CLINICAL STUDY PROTOCOL

A DOUBLE-MASKED, RANDOMIZED, CONTROLLED, MULTIPLE-DOSE STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ULTEVURSEN IN SUBJECTS WITH RETINITIS PIGMENTOSA (RP) DUE TO MUTATIONS IN EXON 13 OF THE *USH2A* GENE (SIRIUS)

Protocol No.	PQ-421a-003
Protocol/Amendment Date:	14 June 2022
Protocol Version:	3.0
Supersedes Version:	2.0
EudraCT/IND Number	2021-002729-74 IND 137660
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands

INVESTIGATOR SIGNATURE PAGE

PRINCIPAL INVESTIGATOR COMMITMENT:

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study drug and the study protocol.

I agree to conduct this clinical study according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all applicable local regulations, Good Clinical Practices (GCP), as well as with the requirements of the appropriate Institutional Review Board(s) (IRB)/Ethics Committee(s) (EC) and any other Institutional requirements.

Printed Name of Principal Investigator

Signature of Principal Investigator

Date

Institution

Address of Institution

Phone Number of Investigator

PROTOCOL APPROVAL PAGE

A Double-Masked, Randomized, Controlled, Multiple-Dose Study to Evaluate the Efficacy, Safety and Tolerability of Ultevursen in Subjects with Retinitis Pigmentosa (RP) due to Mutations in Exon 13 of the *USH2A* Gene (SIRIUS)

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Date

ProQR Therapeutics

1.0 SYNOPSIS

<table>
<tr><td>Name of the Sponsor:
ProQR Therapeutics</td><td colspan="2" rowspan="3">Individual Study Table Referring to Part of the Dossier:
Volume: NA
Page: NA</td><td rowspan="3">For National Authority Use Only</td></tr>
<tr><td>Name of Study Drug:
QR-421a (henceforth ultevursen) Solution for Intravitreal Injection</td></tr>
<tr><td>Name of Active Ingredient:
Ultevursen</td></tr>
<tr><td>Title of Study:</td><td colspan="3">A Double-Masked, Randomized, Controlled, Multiple-Dose Study to Evaluate the Efficacy, Safety and Tolerability of Ultevursen in Subjects with Retinitis Pigmentosa (RP) due to Mutations in Exon 13 of the USH2A Gene (SIRIUS)</td></tr>
<tr><td>Phase of Development:</td><td colspan="3">Phase 2/3</td></tr>
<tr><td>Study Period:</td><td colspan="3">Anticipated to be approximately 34 months</td></tr>
<tr><td>Duration of Subject Participation:</td><td colspan="3">Approximately 27 months (up to 12 weeks screening; 24 months on-study)</td></tr>
<tr><td>Rationale:</td><td colspan="3">There are currently no approved therapies for the treatment of RP due to mutations in exon 13 of the USH2A gene, and disease management is supportive; therefore, a large unmet medical need exists in this sight-threatening condition.

Study PQ-421a-003 will investigate the efficacy and safety of 2 dose regimens of ultevursen in subjects with RP due to mutations in exon 13 of the USH2A gene.</td></tr>
<tr><td colspan="2">Objectives:
<u>Primary</u>
• To evaluate the efficacy of ultevursen</td><td colspan="2">Endpoints:
<u>Primary endpoint</u>
• Mean change from baseline in best corrected visual acuity (BCVA) (based on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart) at 18 months of treatment versus sham-procedure</td></tr>
</table>

