 17. Within 30 days before Visit 1 (Screening), participated in an investigational drug or device study, or have used an investigational drug or device

	18. Allergy or hypersensitivity to the investigational product (IP) or its excipients 19. Significant systemic disease (e.g., uncontrolled diabetes; myasthenia gravis; hepatic, renal, cardiovascular, or endocrine disorders) 20. Uncontrolled systemic disease, defined as, within 30 days before Visit 1 (Screening), a change in disease status or medications that may put the subject at increased risk or confound interpretation of study results 21. Changes within 30 days before Visit 1 (Screening), or anticipated changes during the study, to the dosage of systemic medication that could have a substantial effect on IOP 22. Known bleeding tendencies 23. Acute or chronic disease or illness that would put the subject at increased risk or confound interpretation of study results (e.g., autoimmune disease, connective tissue disease, immunodeficiency, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.) 24. Requires, is likely to require, or is unwilling to discontinue the use of prohibited medications 25. Pregnant, nursing, or planning a pregnancy during the study 26. Unwilling or unable to use an acceptable method of contraception throughout the study if a woman of childbearing potential (WOCBP) 27. Unwilling or unable to use an acceptable method of contraception throughout the study if a male sexual partner of a WOCBP
Investigational Products:	• VVN461, 1.0% • VVN461, 0.5% • Vehicle
Dosing Regimen:	Approximately 90 completed subjects will be randomized in a 1:1:1 ratio to VVN461, 1.0%, VVN461, 0.5%, or a matching Vehicle that does not contain the active pharmaceutical ingredient (API). Subjects will administer 1 eye drop in the study eye four times a day (QID) for 14 days.
Assessments/Evaluations:	**Efficacy:** • Ocular inflammation (Standardization of Uveitis Nomenclature [SUN] Scale) • Post-operative ocular pain (Numeric Pain Rating Scale [NPRS]) **Safety:** • Adverse event (AE) monitoring (ocular and non-ocular) • Clinically relevant changes from baseline in the following: ▪ BCVA ▪ Slit lamp biomicroscopy ▪ IOP ▪ Dilated ophthalmoscopy

Duration of Study:	Subjects will be assessed at 7 visits over approximately 8 weeks. Visits will include a screening visit, the day of cataract surgery, a baseline/randomization visit, and efficacy and safety evaluation visits after 3, 7, and 14 days of QID dosing with IP in the study eye. The study will conclude with a safety follow-up visit approximately 1 week after the end of the planned dosing period.
Statistical Methods:	A sample size of approximately 90 completed subjects will be randomized in a 1:1:1 ratio to VVN461, 1.0%, VVN461, 0.5%, and a matching Vehicle that does not contain the API. With a sample size in each group of 30, the study will have 80% power to detect a difference of 35%, assuming a response rate of 30% in the Vehicle group, and a two-sided 0.05 significance level for a Pearson chi-square test. A drop-out rate of 10% is assumed, resulting in a total sample size of approximately 102 subjects. The Full Analysis Set (FAS) will consist of all subjects who are randomized. Subjects will be analyzed in the group to which they are randomized. This set will be used for the analysis of all efficacy endpoints as the primary analysis. The Per Protocol (PP) Analysis Set is a subset of the FAS and will include all subjects in the FAS who complete study-required treatment and who follow the protocol without significant deviations. The determination of significant protocol deviations will be made before database lock and unmasking. The Safety Analysis Set (SAF) will include all subjects who receive at least one dose of IP, 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 SAF, and only observed data will be included (i.e., missing data will remain missing for the safety analysis). **Primary Estimand**: The primary estimand is treatment difference between VVN461 (1.0% or 0.5%) and the Vehicle in the proportion of subjects with ACC Grade 0 at Visit 6 (Day 14) in the study eye using the FAS. **Target Population**: Subjects undergoing routine cataract surgery who meet the study entry criteria. **Endpoint**: Proportion of subjects with ACC Grade 0 in the study eye at Visit 6 (Day 14). **Treatment Condition(s)**: Treatment condition is based on randomized treatment. **Population-level Summary**: The difference in proportions in subjects with ACC Grade 0 in the study eye at Visit 6 (Day 14) and the corresponding p-value.

