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Clinical Study VVN461-CS201
Protocol
13 February 2024

Title Page

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

Protocol Number:	VVN461-CS-201
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Confidentiality Statement

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 the potential, in the opinion of the Investigator, for postoperative best corrected visual acuity (BCVA) ≤0.2 Logarithm of the Minimum Angle of Resolution (LogMAR) (i.e., 20/32 Snellen or better) 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 2 (Day of Surgery), or be planning to use during the study, corticosteroids, oral or topical non-steroidal anti-inflammatory drugs (NSAIDs), or Omidria® (i.e., phenylephrine and ketorolac injection).

    Note: Low-dose acetylsalicylic acid (i.e., baby aspirin or similar) is allowed
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: o BCVA o Slit lamp biomicroscopy o IOP o 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 ○ 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 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 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.
	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.
	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.

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Abbreviations and Definition of Terms

ACC	anterior chamber cell
ACF	anterior chamber flare
AE	adverse event
API	active pharmaceutical ingredient
BCVA	best corrected visual acuity
CELR	cataract extraction and lens replacement
CFB	change from baseline
CFR	Code of Federal Regulations
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation
IND	Investigational New Drug
IOP	intraocular pressure
IP	investigational product
IRB	Institutional Review Board
JAK	Janus kinase
JAK-STAT	Janus kinase-signal transducer and activator of transcription
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NPRS	Numeric Pain Rating Scale
NSAID	non-steroidal anti-inflammatory drug
PP	Per Protocol
QID	*quater in die* (four times a day)
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SUN	Standardization of Uveitis Nomenclature
TEAE	treatment emergent adverse event
TYK2	tyrosine kinase 2
US	United States
VA	visual acuity
WHODrug	World Health Organization Drug Dictionary
WOCBP	woman of childbearing potential

1 Introduction

1.1 Background

Intraocular inflammation is an anticipated sequela of intraocular surgery, such as cataract extraction and lens replacement (CELR) surgery, and is manifested principally as conjunctival injection, corneal edema, ciliary flush, and aqueous cells and flare. In general, trauma to the internal structures of the eye is accompanied by the production of prostaglandins and other vasoactive moieties, the release of pro-inflammatory cytokines, an increase in blood flow to the affected area, and extravasation of protein and cellular blood elements. Untreated inflammation may lead to complications, such as cystoid macular edema and corneal scarring. Thus, managing and treating post-operative inflammation is an important goal following cataract surgery (Kim et al., 2019).

Current post-operative medication regimens commonly include topical corticosteroids. Treatment with corticosteroids is employed to reduce pain and discomfort, and to facilitate recovery of the blood-aqueous barrier. When administered at the time of surgery and during the immediate post-operative period, corticosteroids can reverse the clinical manifestations of inflammation. In the United States (US), topical corticosteroids are routinely prescribed with up to four times daily (QID) dosing for at least 2 weeks following cataract surgery (Kim et al., 2019).

The Janus kinase (JAK) pathway plays a key role in inflammatory cell regulation, cytokine production, and pro-inflammatory signal transduction. Dysregulation of the JAK pathway is associated with the pathogenesis of various inflammatory and autoimmune disorders. Therefore, JAK inhibitors have the potential to alleviate the inflammatory process. The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is known to be important for inflammatory cell regulation, cytokine production, and pro-inflammatory signal transduction (Wen et al., 2021).

VVN461 is a highly active JAK inhibitor with potent inhibition of JAK1 and tyrosine kinase 2 (TYK2), and moderate inhibition on JAK2. Thus, this molecule is under development in both China and the US for anti-inflammatory activity by oral (QY201), topical dermal (QY211), and ocular (VVN461) routes. VivaVision Biotech (Hong Kong) Ltd. (VivaVision; Sponsor) is conducting clinical studies in China on VVN461 Ophthalmic Solution for the treatment of non-infectious anterior uveitis under a Chinese Investigational New Drug (IND) application. The dosing regimens in these studies differ from those currently intended for the opening study for the US IND application, which is topical ocular treatment of post-operative inflammation and pain following intraocular surgery.

VVN461 Ophthalmic Solution is a preserved multidose product, intended for topical ocular instillation. As a new chemical entity, the intended regulatory route is 505(b)(1).

See the Investigator's Brochure for additional information.

1.2 Study Rationale

VVN461 is a highly active JAK inhibitor with strong inhibition on JAK1/TYK2, and moderate inhibition on JAK2. The JAK-STAT pathway is a group of signaling pathways composed of receptors, JAK proteins, and signal transducers and transcription activators. Many cytokines deliver signals through the JAK-STAT pathway. Therefore, being closely associated with the hematological system and immune system, this signaling pathway plays an important role in immune-mediated inflammation (O'Shea et al., 2015; Stark & Darnell, Jr., 2012; Villarino et al., 2015).

Ocular inflammation is known and expected to occur after routine cataract surgery. As a strong JAK inhibitor, it is theorized that VVN461 may have therapeutic benefits for the treatment of post-operative ocular inflammation in subjects undergoing routine cataract surgery.

1.3 Risk/Benefit Assessment

This section provides high-level information regarding known potential risks and benefits. More detailed information can be found in the Investigator's Brochure.