Secondary • To further evaluate the efficacy of ultevursen • To evaluate the safety and tolerability of ultevursen • To evaluate changes in Patient-Reported Outcome (PRO) measures in subjects treated with ultevursen • To evaluate systemic exposure of ultevursen	**Key Secondary Endpoint (Efficacy)** • Proportion of subjects who maintain vision defined by BCVA loss less than 15 Letters (based on ETDRS) **Other Secondary Endpoints (Efficacy)** • Change from baseline in the following outcome measures: o Other analyses of BCVA o Ellipsoid zone (EZ) area and width as imaged by Spectral domain optical coherence tomography (SD-OCT) o Low Luminance Visual Acuity (LLVA) o Microperimetry o Full-field Stimulus Threshold (FST) **Secondary Endpoints (Safety and Tolerability)** • Ocular and non-ocular adverse events (AEs) **Secondary Endpoints (PRO)** • Change from baseline in PRO measures, as assessed by: o Veterans Affairs Low Vision Visual Functioning Questionnaire (VA LV VFQ-20) o Patient Global Impressions of Severity (PGI-S) o Patient Global Impressions of Change (PGI-C) **Secondary Endpoints (Systemic Exposure)** • Exposure of ultevursen in serum
Number of Subjects (planned):	Approximately 81 subjects
Study Design	PQ-421a-003 is a double-masked, randomized, controlled, multiple-dose study to evaluate the efficacy, safety and tolerability of ultevursen in subjects with RP due to mutations in exon 13 of the *USH2A* gene. At study start subjects will be randomized to one of the following treatment groups: 1) Group 1: Ultevursen 180/60 µg (180 µg loading dose administered on Day 1, 60 µg maintenance dose administered at Month 3 and every 6 months thereafter; n = 27) 2) Group 2: Ultevursen 60/60 µg (60 µg loading dose administered on Day 1, 60 µg maintenance dose administered at Month 3 and every 6 months thereafter; n = 27) 3) Group 3: Sham-procedure (administered on Day 1, Month 3 and every 6 months thereafter; n = 27) The primary endpoint will be assessed at 18 months of treatment. Analysis of all other efficacy and safety parameters will also be reported at that time point. All efficacy and safety parameters will continue to be followed during the 24-month study period.
Study Plan	The study includes screening period of up to 12 weeks. Screening will take place over at least 2 days. The treatment visit (Day 1) should be performed as soon as possible after Screening, where feasible.

	During the screening period, subjects will be assessed according to the eligibility criteria. It is recommended that screening will be conducted in a stepwise manner, so that eligibility is confirmed first with less intensive assessments and more intensive assessments are conducted after eligibility by all other criteria have been confirmed. Subjects who meet all eligibility criteria will be enrolled and randomized into the study and will receive their dose of study treatment on Day 1. Ultevursen will be administered via intravitreal (IVT) injection into the subject's study eye (i.e., treated eye or henceforth TE; see Section 4.2.1.2 for selection of the TE) in accordance with the procedures outlined in the Study Reference Manual. Subjects receiving the sham-procedure will undergo a procedure that will closely mimic the active injection, but there will be no penetration of the globe. Administration of study treatment, as well as clinical monitoring of the subject during and right after administration of study treatment, will be performed by an unmasked physician. All other clinical assessments will be performed by a separate, masked physician, or by masked study personnel. After each administration of study treatment subjects will be monitored clinically for safety, including intraocular pressure (IOP) and signs of inflammation. Frequent study visits and safety monitoring by the Investigator will be in place, together with oversight by the Medical Monitor and the Data Monitoring Committee (DMC) (see Section 9.1). The Investigator or the Medical Monitor (in consultation with the DMC, as appropriate) may decide to hold (delay or skip) or discontinue study treatment for an individual subject. Stopping criteria are described in Section 4.2.3. Subjects who discontinue study treatment will continue to be followed for safety and efficacy. Efficacy and safety assessments, including retinal structure changes, functional assessments of vision and PRO measures will be performed at selected study visits as indicated in the Schedule of Events (SOE) All assessments will be performed on both eyes. A central reading center will grade structural and functional exams in a masked way. Any assessment may be repeated if the results are considered unreliable or of unacceptable quality by the Investigator or the reading center. Samples for systemic exposure analysis will be collected as indicated in the SOE Assessments can be completed over multiple non-consecutive days.
Diagnosis and Main Criteria for Eligibility Relating to Study Initiation:	**Inclusion Criteria Relating to Study Initiation:** The subject is eligible for the study and thus eligible to receive ultevursen or sham-procedure in the TE if all the following inclusion criteria apply at Screening/Day 1: 1. An adult (≥ 18 years) willing and able to provide informed consent for participation prior to performing any study related procedures, and suitable verbal, auditory, written and/or tactile sign language communication as to allow informed consent to be obtained, in the opinion of the Investigator. OR A minor (12 to < 18 years) with a parent or legal guardian willing and able to provide written permission for the subject's participation prior to performing any study related procedures and pediatric subjects able to provide age appropriate assent for study participation. The lower age limit for pediatric