	The proposed procedures to handle missing data and intercurrent events are as follows:
	• Discontinuation of study therapy with continued participation in the study without receipt of rescue therapy
	  o Treatment Policy Approach – no imputation; use observed data
	• Receipt of rescue therapy (topical corticosteroid) in the study eye
	  o Composite Approach – subjects who receive rescue therapy at or before the assessment visit will be assumed to have failed the primary endpoint
	• Missing data with or without withdrawal, regardless of reason
	  o Hypothetical Approach – no imputation; analysis will be based on subjects who have an evaluable anterior chamber in the study eye at Visit 6 (Day 14)
	Pearson's chi-square will be used to test the primary endpoint between the 2 different doses of VVN461 versus the Vehicle. The primary analysis will also be performed on the PP Analysis Set.
	The secondary efficacy endpoints will include the proportion of subjects with ACC Grade 0, the proportion of subjects with ACF Grade 0, and the proportion of subjects requiring rescue medication. These endpoints will be analyzed regardless of the significance of the primary endpoint analysis. Secondary efficacy comparisons with p-values that claim statistical significance should be understood to be "nominal," as they will not be adjusted for multiplicity.
	Exploratory endpoints will be analyzed in a manner similar to the secondary endpoints. Mean CFB in ACC Grade and ACF Grade will be analyzed using mixed model repeated measures. The model will include treatment, visit, and treatment by visit interaction as fixed effects and a covariate for baseline measurement (where appropriate) with a random effect for site. An unstructured covariance among repeated measurements will be assumed. Only data from before the use of rescue medication will be included in these analyses. The proportion of subjects with no post-operative ocular pain in the study eye at Visit 5 (Day 7) and Visit 6 (Day 14) will also be analyzed. Exploratory efficacy comparisons with p-values that claim statistical significance should be understood to be "nominal," as they will not be adjusted for multiplicity.
	Safety analyses will be performed on all subjects in the SAF. The assessment of safety will be based on the summary of ocular and non-ocular AEs, BCVA, and ophthalmic examinations using slit lamp biomicroscopy and dilated ophthalmoscopy. Summaries will be provided by treatment group and, for ocular assessments, separately by eye.

9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

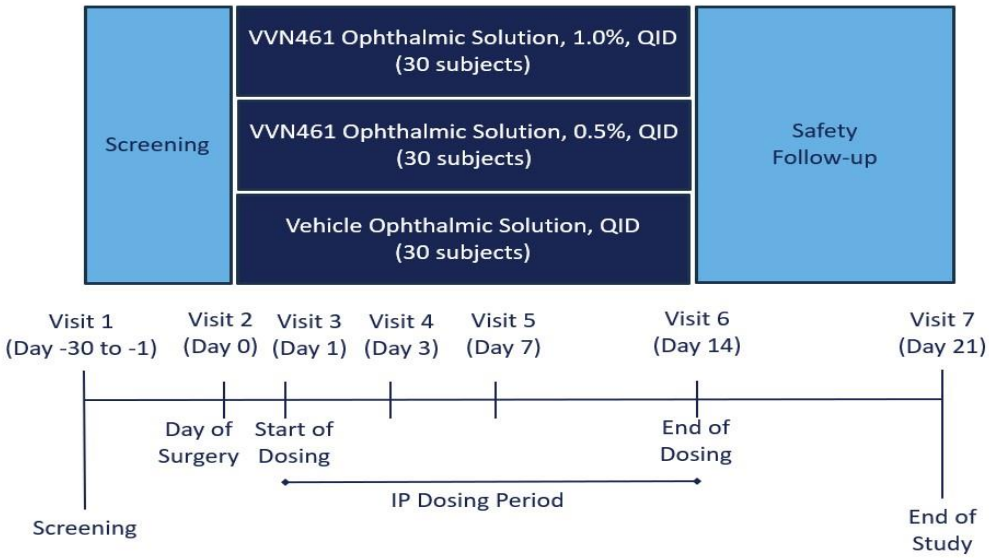
This is a phase 2, multicenter, double-masked, randomized, vehicle-controlled, parallel-comparison study conducted at sites in the US assessing the safety and ocular efficacy of VVN461 for treating post-operative ocular inflammation in subjects who undergo routine unilateral CELR surgery via phacoemulsification without surgical complication. Approximately 90 completed subjects (30 per group) will be randomized in a 1:1:1 ratio. Subjects will administer 1 eye drop in the study eye four times a day (QID) for 14 days. The IP in the study will be:

- VVN461, 1.0%
- VVN461, 0.5%
- Vehicle

There will be a total of 7 visits over approximately 8 weeks for each subject. A detailed Schedule of Procedures and Assessments is provided in Appendix 1: Schedule of Procedures and Assessment, and the general flow of the study is outlined in Figure 1.

Visits will include a screening visit, the day of cataract surgery, a baseline/randomization visit, and efficacy and safety evaluation visits after 3, 7, and 14 days of QID dosing with IP in the study eye. The study will conclude with a safety follow-up visit approximately 1 week after the end of the planned dosing period.

Figure 1: Study Schematic



Abbreviations: IP=investigational product; QID= *quater in die* (four times a day)

9.5.1.1. Visit and Procedure Schedule

Reference Appendix I.

9.5.1.2. Demographics and Baseline Characteristics

9.5.1.2.1. Demographics and Disease Characteristics

Demographic characteristics including age (years), sex, race, ethnicity, study eye(s), abbrieviated physical exam, blood pressure, and heart rate.

9.5.1.2.2. Medical and Surgical History

Ocular and non-ocular medical and surgical history will be collected at Visit 1 (Screening).