1.3.1 Known Potential Risks

There are known risks and complications of routine cataract surgery, including but not limited to ocular inflammation, ocular discomfort, bruising and swelling around the surgical site, changes in intraocular pressure (IOP), and opportunistic infection. In rare instances, longer term complications (e.g., posterior capsular opacification, cystoid macular edema) may occur. These risks are not attributable to the investigational product (IP) but are inherent to the disease state being investigated.

A phase 1 study was conducted in 30 healthy adult subjects to evaluate the safety, tolerability, and pharmacokinetics of VVN461 (formulation strengths 1.0%, 0.5%, and 0.25%). The phase 1 study reported a relatively low incidence of treatment emergent adverse events (TEAEs), with the most common adverse events (AEs) being intraocular pressure test abnormal (2/30; 6.7%), Herpes zoster (1/30; 3.3%), and corneal epithelium defect (1/30; 3.3%). Intraocular pressure test abnormalities were transient, related to IP, and resolved without intervention. The incidence of Herpes zoster was related to IP and resolved with treatment. The incidence of corneal epithelium defect was not related to IP.

1.3.2 Known Potential Benefits

This is the first study of VVN461 in subjects undergoing routine cataract surgery. Therefore, there are no known ocular health benefits for this population.

Pre-clinical studies in Dutch rabbits found that VVN461 was comparable to a corticosteroid commonly used in clinical practice, dexamethasone ophthalmic solution, 0.1%, at controlling ocular inflammation, reducing the exudation of anterior chamber cells (ACCs), and resolving inflammatory lesions in non-infectious uveitis. It is theorized that VVN461 may have therapeutic benefits for the treatment of post-operative ocular inflammation after routine cataract surgery.

1.3.3 Assessment of Benefits and Risks

It is the judgment of VivaVision Biotech (Hong Kong) Ltd. that there is a favorable benefit-risk ratio for the use of VVN461 in subjects experiencing post-operative ocular inflammation after undergoing routine cataract surgery. Pre-clinical studies in Dutch rabbits found that VVN461 performed comparably to dexamethasone ophthalmic solution, 0.1%, at controlling ocular inflammation, and VVN461 may have the advantage of avoiding side effects, such as cataract and increased IOP, that are associated with long-term use of dexamethasone ophthalmic solution, 0.1%.

2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective: 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 Objective:** Evaluate the safety of VVN461	**Primary Endpoint:** • Proportion of subjects with 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)

3 Study Design

3.1 Overall Design of the Study

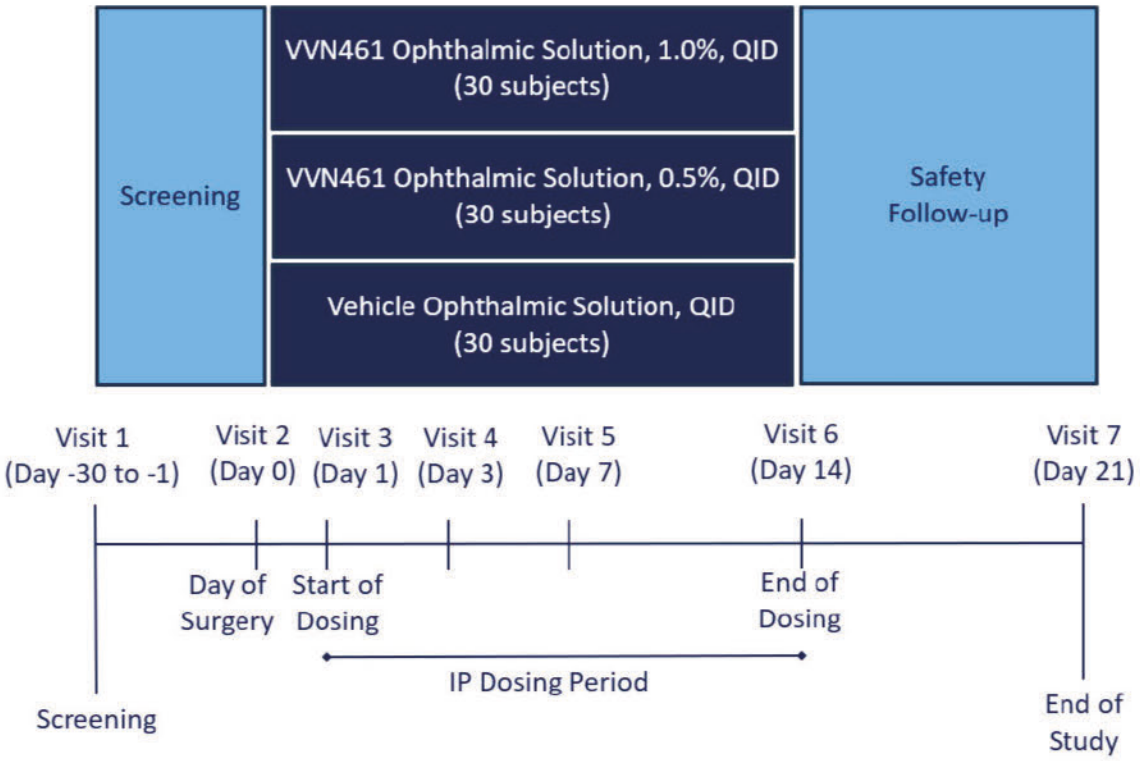
This is a phase 2, multicenter, double-masked, randomized, vehicle-controlled, parallel-comparison study conducted at sites in the US assessing the safety and ocular efficacy of VVN461 for treating post-operative ocular inflammation in subjects who undergo routine unilateral CELR surgery via phacoemulsification 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 Clinical Study Diagram



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

3.2 Rationale for the Study Design

Pre-clinical studies in Dutch rabbits found that VVN461 was comparable to dexamethasone ophthalmic solution, 0.1%, at controlling ocular inflammation, reducing the exudation of ACC, and resolving inflammatory lesions in non-infectious uveitis. It is theorized that VVN461 may have therapeutic benefits for the treatment of post-operative ocular inflammation after routine cataract surgery. The use of Vehicle as a control is standard practice in ophthalmology research.