	populations is subject to local regulatory and ethics committee requirements (e.g., 16 to <18 for Norway). 2. An adult willing to comply with the protocol, follow study instructions, attend study visits as required and willing and able to complete all study assessments. OR A minor able to complete all study assessments and comply with the protocol and has a parent or caregiver willing and able to follow study instructions, and attend study visits with the subject as required. 3. Clinical presentation consistent with RP with Usher syndrome type 2 or non-syndromic form of RP (NSRP), based on ophthalmic, audiologic, and vestibular examinations. 4. A molecular diagnosis of homozygosity or compound heterozygosity for 1 or more pathogenic exon 13 mutations in the *USH2A* gene, based on genetic analysis at screening. 5. BCVA between ≥30 and ≤68 letters (approximate Snellen equivalent 20/250 – 20/50) in the TE, using the mean BCVA reading at Screening (see Section 8.1) and based on the ETDRS. Subjects with a mean BCVA between >68 and ≤73 letters will be allowed with documented historic evidence of a BCVA equivalent decline of >5 letters in both eyes (i.e., >1 line decline using Snellen or >0.1 LogMAR) anytime within the last 18 months relative to Screening. 6. BCVA between ≥30 and ≤73 letters (approximate Snellen equivalent 20/250 – 20/40) in the contralateral eye (CE), using the mean BCVA reading at Screening (see Section 8.1) and based on the ETDRS. 7. A difference in mean BCVA readings at Screening between the TE and CE of ≤10 letters (based on ETDRS). BCVA differences between eyes that are greater than 10 letters may be allowed however, the Investigator should discuss the case with the Medical Monitor. 8. Stable BCVA in the TE and CE, defined as 2 separate BCVA measurements at Screening that fall within ≤ 5 letters (based on the ETDRS) for each respective eye. See Section 8.1 of the protocol. 9. A visible EZ layer on SD-OCT in the TE, as determined by the Investigator. 10. No limitations to SD-OCT image collection that would prevent high quality, reliable images from being obtained in both eyes, as determined by the Investigator. 11. Reliable BCVA, perimetry, and other measurements in both eyes, as described in the Study Reference Manual and Imaging Manual and determined by the Investigator. 12. No visually significant ocular media opacities and adequate pupillary dilation to permit good quality retinal imaging in both eyes, as assessed by the Investigator.