9.5.1.2.3. Prior and Concomitant Medications

All medications that the subject has taken within 30 days before Visit 1 (Screening) and through Visit 7 (Day 21; End of Study) or exit from the study will be recorded in the eCRF and the subject's source documents. Subjects will be asked for details about any changes in documented medications at all visits. 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 or as rescue will be recorded for each medication. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug). Restricted and prohibited prior and concomitant therapy are outlined in the protocol.

Subjects are eligible to be rescued at any time at the Investigator's discretion and placed on appropriate treatment or therapy. Although the use of rescue medication is allowable at any time, advance consultation with the Medical Monitor is preferred, if possible. If a delay in rescue would place the subject at unnecessary risk, the Investigator should proceed with rescue immediately.

The date of rescue medication administration, as well as the name of the rescue medication and dosage regimen, must be recorded as concomitant medications in the eCRF, with a note indicating that the medication was used for rescue. Subjects who require rescue will be counted as treatment failures and undergo follow-up safety assessments and procedures. Every attempt should be made to have subjects continue in the study for safety evaluations, even if subjects discontinue IP. The need for rescue medication itself will not be considered an AE.

9.5.1.3. Efficacy Assessments

Efficacy assessments will be conducted at the timepoints indicated on the Schedule of Procedures and Assessments (Appendix 1: Schedule of Procedures and Assessment). The efficacy assessments selected for the study are common tools within the field of ophthalmology and are generally recognized as reliable, accurate, and relevant in assessing the health and

function of human eyes. Efficacy assessments in the study include Anterior Chamber grading and the Numeric Pain Rating Scale (NPRS).

Anterior Chamber:

The severity of ocular inflammation will be assessed by the Investigator using a slit lamp and graded using the SUN Working Group Grading Scale for the Anterior Chamber (Table 1 Jabs et al., 2005).

Table 1 SUN[1] Working Group Grading Scale for the Anterior Chamber

Anterior Chamber Cells	
Grade	**Cells in Field[2]**
0	0
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50

Anterior Chamber Flare	
Grade	**Description**
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

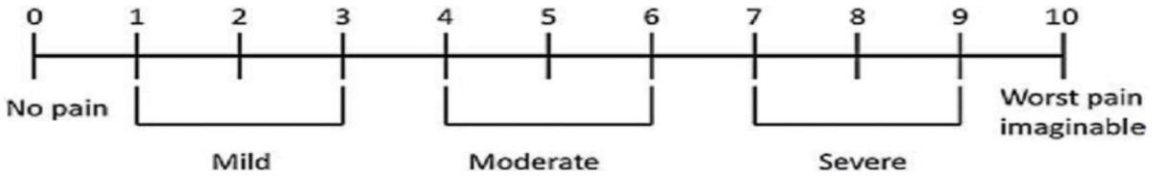
[1] SUN = Standardization of Uveitis Nomenclature

[2] Field size is a 1 mm by 1 mm slit beam

Numeric Pain Rating Scale:

Subjects will be asked at each post-operative visit, excluding Visit 7 (Day 21), to rate their ocular pain in the study eye using an 11-point NPRS scale. Subjects will be provided with pain score training to help harmonize subjective reporting across subjects and across sites.

"0" will represent no ocular pain. "10" will represent the worst ocular pain imaginable.



9.5.1.4. Safety Assessments

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 source documents and recorded in the 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 visit, the Investigator will inquire about the occurrence of AEs/SAEs since the last visit. SAEs 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 subject's condition deteriorates at any time during the study, it will be recorded as an AE.

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
    - Note: An AE is "life-threatening" if, in the view of the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death
- Insubject 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.

Severity of adverse events are described with the following scale:

- **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. Severe events are usually potentially life-threatening or incapacitating. The term "severe" does not necessarily equate to "serious."

Relationship of adverse events to study intervention are classified according to the following scale:

- **Unrelated**: The AE is completely independent of IP administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the Investigator.
- **Unlikely**: A clinical event, including an abnormal laboratory test result, whose temporal relationship to IP administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of IP) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Possibly**: Some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of IP). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).
- **Probably**: Evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the IP, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Definitely**: Clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to IP administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure, package insert, or device labeling, if it is not listed at the specificity or severity that has been observed, or if it is not consistent with the risk information described in the protocol, as amended. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure, package insert, or device labeling as occurring with a class of drugs (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the IP, but are not specifically mentioned as occurring with the particular IP under investigation.

The Investigator and contract research organization, in conjunction with the Medical Monitor and the Sponsor, will be responsible for determining whether an AE is unexpected (i.e., if the nature,

severity, or frequency of the event is not consistent with the risk information previously described for the IP).

9.5.1.4.2. Clinical Laboratory Assessments

9.5.1.4.2.1. Pregnancy

Individuals who are pregnant are not permitted to participate in the study. All pregnancies are to be reported from the time informed consent is signed until the end of the study (Visit 7). Subjects who report becoming pregnant or having a sexual partner (WOCBP) who has become pregnant will have IP withdrawn, will resume standard of care treatment for their condition, and will undergo safety follow-up visits and assessments.