See the Investigator's Brochure for additional information.

3.3 Dose Justification

The IP formulation strengths (1.0% and 0.5%) proposed for the study were selected based on their previous use in a phase 1 study in healthy adult human subjects and are further supported by extensive non-clinical and pre-clinical testing in animal models.

See the Investigator's Brochure for additional information.

3.4 End of Study Definition

A subject is considered to have completed the study if the subject has completed the last visit or the last scheduled procedure shown in the Schedule of Procedures and Assessments (Appendix 1: Schedule of Procedures and Assessment). The end of the study is defined as completion of the last visit or procedure shown in the schedule in the study globally.

4 Study Population

The study population will consist of subjects who have undergone routine unilateral CELR surgery via phacoemulsification without surgical complication.

4.1 Inclusion Criteria

Subjects who meet all inclusion criteria at Visit 1 (Screening) and/or Visit 3 (Baseline/Randomization) will be eligible for study participation.

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 the potential, in the opinion of the Investigator, for postoperative best corrected visual acuity (BCVA) ≤0.2 Logarithm of the Minimum Angle of Resolution (LogMAR) (i.e., 20/32 Snellen or better) 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

4.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible for study participation.

Ophthalmic (Either Eye)

1. Any ocular pain at Visit 1 (Screening)
2. Used within 1 week before Visit 2 (Day of Surgery), or be planning to use during the study, corticosteroids, oral or topical non-steroidal anti-inflammatory drugs (NSAIDs), or Omidria® (i.e., phenylephrine and ketorolac injection).
   Note: Low-dose acetylsalicylic acid (i.e., baby aspirin or similar) is allowed

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. 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 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; Appendix 2: 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

4.3 Screen Failures

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

Prospective subjects who do not meet the criteria for study participation (screen failure) because of transient conditions that are expected to change, including but not limited to screen failures for high IOP, may be rescreened at Investigator discretion (maximum of 1 rescreen per prospective subject). Rescreened subjects should be assigned a new subject identification number, and the original subject identification number should be recorded as a screen failure.

5 Study Treatment(s) or Intervention(s)

5.1 Investigational Products

Three (3) IPs will be administered during the study:

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

The matching Vehicle will be identical to the active doses of IP, except Vehicle will not contain the active pharmaceutical ingredient (API). All IP will be administered topically to the study eye as eye drops.

5.1.1 Description

Both formulations of VVN461 and the matching Vehicle are colorless to light yellow sterile solutions packaged in 5 mL multidose low-density polyethylene eye drop bottles. The IP will be provided in identical primary packaging. IP will be supplied to sites in cartons. Each carton will contain 1 low-density polyethylene eye drop bottle.

5.1.2 Dosage and Administration

Subjects will be randomized to 1 of 3 possible groups in a 1:1:1 ratio. 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.

All subjects, irrespective of group, will administer 1 eye drop in the study eye QID for a period of 14 days. If the subject misses their eye while administering an eye drop, a second eye drop may be administered. If the subject misses their eye while administering a second eye drop, a third eye drop may not be administered. The missed dose should be recorded in the dosing diary.

If a subject forgets or misses a scheduled dose of IP, the subject should administer the missed dose as soon as possible. The missed dose should be recorded in the dosing diary. The QID dosing schedule should then be resumed. Subjects will administer their first dose of IP and make their first dosing diary entry in the clinic under the supervision of study personnel to ensure proper dosing technique and dosing diary use.

5.2 Preparation/Storage/Handling/Accountability

5.2.1 Acquisition and Accountability

IP will be provided to each site. Once the IP has been delivered to the site, it will be stored in a limited-access area only accessible to trained study personnel. Used and unused IP will be maintained at the site for accountability by the clinical study monitor.

When authorized by the Sponsor, and after the clinical study monitor has verified drug accountability is complete and accurate, used and unused IP either will be returned to the Sponsor or designee, or will be disposed/destroyed by the sites in accordance with the requirements of applicable local authorities and regulatory bodies to ensure disposal of IP does not expose human beings to risks from the drug.

5.2.2 Product Formulation, Appearance, Packaging, and Labeling

IP will be delivered to sites in identical packaging and labeled in accordance with federal regulations for investigational new drugs. Labels will include verbatim the following statement: "Caution: New Drug – Limited by Federal law to investigational use."

The formulation includes polyethylene glycol (a cosolvent), hydroxypropyl beta-cyclodextrin (a solubilizer), citric acid (a pH buffer), sodium citrate (a pH buffer), sodium chloride (a tonicity agent), and a preservative, benzalkonium chloride 0.02% (w/v). Water for injection is used as the final diluent for this product. There are no novel excipients used in the formulation. The product is manufactured aseptically and is intended to be used as a sterile product as Vehicle (0.0% VVN461), 0.5% VVN461, and 1.0% VVN461.