	Exclusion Criteria Relating to Study Initiation: The subject is ineligible for the study if any of the following criteria apply at Screening/Day 1: 1. Presence of additional non-exon 13 *USH2A* pathogenic mutation(s) on the *USH2A* allele carrying the exon 13 mutation in subjects who have mono-allelic exon-13 mutations. 2. Presence of non-exon 13 *USH2A* pathogenic mutation(s) on both *USH2A* alleles in subjects who have biallelic exon 13 mutations. 3. Presence of pathogenic mutations in genes (other than the *USH2A* gene) associated with Usher syndrome Type 2 or NSRP, or other inherited retinal degenerative diseases or syndromes. Note: The confirmed presence of homozygous or compound heterozygous known disease-causing mutations in other genes involved in recessive retinal dystrophies (RD), or the confirmed presence of known disease-causing mutations in genes involved in dominant or X-linked retinal dystrophies is exclusionary. 4. Presence of any significant ocular (in either eye) or non-ocular disease/disorder (or medication and/or laboratory test abnormalities) which, in the opinion of the Investigator and with concurrence of the Medical Monitor, may either put the subject at risk because of participation in the study, may influence the results of the study, or the subject's ability to participate in the study. This includes but is not limited to a subject who has uncontrolled cystoid macular edema (CME). CME is permissible if stable for 3 months (with or without treatment). Past CME is permissible if resolved for more than 1 month. 5. History or presence of ocular herpetic diseases (including herpes simplex virus, varicella zoster or cytomegalovirus) in either eye. 6. Presence of any suspected active ocular or periocular infection in either eye. 7. Presence of any of the following lens opacities in either eye based on the age-related eye diseases study (AREDS) lens grading scale: cortical opacity ≥ +2, posterior subcapsular opacity ≥ +2, or a nuclear sclerosis ≥ +2, and which are: 1) clinically significant in the opinion of the Investigator, 2) would adequately prevent clinical and photographic evaluation of the retina. 8. History of amblyopia in either eye that resulted in significant vision loss, in the opinion of the Investigator. 9. Receipt within 3 months prior to Screening of any intraocular or periocular surgery (including refractive surgery), or an IVT injection, or planned intraocular surgery or procedure in either eye during the course of the study. For YAG laser treatment of a posterior capsular opacity, receipt within 1 month prior to Screening or planned procedure in either eye during the course of the study. 10. Current treatment or treatment within the past 12 months with therapies known to influence the immune system (including but not limited to steroid implants, cytostatics, interferons, tumor necrosis factor (TNF)-binding proteins, drugs acting on immunophilins, or antibodies with known impact on the immune system). Subjects that have been treated with systemic steroids within the past 12 months or that require intermittent use of topical steroids may be considered for inclusion following approval by the Medical Monitor. 11. A history of glaucoma or an IOP greater than 21 mmHg in either eye that is not controlled with medication or surgery. IOP measurements between 21 and 24 mmHg may be allowed however, the Investigator should discuss the case with the Medical Monitor.

	12. Use of any investigational drug or device within 90 days or 5 half-lives preceding the first dose of study medication, whichever is longer, or plans to participate in another study of an investigational drug or device during the course of the study. 13. Any prior treatment with genetic or stem-cell therapy for ocular or non-ocular disease. 14. History of malignancy within 2 years prior to Screening, except adequately treated squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. 15. Known hypersensitivity to antisense oligonucleotides or any constituents of the injection. 16. Pregnant and breastfeeding subjects. Females of childbearing potential and males must comply with using highly effective methods of contraception as defined in Section 6.2.2. Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the criteria in the protocol (see Section 6.2.2).
Study Drug, Dosage and Mode of Administration:	Two dose regimens will be tested: 1. 180 µg loading dose, and 60 µg maintenance doses (180/60 µg) 2. 60 µg loading dose, and 60 µg maintenance doses (60/60 µg)
Duration of Treatment:	24 months The Sponsor plans on providing access to ultevursen drug after the end of study (EOS) in an open-label extension study.
Reference Therapy, Dosage and Mode of Administration:	Sham procedure
Statistical Methods:	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AON	Antisense Oligonucleotide
AREDS	Age-Related Eye Diseases Study
AST	Aspartate Aminotransferase
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CE	Contralateral Eye
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CME	Cystoid Macular Edema
CRP	C-Reactive Protein
CSR	Clinical Study Report
DHA	Docosahexaenoic Acid
DMC	Data Monitoring Committee
DP	Drug Product
EC	Ethics Committee
EZ	Ellipsoid Zone
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
ERG	Electroretinogram
FAS	Full-Analysis Set
FDA	Food and Drug Administration
FIH	First-in-human
FST	Full-field Stimulus Threshold
GCP	Good Clinical Practice