Any report of pregnancy from a subject must be reported within 24 hours to the Sponsor or its delegate using the Pregnancy Report Form.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within approximately 30 calendar days after the initial notification and approximately 30 calendar days after delivery, if applicable.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to the Sponsor using the Serious Adverse Event Form. Elective abortions are not considered an SAE.

9.5.1.4.3. Vital Signs

Vital signs including seated systolic blood pressure, diastolic blood pressure and heart rate were obtained at Visit 1 (Screening).

9.5.1.4.4. Physical Examination

An abbreviated physical examination was obtatined at Visit 1 (Screening). Any clinically significant findings will be noted.

9.5.1.4.5. Slit Lamp Biomicroscopy

The slit lamp biomicroscopy examination will be performed with the slit lamp using a beam width and intensity that provides optimal evaluation of the anterior segment. The slit lamp biomicroscopy examination does not require fluorescein dye, although fluorescein dye may be used at Investigator discretion.

The slit lamp biomicroscopy examination must be performed before any procedures that would require contact with the eye and before the application of any dilating or anesthetic eye drops. The Investigator should use their standard examination technique. This procedure should be performed in the same manner for all subjects. When possible, the same Investigator should conduct all slit lamp biomicroscopy examinations at each visit for a given subject throughout the study to ensure consistent grading.

The Investigator must examine each eye (right eye first, then left eye) and record a grade for each tissue/structure listed in Table 2. Observations should be recorded in the source document and logged in the appropriate eCRF.

All subjects will undergo routine cataract surgery and implantation of an intraocular lens; therefore, all subjects will change from phakic to pseudophakic. This should not be considered an AE, as it is a planned part of the study design.

Table 2 Slit Lamp Tissue/Structure Assessments

Tissue/Structure	Grade
Eyelids & Adnexa	0 = Normal; no swelling/abnormality of the eyelid tissue 1 = Abnormal Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Conjunctiva **Conjunctival Hyperemia** **Edema (Chemosis)** **Conjunctival Discharge/Exudate**	0 = None 1 = Mild 2 = Moderate 3 = Severe
Cornea **Corneal Edema**	0 = None 1 = Mild 2 = Moderate 3 = Severe
Iris	0 = Normal 1 = Abnormal Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Tissue/Structure	**Grade**
Pupil	0 = Normal 1 = Abnormal Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Sclera	0 = Normal; without any redness/abnormality 1 = Abnormal Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Crystalline Lens Status	Phakic Pseudophakic Aphakic

9.5.1.4.6. Dilated Ophthalmoscopy (Fundus Exam)

A dilated fundus examination will be performed after the application of dilating drops (1% tropicamide) and upon the Investigator confirming with a pen light that both eyes are fully dilated after waiting 20 minutes. If the pupils are still responsive to light, an additional drop will be added to each eye, and the Investigator will wait to proceed until the pupils no longer respond to the pen light. Since dilating drops are being applied, the fundus examination must be performed after visual acuity, IOP, and slit lamp examination.

The evaluation will include assessment of the vitreous, retina, macula, choroid, optic nerve, and optic nerve cup-to-disc ratio. After the procedure, the Investigator will determine if findings are within normal limits or are abnormal. Only shifts from Normal to Abnormal, Clinically Significant, or from Abnormal, Not Clinically Significant, to Abnormal, Clinically Significant, will be recorded as AEs.

Vitreous	Normal: Absence of any opacity Abnormal: Presence of opacity Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Retina	Normal: Absence of active inflammation or significant structural changes Abnormal: Presence of active inflammatory signs or significant structural changes Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Macula	Normal: Absence of active inflammation or significant structural changes Abnormal: Presence of active inflammatory signs or significant structural changes Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Choroid	Normal: Absence of active inflammation or significant structural changes Abnormal: Presence of active inflammatory signs or significant structural changes Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Optic Nerve	Normal: Absence of any damage Abnormal: Presence of any damage Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____
Cup-to-Disc Ratio	Vertical Optic Nerve Cup-to-Disc Ratio: __. __ __ Horizontal Optic Nerve Cup-to-Disc Ratio: __. __ __

Other	**Indicate any other dilated fundus ophthalmoscopy findings:** Normal Abnormal Not Clinically Significant Clinically Significant If Abnormal, Clinically Significant, specify: _____

9.5.1.4.7. Intraocular Pressure

Intraocular pressure measurements (1 measurement per eye) should be conducted after the slit lamp examination is completed and before pupil dilation. This method requires the administration of proparacaine 0.5% to the eye before testing. There should always be ≥30 minutes between the administration of topical anesthetic and IP.

IOP measurements should be performed using a Goldmann applanation tonometer, handheld contact tonometer, or pneumatonometer according to the Investigator's standard procedure. The same method of measuring IOP should be used on the same subject at all visits. Non-contact and rebound methods of testing IOP are not permitted.

Measurements should be taken with the subject seated. All pressures should be recorded in mmHg, and measurements should be recorded in the eCRF.