Additional details may also be included on the label, provided that these details do not pose a risk to study masking. This may include but is not limited to the protocol number, IP volume per container, storage requirements, manufacturer, and lot number.

5.2.3 Product Storage and Stability

IP will be stored at ambient room temperature (15°C to 25°C [59°F to 77°F]) and protected from light in a limited-access area accessible only to trained study personnel. One-day temperature excursions during handling, warehousing, and shipping operations are permitted up to 40°C (104°F), based on stability data.

Opened and unopened bottles of IP will be maintained at the site for accountability by the clinical study monitor.

5.3 Measures to Minimize Bias: Randomization and Masking

Eligible subjects will be randomized in a 1:1:1 ratio in the electronic data capture system. The IP will be dispensed to subjects by trained study personnel only.

The randomization schedule will be computer-generated in the electronic data capture system, and all IP will be masked to the Sponsor, study personnel, and study subjects throughout the study until after the final database has been locked. Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. Unless the subject's safety requires otherwise, and if time permits, the decision to unmask a treatment assignment is to be made jointly by the Investigator and the Medical Monitor after consultation with the Sponsor.

If unmasking is required during the study, the integrity of the study assessments and collected data will be maintained by limiting access to the unmasked data.

5.4 Dosing Adherence and Dosing Diary

5.4.1 Dosing Adherence

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.

5.4.2 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.

5.5 Prior and Concomitant Therapy

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 electronic case report

form (eCRF) are concomitant prescription medications, over-the-counter medications, supplements, and medications provided at Visit 2 (Day of Surgery) as part of site's standard practice during routine cataract surgery. (**Note:** Corticosteroids, oral or topical NSAIDs [excluding low-dose acetylsalicylic acid], and Omidria® [i.e., phenylephrine and ketorolac injection] are prohibited.)

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).

5.5.1 Prohibited Medications and Procedures

Medications that are not explicitly prohibited by the protocol may be used, as needed, throughout the study and recorded as concomitant medications. All medications taken by a subject during the study, whether allowed or prohibited, should be recorded as concomitant medications. Table 1 lists the prohibited medications and procedures for the purposes of the study, as well as the minimum timeframes for discontinuation needed for study eligibility.

Table 1 Prohibited Medications and Procedures

Medications and Procedures Not Permitted	Timeframe
Ophthalmic (Study Eye)	
Microinvasive glaucoma surgery, any incisional ocular surgery, or intracameral drug depot to lower IOP	Any history and throughout study
Intraocular surgery	6 months before surgery and throughout study (excluding planned cataract surgery)
Laser surgery, limbal relaxing incision procedure, eyelid surgery **Note:** Limbal relaxing incisions (laser-assisted and non-laser) are allowed in the study eye at Visit 2 (Day of Surgery)	3 months before surgery and throughout study
Contact lenses a. Polymethyl methacrylate contact lenses b. Gas permeable rigid lenses c. Extended wear or daily soft lenses	Throughout study and within defined windows before Visit 2 (Day of Surgery) a. 6 months before surgery b. 1 month before surgery c. 7 days before surgery
Ophthalmic (Non-study Eye)	
Cataract surgery	14 days before Visit 1 (Screening) or will require cataract surgery <1 day after Visit 2 (Day of Surgery)
General	
Other investigational drug or device	30 days before Visit 1 (Screening) and throughout study
Changes to systemic medication that could have a substantial effect on IOP	30 days before Visit 1 (Screening) and throughout study
Corticosteroids, oral or topical NSAIDs, or Omidria® (i.e., phenylephrine and ketorolac injection) **Note**: Low-dose acetylsalicylic acid (i.e., baby aspirin or similar) is allowed	1 week before Visit 2 (Day of Surgery) and throughout study

Abbreviations: IOP=intraocular pressure; NSAID=nonsteroidal anti-inflammatory drug

5.5.2 Rescue Medication

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.

6 Study Discontinuation/Subject Withdrawal

6.1 Discontinuation of Investigational Product

A subject may be discontinued from IP at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. Subjects may have IP withdrawn by the Investigator due to an AE or due to the need for rescue. Subjects who have IP withdrawn due to an AE should be followed for at least 1 week for safety monitoring, or until the AE has resolved.

6.2 Subject Discontinuation/Withdrawal from the Study

Subjects are free to withdraw from participation in the study at any time upon request. An Investigator may discontinue or withdraw a subject from the study for any reason, including but not limited to the following:

- Adverse event
- Failure to meet randomization criteria
- Lost to follow-up
- Investigator decision
- Pregnancy
- Protocol deviation
- Withdrawal of consent

The reason for subject discontinuation or withdrawal from the study will be recorded in the eCRF. Subjects who sign the informed consent form and are randomized but do not receive IP may be replaced. Subjects who sign the informed consent form, are randomized, receive at least 1 dose of IP, and subsequently withdraw or are withdrawn/discontinued from the study may not be replaced.

6.3 Lost to Follow-Up

A subject will be considered lost to follow-up if they fail to return for a scheduled visit and are unable to be contacted by study personnel.