Abbreviation	Definition
γGT	Gamma-Glutamyl Transferase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
INR	International Normalized Ratio
IOP	Intraocular Pressure
iPSC	Induced Pluripotent Stem Cells
IRB	Institutional Review Board
IVT	Intravitreal
IWRS	Interactive Web Response System
LDH	Lactic Dehydrogenase
LLVA	Low Luminance Visual Acuity
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
NSRP	Non-syndromic Retinitis Pigmentosa
PBS	Phosphate buffered saline
PGI-C	Patient Global Impressions of Change
PGI-S	Patient Global Impressions of Severity
PRO	Patient Reported Outcome
ProQR	ProQR Therapeutics
PT	Preferred Term
RNA	Ribonucleic Acid
RD	Retinal Dystrophies
RP	Retinitis Pigmentosa
RTU	Ready to Use
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SMP	Safety Management Plan
SOC	System Organ Class
SOE	Schedule of Events
SUSAR	Suspected Unexpected Serious Adverse Reaction
TE	Treated Eye
TEAE	Treatment Emergent Adverse Event

Abbreviation	Definition
TLF	Table Listing Figure format
TNF	Tumor Necrosis Factor
US	United States
VA LV VFQ-20	Veterans Affairs Low Vision Visual Functioning Questionnaire
VF	Visual Field
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

2.0 INTRODUCTION

ProQR Therapeutics (ProQR) is developing an oligonucleotide product, ultevursen, for the treatment of patients with retinitis pigmentosa (RP) caused by mutations in exon 13 of the *USH2A* gene. The primary goal of the development plan for ultevursen is to provide treatment to overcome the genetic defect in patients with pathogenic mutations in exon 13 of the *USH2A* gene, resulting in functional vision restoration or preservation. The intended route of administration is intravitreal (IVT) injection.

2.1 Retinitis Pigmentosa

Retinitis pigmentosa is a clinically and genetically heterogeneous condition and mutations in over 100 genes have been implicated. *USH2A* mutations represent the most common cause of autosomal recessive RP (Hartong 2006).

Pathogenic mutations in the *USH2A* gene disrupt the production of usherin, a protein expressed in photoreceptors where it is required for their maintenance (Liu 2007). In the eye, defects in usherin cause RP. Usherin is also expressed in the ear, where it is required for normal development of cochlear hair cells and hence, normal hearing.

Mutations in exon 13 of the *USH2A* gene result in both non-syndromic and syndromic forms of RP. In the NSRP, RP is not associated with other signs and symptoms as part of a genetic syndrome. In the syndromic form, known as Usher syndrome type 2, patients present with congenital moderate to severe hearing loss, and later detection of the retinal disease (i.e., RP). Affected patients first experience defective dark adaption, with decreased night vision, around the second decade of life, and subsequent loss of peripheral visual field (VF) when photoreceptor degeneration progresses, eventually leading to only a residual central island of vision, which ultimately progresses to complete blindness. Early onset deafness is attributable to genetic causes in at least 50% of cases (Marazita 1993).

The number of patients with RP due to mutations in exon 13 of the *USH2A* gene is estimated to be around 16,000 in the Western World (United States, Canada, Europe, and Australia) from gene databases. While the hearing deficit in patients with Usher syndrome can be at least partially restored using hearing aids or cochlear implants, there is no approved treatment for the retinal disease in NSRP or RP in Usher syndrome type 2 and disease management is supportive. Vitamin A and docosahexaenoic acid (DHA) supplementations have been proposed as pharmacological treatment options. Both therapies showed a good safety profile but limited clinical benefit.

2.2 Ultevursen for the Treatment of RP due to Mutations in Exon 13 of the *USH2A* Gene

The primary goal of the development plan for ultevursen is to provide treatment to overcome the genetic defect in patients with pathogenic mutations in exon 13 of the *USH2A* gene, resulting in functional vision restoration or preservation.