9.5.1.4.8. Best Corrected Visual Acuity

BCVA testing should precede any examination requiring contact with the eye and should precede pupil dilation or instillation of anesthetic eye drops. BCVA testing will be performed following manifest refraction. Subjects will be tested in their right eye first, followed by the left eye. Testing of the study eye (pre-surgery) will be completed using a pinhole occluder to determine potential visual acuity (VA).

BCVA will be evaluated in each eye individually using ETDRS charts at a distance of 4 meters and scored on a LogMAR scale. BCVA should be evaluated consistently throughout the study using the same method, equipment, and lighting conditions at each site.

Subjects will be instructed to read the letters on the ETDRS chart from the top left-hand corner along each row, one letter at a time, then down each row, one at a time. There are no numbers on the chart, only letters. If a subject reads a number, the examiner should remind the subject that the chart contains no numbers, and the examiner should then request a letter instead of a number from the subject. Subjects should be encouraged to guess if a letter appears unclear. If a subject identifies a letter as 1 of 2 possible letters, the examiner should ask the subject to pick 1 letter only.

Subjects will be instructed to read slowly at a rate of about 1 letter per second. If at any point the subject reads too quickly, the examiner should stop the subject and remind the subject to read slowly in order to achieve the best identification of each letter. If a subject loses their placement

in the chart, the examiner should ask the subject to go back to the line where the place was lost. The subject should not proceed to the next letter until they have given a definite response. If a subject changes a response before moving on to the next letter, the examiner must accept the change. The examiner should circle each correct letter on the VA worksheet and draw a single line through each incorrect letter.

At the end of the test, the examiner will count the number of letters incorrectly identified, up to and including the last line read, and will record the results on the source document. A VA letter score will be calculated and recorded in the source documents and in the eCRF.

Each letter has a score value of 0.02 log units. Since there are 5 letters per line, the total score for a line on the LogMAR chart represents a change of 0.1 log units. The formula used in calculating the score is:

Calculation: LogMAR VA = Baseline value + (n X 0.02)

where: Baseline value is the LogMAR number of the last line read (at least 1 letter read correctly in this line), and

"n" is the total number of letters missed, up to and including the last line read, and

"0.02" is the value for each letter

9.5.2. 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 is difference in proportions in subjects with ACC Grade 0 in the study eye at Visit 6 (Day 14)

9.5.4. Drug Concentration Measurements

No drug concentration measurements will be made for this study.

9.6. DATA QUALITY ASSURANCE

Each site will perform internal quality management of study conduct, data, and documentation and completion. An individualized quality management plan may be developed to describe a site's quality management.

Quality control procedures will be implemented beginning with the data entry system, and data quality control 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, the monitors will verify that the clinical study is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, ICH Good Clinical Practice (GCP), and applicable regulatory requirements (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practice [GMP]).

The site will provide direct access to all study-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

Study personnel will provide training to subjects on proper eye drop administration, proper IP storage when not in use, and proper use of the dosing diary. Subjects will also receive written instructions. Subjects will receive a new supply of IP, as applicable, as indicated in Appendix 1: Schedule of Procedures and Assessment. Study personnel will review subject dosing adherence, as recorded in the dosing diary, at each planned visit and will provide reminders and instruction about the QID dosing schedule and dosing adherence, as needed.

9.6.2. Dosing Diary

Subjects will be asked to record their daily use of IP in a dosing diary that will be collected and reviewed with them during each planned visit. Subjects will receive verbal and written instruction on the proper use of the dosing diary at Visit 3 (Baseline/Randomization), as well as verbal and written instruction on proper eye drop administration and proper IP storage when not in use for dosing.

Empty field entries in the dosing diary will be counted as missed doses, once verified with the subject, for the purpose of measuring dosing adherence. Study personnel will review subject dosing adherence, as recorded in the dosing diary, at each planned visit and will provide reminders and instruction about proper use of the dosing diary, as needed.

9.6.3. Monitoring of Study Sites

Lexitas Pharma Services, Inc., will conduct the clinical monitoring for the study. A clinical monitoring plan may be used and 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.

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

Data collection is the responsibility of study personnel 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 ensure accurate interpretation of data.

Copies of the study visit worksheets may be provided for use as source document worksheets for recording data for each subject enrolled in the study. 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 an electronic data capture system provided by Lexitas Pharma Services, Inc. The electronic data capture system will be compliant with 21 CFR Part 11. 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.

9.6.5. Clinical Study Report

The final clinical study report will be reviewed and approved by the sponsor and, when appropriate, medical, clinical, statistical, and/or regulatory staff from Lexitas.

9.6.6. Inter-Laboratory Standardization Methods

Not applicable.

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 unmasking.. 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 subjects 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 subjects in each category. Unless otherwise noted, the denominator to determine

the percentage of subjects in each category will be based on the number of subjects with available data. 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, other quartiles, and confidence limits will be calculated to one more decimal place than the source data. Standard deviations will be calculated to two more decimal places than the source data. Percentages will be calculated to the nearest one decimal place. 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 High Dose, Low Dose, Vehicle.