The following actions must be taken if a subject fails to return to a site for a required visit:

- The site will attempt to contact the subject and reschedule the missed visit. The site will counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary,

a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.

- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 Study Procedures

Written informed consent and relevant privacy authorization(s) will be obtained from all subjects before any procedures related to the study are performed. The Schedule of Procedures and Assessments (Appendix 1: Schedule of Procedures and Assessment) lists the procedures that should occur at each study visit.

7.1 Visit Descriptions

Procedures should be performed in the order listed; procedures followed by an "*" may occur at other times during the visit, if needed, to accommodate site operations and/or subject bodily functions, provided the procedure is completed before in-clinic administration of IP.

7.1.1 Visit 1 (Screening; Day -30 to Day -1)

The following procedures will be performed at Visit 1 (Screening; Day -30 to Day -1):

- Explain the purpose and conduct of the study to the subject, answer subject questions, and obtain written informed consent and privacy authorization(s)
- Obtain information, including: demographics, concomitant medications, and ocular and systemic medical and medication history and surgical history
- Heart rate and blood pressure
- Subject administration of test eye drop
- Pain score training
- BCVA
- Slit lamp biomicroscopy
- IOP
- Dilated ophthalmoscopy
- Urine pregnancy test (only for WOCBP)*
- Abbreviated physical examination*
- Determine study eligibility based on Inclusion/Exclusion criteria

7.1.2 Visit 2 (Day of Surgery; Day 0)

At Visit 2 (Day of Surgery; Day 0), subjects will undergo routine CELR surgery via phacoemulsification extraction and implantation of an intraocular lens. Investigators should use their standard procedure for routine cataract surgery.

Limbal relaxing incisions (laser-assisted and non-laser) and intracameral injections and medications are allowed during the surgery. (**Note:** Corticosteroids, oral or topical NSAIDs

[excluding low-dose acetylsalicylic acid], and Omidria® [i.e., phenylephrine and ketorolac injection] are prohibited.)

All medications given to subjects as part of the cataract surgery procedure, including but not limited to sedatives, local anesthetics, and topical antibiotics, should be recorded in the eCRF as concomitant medications.

After the cataract surgery, subjects should not be provided with any prescription or over-the-counter pain medication, or medications intended to minimize ocular inflammation. Subjects will be assessed for safety and randomized at Visit 3 (Baseline/Randomization; Day 1).

The following procedures will be performed at Visit 2 (Day of Surgery):

- AE monitoring
- Concomitant medication update
- Urine pregnancy test (only for WOCBP)*
- Cataract surgery

7.1.3 Visit 3 (Baseline/Randomization; Day 1)

The following procedures will be performed at Visit 3 (Baseline/Randomization; Day 1):

- AE monitoring
- Concomitant medication update
- Pain score training
- Numeric Pain Rating Scale (NPRS)
- BCVA
- Slit lamp biomicroscopy
- IOP
    - **Note**: The IOP procedure 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.
- Determine study eligibility based on Inclusion/Exclusion criteria
- Randomization
- Dispense IP
- Provide instructions for IP use, dosing adherence, and dosing diary entries
- Supervised first dose of IP
- Schedule or confirm next visit and remind subject to return with dosing diary

7.1.4 Visit 4 (Day 3 ± 1)

The following procedures will be performed at Visit 4 (Day 3 ± 1):

- AE monitoring
- Concomitant medication update
- NPRS
- BCVA
- Slit lamp biomicroscopy
- IOP
- Review dosing adherence and dairy entries
- Schedule or confirm next visit and remind subject to return with IP and dosing diary

7.1.5 Visit 5 (Day 7 ± 1)

The following procedures will be performed at Visit 5 (Day 7 ± 1):

- AE monitoring
- Concomitant medication update
- NPRS
- BCVA
- Slit lamp biomicroscopy
- IOP
- Collect unused IP
- Review dosing adherence and dairy entries
- Dispense IP
- Schedule or confirm next visit and remind subject to return with IP and dosing diary

7.1.6 Visit 6 (End of Treatment; Day 14 ± 2)

The following procedures will be performed at Visit 6 (End of Treatment; Day 14 ± 2):

- AE monitoring
- Concomitant medication update
- NPRS
- BCVA
- Slit lamp biomicroscopy
- IOP
- Collect unused IP
- Review dosing adherence and dairy entries
- Urine pregnancy test (only for WOCBP)*
- Schedule or confirm next visit

7.1.7 Visit 7 (End of Study; Early Termination; Day 21 ± 2)

The following procedures will be performed at Visit 7 (End of Study; Early Termination; Day 21 ± 2):

- AE monitoring
- Concomitant medication update
- BCVA
- Slit lamp biomicroscopy
- IOP
- Dilated ophthalmoscopy
- Urine pregnancy test (only for WOCBP)*
- Release subject from study

7.1.8 Unscheduled Visits

Safety procedures and efficacy assessments conducted at unscheduled visits are at the discretion of the Investigator. Information will be collected during unscheduled visits about changes to concomitant medications and any AEs experienced since the last visit.

If a subject reports their supply of IP to be lost, destroyed, or unusable due to unacceptable temperature excursions, a new supply of IP may be dispensed to the subject.