- Reference is made to the IB for further details.

2.3 Benefit Risk Assessment

Retinitis Pigmentosa is a group of inherited eye disorders causing slow photoreceptor degeneration, leading to progressive vision loss. Affected patients first experience defective dark adaption, peripheral visual field loss when photoreceptor degeneration progresses, and eventually have only a residual central island of vision, which ultimately progresses to complete blindness. There are currently no approved therapies for the treatment of RP patients with mutations in exon 13 of the *USH2A* gene and disease management is supportive. They may receive adaptive support, when necessary. In addition, patients usually receive genetic counselling on the risks of passing the condition on to their children and regular medical follow up. A significant unmet medical need exists in this sight-threatening condition.

The design of this study has been selected to provide a sufficient benefit-risk ratio to justify the participation of subjects. Planned doses are expected to result in retinal concentrations in the efficacious range. In addition, multiple measures are incorporated to ensure the safety of participating subjects.

To address the potential risks defined in the toxicology studies, the reported risks from oligonucleotides administered by IVT injection, and the risks associated with the IVT injection procedure, extensive monitoring to protect subject safety is incorporated in this study. This will include assessments of subjects' ophthalmic function and anatomy, in particular, monitoring of anterior, intermediate and posterior segment inflammation by slit-lamp biomicroscopy, clinical lens grading using the Age-Related Eye Diseases Study (AREDS) Clinical Lens Grading System, and monitoring for retinal changes by OCT and dilated fundus examinations. This extensive clinical monitoring provides a means to allow early detection of potential AEs, such as macular edema, changes in BCVA and IOP, detection of intraocular inflammation, lens opacities, and retinal structural modifications. In addition, the visit schedule is designed to monitor subjects one day following IVT injection and a second time within 1 week of IVT injection to monitor for signs of endophthalmitis and intraocular inflammation, consistent with guidelines for IVT injections (Avery 2014).

While the number of subjects is small, these results, and the positive benefit-risk assessment support continued clinical testing of ultevursen.

Detailed information about benefits and potential risks of ultevursen, as well as information on nucleotide AONs as a class of therapeutics can be found in the IB.

There is a risk with the ongoing COVID-19 pandemic, that subjects may be exposed and contract COVID-19 while attending the clinic for scheduled visits, or unable to attend the clinic due to regional restrictions associated with pandemic response measures. COVID-19 exposure mitigation strategies, in accordance with local regulatory and site standard of care medical practices will be in place to minimize exposure risk. Extensions of the visit window or alterations in the SOE can be approved by the Medical Monitor, where required. Any modifications will be in accordance with applicable local regulatory guidelines and documented as a deviation.

2.4 Study Rationale

There are currently no approved therapies for the treatment of RP due to mutations in exon 13 of the *USH2A* gene and disease management is supportive; therefore, an important unmet medical need exists in this condition.

Study PQ-421a-003 aims to define safety and quantify the treatment effect of ultevursen administered via IVT injection in subjects with RP due to mutations in exon 13 of the *USH2A* gene, relative to masked, untreated control subjects, at 2 dose regimens of ultevursen.

2.5 Measures to Minimize Bias

To facilitate interpretation of clinical data, inclusion of randomized, concurrent parallel control groups is recommended for clinical studies whenever possible. Masking of participating subjects, treating physicians and study staff is of particular importance when subject effort or perception

could bias evaluation of study endpoints, such as for measurement of visual acuity (Glassman 2012).

IVT injection is a well-established route of administration within ophthalmic indications that permits targeting of the therapeutic agent to the eye, while minimizing systemic absorption. IVT injection is used in several products for the chronic treatment of ophthalmic diseases (e.g., Lucentis®, Eylea™, Macugen®) and the risk of complications is low when injections are performed by trained ophthalmologists (AAO 2015, Avery 2014).