Results that cannot be calculated (such as standard deviation for a single subject or due to small sample sizes that lead to convergence issues) will be reported as "--".

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 measurement prior to dosing of double-masked study medication. Ocular measurements will use the most recent measurement for each eye.

All data collected in this study will be presented in individual subject data listings for all subjects.

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

Strata and Covariates

For analysis of continuous efficacy endpoints, mixed-effect repeated measures (MMRM) models will model the change from baseline of each endpoint as the dependent variable with the baseline measurement of the corresponding endpoint as a covariate with treatment, visit, and treatment by visit interaction as fixed effects.

Subgroups

Subgroup analyses may be conducted based on baseline characteristics on a post hoc basis.

Multiplicity

For the primary endpoint, a sequential testing procedure will be employed to control the overall Type I error rate at two-sided 5% with respect to multiple comparisons for the following hypotheses: VVN461, 1.0%, to Vehicle (H1) and VVN461, 0.5%, to Vehicle (H2). The testing procedure will be done in a hierarchical order as H1 and H2. If H1 is not significant, then H2 will not be tested. The secondary and exploratory efficacy endpoints will be analyzed regardless

of the significance of the primary endpoint analysis. Both, between group and within group, comparisons with p-values that claim statistical significance should be understood to be "nominal," as they will not be adjusted for multiplicity.

Missing Data and Outliers

Missing data for continuous endpoints will be considered missing at random with the analysis using mixed model repeated measures. Otherwise, observed data will be analyzed at each visit.

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 AEs 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 available date data.

Interim Analysis

Not applicable.

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 is a subset of the FAS and will include all subjects in the FAS who completed study-required treatment and who followed the protocol without significant deviations. The determination of significant protocol violations will be made prior to locking the final database and unmasking. Reasons for exclusion will include but are not limited to:

- Subjects with poor study-drug compliance

- Non-compliance with the protocol
- Prohibited medication use
- Assessments performed out of order
- Visits out of window

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).

9.7.1.1.2. Analysis Eyes

The study eye is the eye that meets all inclusion and no exclusion criteria. If both eyes are eligible, the Investigator will designate the study eye. The study eye is the surgical eye. Efficacy analyses will be performed on the study eye using the FAS. Sensitivity analyses will be performed for primary and secondary endpoints using the PP Analysis Set.

Safety analyses will be presented for the study eye and the 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. The reasons for discontinuation will be listed 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 randomized subjects.

- Number of subjects screened
- Number and percentage of subjects treated
- Number and percentage of subjects in the Full Analysis Set
- Number and percentage of subjects in the Per-Protocol Analysis Set
- Number and percentage of subjects in the Safety Analysis Set
- Number and percentage of subjects treated who completed the study
- Number and percentage of subjects treated who discontinued from the study
- The reasons for study discontinuation
- Number and percentage of subjects attending each visit

A table of protocol deviations will be presented using the FAS.

A listing of subjects who do not meet all inclusion criteria or meet exclusion criteria will be provided.

9.7.1.3. Analysis of Demographic and Baseline Characteristics

9.7.1.3.1. Demographics and Disease Characteristics

Demographic characteristics include age (years), age group (<65 years, ≥65 years), sex, race, and ethnicity. These characteristics, as well as clinically significant findings during abbreviated physical exam, systolic and diastolic blood pressure, and heart rate, will be summarized descriptively by treatment group and overall using the FAS, PP, 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.

9.7.1.3.2. Medical and Surgical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Mozzicato, 2009). The frequency and percentage of subjects with any medical and/or surgical history was 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 High Dose;
2. Descending frequency within Low Dose;
3. Descending frequency within Vehicle;
4. PT in alphabetical order.

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

9.7.1.3.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (B3 WHO Drug Global, Lagerlund et al., 2020) for anatomical therapeutic chemical classification (ATC) 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 was 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 High Dose;

2. Descending frequency within Low Dose;
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 and non-study eye.

Prior medications are defined as any medications that started and stopped prior to the date of cataract surgery. Concomitant medications are defined as any medications that are ongoing or start after the start of cataract surgery, including medications provided at Visit 2 (Day of Surgery) as part of the cataract surgery, through the end of study/exit from study visit. Medications taken after Visit 7 or withdrawal from the study are not considered concomitant.

9.7.1.4. Analysis of Study Medication Compliance 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 5 questions: Did subject return IP at this visit, and if so, how many used vitals and how many un-used vials, did subject miss any doses since the last visit, 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.

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 by the study eye.

For subjects who discontinue treatment prior to the Visit 7, the data collected on the Early Termination eCRFs will not be summarized unless the termination within the visit windows of a particular visit.

All longitudinal models will be fit using the MIXED procedure in SAS. Categorical analyses will be conducted using the FREQ procedure.

Secondary and exporatory endpoints will be analyzed in a similar manner to the primary endpoint regardless of the significance of the primary endpoint analysis. All efficacy analyses will be conducted using the FAS and PP Analysis Sets.