7.1.9 Early Termination

In the event that a subject withdraws or is terminated from the study before the end of the study, every attempt will be made to ensure that the subject returns to the site as soon as possible and completes the Visit 7 (End of Study; Early Termination) assessments before being discharged from the study. Any unused IP should be collected during an early termination visit.

8 Study Assessments

The Schedule of Procedures and Assessments (Appendix 1: Schedule of Procedures and Assessment) provides a list of study assessments and evaluations to be performed and the timing of each.

8.1 Efficacy Evaluations

Efficacy assessments will be conducted at the timepoints indicated on the Schedule of Procedures and Assessments (Appendix 1: Schedule of Procedures and Assessment) and as detailed in the corresponding appendices. 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:

- Slit lamp biomicroscopy (Appendix 3: Slit Lamp Biomicroscop)
    - Ocular inflammation (Standardization of Uveitis Nomenclature [SUN] Scale)
- Numeric Pain Rating Scale (Appendix 4: Numeric Pain Rating Scale (NPRS))

8.2 Safety Evaluations

Safety assessments will be performed at the timepoints indicated on the Schedule of Procedures and Assessments (Appendix 1: Schedule of Procedures and Assessment) and as detailed in the corresponding appendices. The safety assessments selected for the study are all 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. Safety assessments in the study include:

- AE monitoring (ocular and non-ocular)
- Pregnancy test (urine; only for WOCBP as defined in Appendix 2: Woman of Childbearing Potential (WOCBP))
- Best corrected visual acuity (Appendix 5: Best Corrected Visual Acuity (BCVA)
- Slit lamp biomicroscopy (Appendix 3: Slit Lamp Biomicroscop)
- Intraocular pressure (Appendix 6: Intraocular Pressure (IOP))
- Dilated ophthalmoscopy (Appendix 7: Dilated Ophthalmoscop)

8.2.1 Adverse Events and Serious 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.

8.2.1.1 Definitions

An AE is any untoward medical occurrence in a subject temporally associated with the use of IP, whether or not considered related to the IP. 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 IP without any judgment on causality.

An AE is considered "serious" if it:

- Results in death
- Is 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
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is 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 these outcomes.

8.2.1.2 Classification of Adverse Events

Severity of Adverse Events

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

- **Mild:** Requires minimal or no treatment and does 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."

Relationship of Adverse Events

All AEs must have their relationship to IP assessed by the Investigator who examines and evaluates the subject based on temporal relationship and their clinical judgment. In a clinical study, the IP must always be suspect.

The relationship of an AE to the IP will be determined using the below categories. Final determination of AE attribution and expectedness will be determined by the Sponsor in consultation with the Medical Monitor.

- **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).

8.2.1.3 Adverse Event Reporting Requirements

According to federal regulations, an Investigator must immediately report to the Sponsor any SAE, whether or not considered drug-related, including those listed in the protocol or Investigator's Brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

According to federal regulations, the Sponsor must notify the US Food and Drug Administration (FDA) and all participating Investigators as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that a potential serious risk arising from a clinical study qualifies for reporting. Sponsor must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE (See 21 Code of Federal Regulations [CFR] 312.32[c][1]).

Furthermore, the Sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information (See 21 CFR 312.32[c][2]).

8.2.1.4 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.

8.2.2 Heart Rate, Blood Pressure, and Other Safety Evaluations

Safety evaluations will be assessed at the timepoints indicated on the Schedule of Procedures and Assessments (Appendix 1: Schedule of Procedures and Assessment). An abbreviated physical examination will be completed at Visit 1 (Screening), and heart rate and blood pressure will be checked.

9 Statistical Considerations

A separate Statistical Analysis Plan (SAP) will be prepared before the database is locked and the study is unmasked and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses.

Continuous measures will be summarized descriptively by the mean, standard deviation, median, and minimum and maximum values. Categorical measures will be summarized by the frequency and percentage of subjects.

9.1 Statistical Hypothesis

The primary efficacy endpoint is the proportion of subjects with ACC Grade 0 in the study eye at Visit 6 (Day 14).

The Null Hypothesis: At post-operative Day 14, there is no difference in proportion of subjects with ACC Grade 0 in the study eye between an active treatment group (VVN461, 1.0%, or VVN461, 0.5%) and the Vehicle group.

Alternative Hypothesis: At post-operative Day 14, there is a difference in proportion of subjects with ACC Grade 0 in the study eye between an active treatment group (VVN461, 1.0%, or VVN461, 0.5%) and the Vehicle group.

The primary hypothesis for the study is that at least one dose regimen of VVN461 is superior to Vehicle with respect to the proportion of subjects with ACC Grade 0 in the study eye at Visit 6 (Day 14).

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 (H_1) and VVN461, 0.5%, to Vehicle (H_2). The testing procedure will be done in a hierarchical order as H_1 and H_2. If H_1 is not significant, then H_2 will not be tested.

9.2 Sample Size Determination

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).

9.3 Analysis Populations

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).

9.4 Statistical Analyses

The statistical analyses of the study will be performed on the data through Day 21, after all subjects have either completed the Day 21 visit or discontinued early from the study, and after the study database has been cleaned, verified, and locked. It is planned that the data from all sites that participate in the study will be combined so that the target sample size will be available for analysis.

9.4.1 Baseline Descriptive Analyses

Demographic characteristics, including age (years), sex, race, ethnicity, and other baseline characteristics, will be summarized descriptively by treatment group and overall. Medical history (coded using the Medical Dictionary for Regulatory Activities [MedDRA]) and prior and concomitant medications (coded using WHODrug) will be summarized by treatment and overall.