However, potentially severe complications to IVT injections exist, including endophthalmitis, intraocular inflammation, cataract, retinal detachment, and vitreous hemorrhage. Although the risk of severe complications is small, it is well documented (Jager 2004). Therefore, while IVT injection of the vehicle alone is theoretically feasible as a placebo control, it is not considered ethical since the physical properties of such an injection do not have potential therapeutic benefit. Hence, placebo injections will not be administered in this study to preserve subject safety.

Other possibilities than placebo injections to effect masking include alternative dosing regimens, alternative dose levels, and existing products approved for the indication being sought. There are no existing approved products for the indication under investigation.

Use of sham-procedures (i.e., no penetration of the globe) to mask subjects to treatment assignment in studies of products administered via IVT injections eliminates the risk of complications due to injection in the control arm. The sham-procedure, which closely mimics the injection procedure used for product delivery can effectively mask participants to treatment assignment; however, the masking effect is less pronounced in the case that a single subject receives both the real and sham injections in their 2 eyes (Glassman 2012).

To reduce bias due to effort and subjectivity, masking will be achieved by use of a sham-procedure (see Study Reference Manual for details) as well as testing of 2 different dose levels, and no subject will receive both ultevursen and sham injection.

Drug administration, as well as clinical monitoring of the subject during and right after administration of study treatment, will be performed by a separate, unmasked physician (see Section 4.2.1.3), and clinical assessments (including efficacy and safety assessments) will be performed by a masked physician. A masked central reading center will be used for ophthalmologic assessments including microperimetry, FST, and SD-OCT.

2.6 Dose Selection

The target regimen of ultevursen will consist of a loading dose of 180 µg, followed by maintenance doses of 60 µg after 3 months, and at 6 monthly intervals thereafter. The use of a loading dose followed by maintenance doses aims at reaching steady state (efficacious) levels in the retina from the first injection, to maximize clinical response and the potential to provide benefit to the subject. A second arm will test the efficacy and safety of a dose regimen of ultevursen without a high loading dose (i.e., 60 µg loading dose, followed by 60 µg maintenance dose at month 3, and every 6 months thereafter).

As AONs are readily distributed to all eye tissues, and the vitreous is not acting as a drug reservoir, the axial length and overall eye volume are considered the most important parameter for determining the ultevursen dose and the highest recommended IVT injection volume. At around 3 years of age, the human eye is fully developed, and the compartmental volume is 90% of that in adulthood (Fledelius 2014, Vinekar 2015). The axial length of the eye changes from approximately 16 to 18 mm at birth, 19.5 mm in infants, 23 mm in 3-year-olds, until 22 to 24 mm in adults (Hellstrom 1997).

2.7 Study Population

Eligible subjects will be 12 years of age or older and have a molecular diagnosis of either homozygosity or compound heterozygosity for at least one pathogenic mutation in exon 13 of the *USH2A* gene. All subjects must be free of confounding non-exon 13 *USH2A* mutations and/or other pathologies that may interfere with the interpretation of study results, with participation and/or compliance in the study, or put the subject at increased risk due to participation.

At the time of screening, to determine eligibility, subjects will undergo anatomical and structural assessments of both eyes and must exhibit a clinical presentation consistent with RP due to Usher syndrome type 2 or NSRP, as assessed by the Investigator.

Reference is made to Section 5.3 for specific eligibility requirements.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of ultevursen.

3.2 Secondary Objective

The secondary objectives of the study are:

- To further evaluate the efficacy of ultevursen
- To evaluate the safety and tolerability of ultevursen
- To evaluate changes in PRO measures in subjects treated with ultevursen
- To evaluate the systemic exposure of ultevursen

4.0 STUDY OVERVIEW

4.1 Criteria for Evaluation

The primary endpoint will be assessed at 18 months of treatment. All other efficacy and safety parameters will also be reported at that time point. All efficacy and safety assessments will continue to be followed up until Month 24.