9.7.1.5.1. Primary Efficacy Analysis

Primary Estimand: The primary estimand is treatment difference between VVN461 (1.0% or 0.5%) and the Vehicle in the proportion of subjects with ACC Grade 0 at Visit 6 (Day 14) in the study eye using the FAS.

Target Population: Subjects undergoing routine cataract surgery who meet the study entry criteria.

Endpoint: Proportion of subjects with ACC Grade 0 in the study eye at Visit 6 (Day 14).

Treatment Condition: Treatment condition is based on randomized treatment.

Population-Level Summary: The difference in proportions in subjects with ACC Grade 0 in the study eye at Visit 6 (Day 14) and the corresponding p-value.

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 Approach – no imputation; use observed data
- Receipt of rescue therapy (topical corticosteroid) in the study eye
  - Composite Approach – subjects who receive rescue therapy ~~at or~~ before the assessment visit will be assumed to have failed the primary endpoint
- Missing data due to discontinuation due to Lack of Efficacy or Advese Event
  - Composite Approach – subjects who discontinue due to Lack of Efficacy or Adverse Event before the assessment visit will be assumed to have failed the primary endpoint
- Missing data with or without withdrawal, regardless of reason
  - Hypothetical Approach – no imputation; analysis will be based on subjects who have an evaluable anterior chamber in the study eye at Visit 6 (Day 14)

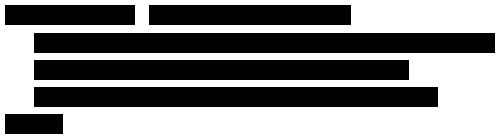
Pearson's chi-square will be used to test the primary endpoint between the 2 different doses of VVN461 vs the Vehicle. Analyses will be also performed on observed data without failure criteria for rescue. These analyses will also be performed on the PP Analysis Set.

A sensitivity analysis with control-based multiple imputation method will be carried out in the following three steps:

1) Imputation: Missing binary data will be filled in 25 different times to generate 25 imputed datasets. The following code will be used to impute the 25 datasets with data of subjects prior to rescue medications.

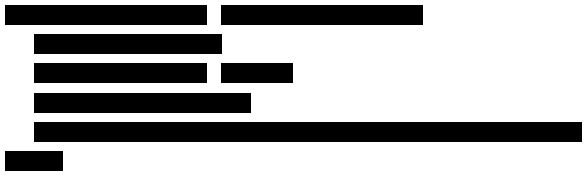
The control is where treatment = 3. This imputes data for all arms according to the control treatment.

2) Analysis: Each of the 25 imputed datasets will be analyzed at Visit 6 using PROC FREQ where the propotions of responders in each treatment arm will be calculated:

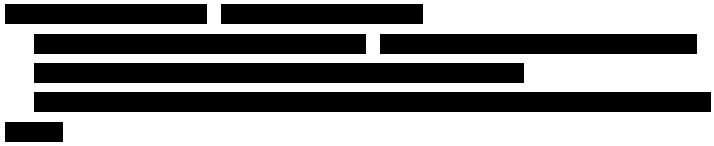


3) Pooling: The results from the 25 imputed datasets will be combined for estimation using PROC MIANALYZE.

   Results will include treatment arm proportions:



   As well the difference between proportions:



The sensitivity analyses will only be performed on the primary endpoint at Visit 6. All analyses will each be performed with the FAS and Per Protocol Analysis Sets.

9.7.1.5.2. Secondary Efficacy Analyses

The secondary efficacy endpoints include the following:

- Proportion of subjects with ACC Grade 0 in the study eye at Visit 5 (Day 7)
- Proportion of subjects with anterior chamber flare (ACF) Grade 0 in the study eye at Visit 6 (Day 14)
- Proportion of subjects with ACF Grade 0 in the study eye at Visit 5 (Day 7)
- Proportion of subjects requiring rescue medication before Visit 6 (Day 14)

9.7.1.5.3. Exploratory Efficacy Analysis

Exploratory endpoints will include the proportion of subjects with no postoperative ocular pain (NPRS = 0) in the study eye at Visit 5 (Day 7) and at Visit 6 (Day 14).

Observed mean NPRS prior to rescue mediation will also be analyzed at each given visit.

The following study eye endpoints will be analyzed at each visit using a mixed model repeated measures:

1) Mean CFB in ACC Grade
2) Mean CFB in ACF Grade
3) Mean NPRS

The model will include treatment, visit, and treatment by visit interaction as fixed effects and a covariate for baseline measurement (where appropriate) with a random effect for site. An unstructured covariance among repeated measurements will be assumed. If the model fails to converge using this covariance structure, spatial power or compound symmetry will be implemented in this order until convergence is reached. If convergence is not reached, values will be denoted as "--". Only data from before the use of rescue medication will be included in these analyses.

[redacted]

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run;
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9.7.1.6. Analysis of Safety

Safety will be evaluated by AEs, changes from baseline in IOP measurements and Best Corrected Visual Acuity (BCVA), as well as, Slit Lamp Biomicroscopy and Dilated Ophthalmoscopy Exams.