The numbers of subjects who were enrolled and completed each visit of the study will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reasons (e.g., lost to follow-up). A list of discontinued subjects, protocol deviations, and subjects excluded from the analysis sets will be provided as well.

Exposure to IP and adherence to the dosing schedule will be summarized by treatment and overall.

9.4.2 Efficacy Analyses

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 and will only include data from before the earliest observed instance of rescue therapy. In other words, data that occurs after the earliest observed rescue therapy will be set to missing.

Efficacy analyses will be conducted using the FAS, in general, and sensitivity analyses for primary and secondary endpoints will be conducted using the PP Analysis Set.

9.4.2.1 Primary Efficacy Analyses

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 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. The primary analysis will also be performed on the PP Analysis Set.

9.4.2.2 Secondary Efficacy Analyses

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.

9.4.3 Safety Analyses

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.

9.4.3.1 Adverse Events

AEs will be coded using MedDRA and categorized by system organ class using preferred terms. Separate summaries of AEs related to treatment (as reported by the Investigator) and by severity will be presented. The number of deaths and SAEs will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

9.4.3.2 Clinical Laboratory Tests

There will not be any analysis of clinical laboratory data. Urine pregnancy tests will be conducted at Visit 1 (Screening), Visit 2 (Day of Surgery; Day 0), Visit 6 (Day 14), and Visit 7 (Day 21) for WOCBP. Results of urine pregnancy tests will be presented in a listing.

9.4.3.3 Other Safety Evaluations

Summary statistics for observed and CFB for BCVA and IOP will be presented. Abnormalities in slit lamp biomicroscopy and dilated ophthalmoscopy will be summarized by frequency and percentage. The frequency and proportion of subjects treated with rescue medications will be summarized.

Heart Rate and Blood Pressure

Heart rate and blood pressure will be assessed during screening. These measurements will be presented in a listing.

Physical Examinations

An abbreviated physical examination will be conducted during screening. The results will be shown in a listing.

9.5 Interim Analysis

No interim analysis is planned for the study.

9.6 Subgroup Analyses

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

9.7 Exploratory Analyses

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.

9.8 Missing, Unused, or Spurious Data

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.

9.9 Tabulation of Individual Subject Data

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

10 Supporting Documentation and Operational Considerations

10.1 Regulatory Issues, Ethical Concerns, and Study Oversight

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent Documents

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the subject, and written documentation of informed consent and privacy authorization will be required before starting intervention/administering IP. The written consent document will embody the elements of informed consent as described by the International Council for Harmonisation (ICH) and will also comply with local regulations.

If appropriate and required by the local Institutional Review Board (IRB), assent from the subject will also be obtained. If a subject is unable to sign the informed consent form, a legal representative may sign for them.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated before a prospective subject agrees to participate in a clinical study, and this process continues throughout study participation. Informed consent forms will be approved by the IRB, and the subject will be asked to read and review the document. The Investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as a research subject. The subject will have the opportunity to carefully review the written consent form and ask questions before signing. The subject should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate in the study. The subject will sign and date the informed consent form before any procedures are done specifically for the study. The subject must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed and dated informed consent form will be given to the subject for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed and dated, before the subject undergoes any study-specific procedures. The rights and welfare of the subject will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

10.1.2 Study Discontinuation and Closure

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to subjects, Investigators, funding agency (if applicable), the Sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the Investigator will promptly inform subjects, the IRB, and the Sponsor and will provide the reason(s) for the termination or suspension. Subjects will be contacted, as applicable, and be informed of changes to visit schedules.

Circumstances that may warrant termination or suspension may include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB, and/or FDA.

10.1.3 Confidentiality and Privacy

Subject confidentiality and privacy will be strictly held in trust by the participating Investigators, study personnel, and the Sponsor(s) and their interventions. This confidentiality will be extended to cover clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the study data will be released to any unauthorized third party without advanced written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The Study Monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies, and the pharmaceutical company supplying IP will be able to inspect all documents and records required to be maintained by the Investigator, including, but not limited to, medical records (i.e., office, clinic, or hospital) and pharmacy records for the subjects in the study. Sites will permit access to such records.

The study subject's contact information will be securely stored at each site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in an electronic data capture system. This will not include the

subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by sites and by contract research organization study personnel will be secured and password protected.

10.1.4 Key Roles and Study Governance

Table 2 Study Administrative Structure

Title/Role	Contact Information
Sponsor:	VivaVision Biotech (Hong Kong) Limited [redacted]
Chief Medical Officer:	[redacted]
Medical Monitor:	[redacted]
Contract Research Organization:	[redacted]

10.1.5 Clinical Monitoring

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.

10.1.6 Quality Assurance and Quality Control

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.

10.1.7 Data Handling and Record Keeping

10.1.7.1 Data Collection and Management Responsibilities

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.

10.1.7.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without advance written

consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.1.8 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol, ICH GCP, or Manual of Procedures requirements. The non-compliance may be on the part of the subject, the Investigator, or the study personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Non-compliance, sections 5.20.1, and 5.20.2.

It is the Investigator's responsibility to use continuous vigilance to identify and report protocol deviations. All protocol deviations must be addressed in study source documents and reported to the Sponsor and the reviewing IRB per their policies. The Investigator is responsible for knowing and adhering to the reviewing IRB's requirements.

10.1.9 Publication and Data Sharing Policy

The study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, the study will be registered at ClinicalTrials.gov, and the results from the study will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

The institutions and Investigators participating in the study shall have no right to publish or present the results of the study without advance written consent from the Sponsor.

10.1.10 Conflict of Interest Policy

The independence of the study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of the study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of the study.

11 References

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

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O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, & Laurence A. The JAK-STAT pathway: Impact on human disease and therapeutic intervention. *Annual Review of Medicine*. 2015;66:311-328.

Stark GR & Darnell JE Jr. The JAK-STAT pathway at twenty. *Immunity*. 2012;36(4):503-514.

Villarino AV, Kanno Y, Ferdinand JR, & O'Shea JJ. Mechanisms of Jak/STAT signaling in immunity and disease. *Journal of Immunology*. 2015;194(1):21-27.

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12 Appendices

12.1 Appendix 1: Schedule of Procedures and Assessments

Study Period	Screening	Cataract Surgery	Treatment Period			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.

12.2 Appendix 2: Woman of Childbearing Potential (WOCBP)

Pregnancy or refusal to adhere to contraception requirements is exclusionary.

Female subjects and female partners of male subjects are considered of non-childbearing potential if they have been in menopause for at least 1 year, have had a tubal ligation at least 1 year before Visit 1 (Screening), or have had a total hysterectomy. Contraception is not required during the study for those of non-childbearing potential.

Sexually active female subjects of childbearing potential with a partner capable of fathering children must be willing to use 1 or more of the following forms of contraception from the time of signing the informed consent form for the duration of the study:

- Hormonal contraception (oral, implantable, injectable, transdermal)
- Mechanical contraception (spermicide in conjunction with a barrier method such as a condom or diaphragm)
- Intrauterine device
- Vasectomized partner(s) (6 months minimum)
- When in keeping with a subject's usual lifestyle and preferences, abstinence may also be regarded as an adequate method of birth control, where abstinence in this context is defined as refraining from any sexual activities or contact that may result in creation of a zygote.
    - **Note:** If a subject who was abstinent under this definition becomes sexually active during the study, they must agree to use acceptable contraception as defined above for the remainder of the study.

Sexually active male subjects with partners who are WOCBP must be willing to use 1 or more of the above forms of birth control for either themselves or their partner, as appropriate, from the time of signing the informed consent form for the duration of the study.

- Male subjects who underwent a vasectomy at least 6 months before Visit 1 (Screening) are not required to use any other forms of contraception during the study.

12.3 Appendix 3: 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 3. 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 3 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

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 4).

Table 4 SUN Working Group Grading Scale for the Anterior Chamber

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

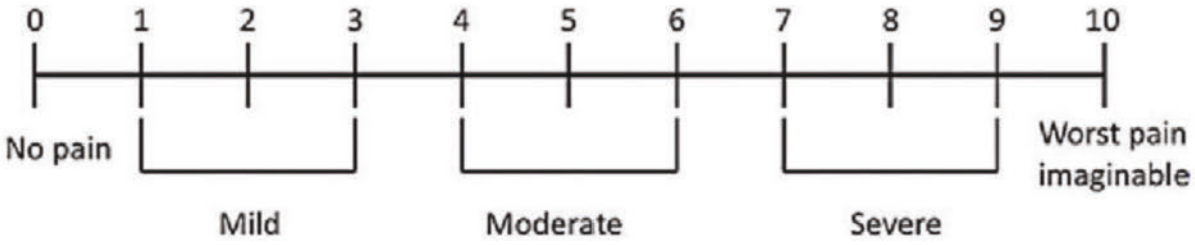
Anterior Chamber Flare	
Grade	**Description**
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Abbreviations: SUN=Standardization of Uveitis Nomenclature
[1]Field size is a 1 mm by 1 mm slit beam
Reference: Jabs et al., 2005

12.4 Appendix 4: Numeric Pain Rating Scale (NPRS)

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.



12.5 Appendix 5: Best Corrected Visual Acuity (BCVA)

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.

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

12.6 Appendix 6: Intraocular Pressure (IOP)

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.

12.7 Appendix 7: Dilated Ophthalmoscopy

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: _____

12.8 Appendix 8: Compliance Statement

The study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and as stipulated in the Declaration of Helsinki with respect to the use of human subjects in clinical studies and investigations.

[redacted]

[redacted]

[redacted]

[redacted]

Name (printed)

[redacted]

12.9 Appendix 9: Investigator Agreement

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

Version Number: 4.0

Issue Date: 13 February 2024

I have read the clinical study protocol and understand it. I agree to conduct the study as outlined in this document and in accordance with GCP, all local and federal requirements and regulations, and in compliance with those precepts set forth in the Declaration of Helsinki with respect to the use of human subjects in clinical studies and investigations.

The Investigator will assure that no deviation from, or changes to, the protocol will take place without advance agreement from the Sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to subjects. All personnel involved in the conduct of the study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB in advance for review and approval. Approval of both the protocol and the informed consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be approved by the IRB; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided informed consent using a previously approved version of the consent form.

Further, I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Investigator:

Name (printed)	Signature	Date