The Safety Analysis Set will be used for all safety analyses. All data, including data after rescue therapy, 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. 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. Pretreatment adverse events are events that begin prior to the date 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 are summarized separately and will each be summarized separately for treatment-emergent adverse events. Ocular AEs will be presented by study eye and non-study 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 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 High Dose;
2. Descending frequency within Low Dose;
3. Descending frequency within Vehicle;
4. Descending frequency within Low Dose;

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. *C*linical Laboratory Tests

The results of pregnancy tests for women of childbearing potential will be listed only.

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 the study eye and non-study eye. The percentages are calculated based on the number of subjects at each visit in each treatment group based on non-missing observations of the Safety Analysis Set. The percentages for the shift will be calculated based on the number of subjects with both baseline and post-baseline values.

9.7.1.6.4. Dilated Ophthalmoscopy (Fundus Exam)

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 the study eye and non-study eye. The percentages are calculated based on the number of subjects at each visit in each treatment group based on non-missing observations of the Safety Analysis Set. The percentages for the shift will be calculated based on the number of subjects with both baseline and post-baseline values.

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

9.7.1.6.5. Intraocular Pressure

Descriptive summaries of the observed values at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for the study eye and non-study eye.

9.7.1.6.6. Best Corrected Visual Acuity

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 the study eye and non-

study eye. A categorical analysis of subjects who lose 3 or more lines ETDRS in either eye at each visit or final visit will be conducted.

9.7.2. Determination of Sample Size

A sample size of approximately 90 completed subjects will be randomized in a 1:1:1 ratio to VVN461, 1.0%, VVN461, 0.5%, and a matching Vehicle that does not contain the API. With a sample size in each group of 30, the study will have 80% power to detect a difference of 35%, assuming a response rate of 30% in the Vehicle group, and a two-sided 0.05 significance level for a Pearson chi-square test.

A drop-out rate of 10% is assumed, resulting in a total sample size of approximately 102 subjects (34 for VVN461, 1.0%, 34 for VVN461, 0.5%, and 34 for Vehicle).

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

9.8.1. Protocol Amendments

Protocol, Amendment 1 (Version 2.0) – 16 November 2023

1) Add additional occurrences of existing safety procedures scheduled during study conduct.
2) Additional updates were made for consistency with the changes outlined above or changes administrative in nature.

Protocol, Amendment 2 (Version 3.0) – 04 December 2023

1) Revise the primary endpoint grading scale.
2) Additional updates were made for consistency with the changes outlined above or changes administrative in nature.

9.8.2. Changes from Protocol-Specified Analyses

Exploratory Efficacy Analysis:

1) Observed analysis of NPRS
2) Mean NPRS analysis using mixed model repeated measures

9.8.3. SAP Amendments

Not applicable.

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3. 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.
4. SAS Institute Inc. What's New in Base SAS® 9.4 and SAS® Viya®. (2013). SAS Institute Inc., Cary, NC, USA.
5. SAS Institute Inc. (2020). SAS/STAT User's Guide. SAS Institute Inc., Cary, NC, USA.

Appendix I: Schedule Of Assessments

Table 3 Schedule of Assessments

Study Period	Screening	Cataract Surgery	Treatment Perio d			End of Treatment	End of Study
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day	**Day -30 to -1**	**Day 0**	**Day 1**	**Day 3 ± 1**	**Day 7 ± 1**	**Day 14 ± 2**	**Day 21 ± 2**
Informed consent/Assent	X						
Inclusion/Exclusion criteria	X		X[1]				
Demographics	X						
Medical/Ocular/Surgical history	X						
Heart rate and blood pressure	X						
Abbreviated physical examination	X						
Urine pregnancy test	X	X				X	X
Prior/Concomitant medications	X	X	X	X	X	X	X
Subject administration of test eye drop	X						
Randomization			X				
Dispense IP			X		X		
Collect unused IP					X	X	
In-clinic administration of IP			X				
Pain score training	X		X				
NPRS			X	X	X	X	
Dosing adherence				X	X	X	
AE monitoring		X	X	X	X	X	X
Slit lamp biomicroscopy	X		X	X	X	X	X
BCVA	X		X	X	X	X	X
IOP	X		X	X	X	X	X
Dilated ophthalmoscopy	X						X

Abbreviations: ACC=anterior chamber cell; AE=adverse event; BCVA=best corrected visual acuity; CELR=cataract extraction and lens replacement; IOP=intraocular pressure; IP=investigational product; NPRS=Numeric Pain Rating Scale

[1] Inclusion and exclusion criteria will be assessed at Visit 1 (Screening); subjects who meet eligibility requirements at Visit 1 (Screening) will continue to be eligible for study participation if they present at Visit 3 (Baseline/Randomization) with ACC inflammation ≥2 in the study eye after having completed CELR surgery at Visit 2 (Day of Surgery) without surgical complications.