4.1.1 Primary Endpoints

- Mean change from baseline in BCVA (based on ETDRS chart) at 18 months of treatment versus sham-procedure

4.1.2 Secondary Endpoints

The order in which the secondary endpoints will be analysed will be defined in the SAP.

Key Secondary Endpoints (Efficacy)

- Proportion of subjects who maintain vision defined by BCVA loss less than 15 Letters (based on ETDRS)

Other Secondary Endpoints (Efficacy)

- Other analyses of BCVA
- EZ area and width as imaged by SD-OCT
- LLVA
- Microperimetry
- FST

Secondary Endpoints (Safety and Tolerability)

- Ocular and non-ocular AEs

Secondary Endpoints (PROs)

- Change from baseline in PRO measures, as assessed by:
  - Veterans Affairs Low Vision Visual Functioning Questionnaire (VA LV VFQ-20) (Stelmack 2007)
  - Patient Global Impressions of Severity (PGI-S)
  - Patient Global Impressions of Change (PGI-C)

Secondary Endpoints (Systemic Exposure)

- Exposure of ultevursen in serum

4.2 Study Design

PQ-421a-003 is a double-masked, randomized, controlled, multiple-dose study to evaluate the efficacy, safety, and tolerability of ultevursen in subjects with RP due to mutations in exon 13 of the *USH2A* gene.

At study start subjects will be randomized to one of the following treatment groups:

- Group 1: Ultevursen 180/60 µg (180 µg loading dose administered on Day 1, 60 µg maintenance dose administered at Month 3 and every 6 months thereafter; n = 27)
- Group 2: Ultevursen 60/60 µg (60 µg loading dose administered on Day 1, 60 µg maintenance dose administered at Month 3 and every 6 months thereafter; n = 27)
- Group 3: Sham-procedure (administered on Day 1, Month 3 and every 6 months thereafter; n = 27)

The primary endpoint will be assessed at 18 months of treatment. Analysis of all other efficacy and safety parameters will also be reported at that time point. All efficacy and safety parameters will continue to be followed until Month 24.

The same safety monitoring protocol and efficacy assessments will apply to both eyes.

Dosing will be only in the TE (i.e., study eye). The CE will not be dosed.

Changes to the above-described treatment plan may be warranted and will be guided by the ongoing assessment of benefit-risk, with concurrence from the Medical Monitor.

4.2.1 Study Plan

4.2.1.1 Screening

During the screening period, subjects will be assessed according to the eligibility criteria. Subjects who meet all eligibility criteria will be enrolled into the study. Reference is made to Section 7.2 for more details on the screening process.

Assessments can be completed over multiple, non-consecutive days instead of 1 full day, at the discretion of the Investigator.

4.2.1.2 Study Drug Administration

Subjects will receive study drug via IVT injection in accordance with the procedures outlined by the current international guidelines (AAO 2015; Avery 2014) and as outlined in the Study Reference Manual.

Administration of study treatment, as well as clinical monitoring and evaluation of subject's safety during and right after administration of study treatment, will be performed by an unmasked physician, but clinical assessments (including efficacy and safety assessments) will be performed by a separate, masked physician. Specific study drug and sham-procedure administration procedures can be found in the Study Reference Manual.

After each dosing, subjects will be assessed for safety and tolerability at follow-up visits.

4.2.1.3 Assessments and Follow-up

On the dosing days post study treatment, subjects will be monitored for safety, including IOP, optic nerve swelling and signs of inflammation. An unmasked physician will administer the study treatment and monitor right after administration. The clinical monitoring and evaluation of subject's safety by the unmasked physician during and right after administration of the study treatment include e.g., IOP, verification that the retina is attached, and checking for hemorrhage and signs of intraocular inflammation.

The frequency of all assessments is presented in the SOE - See Section 7.2 for details on dosing and follow-up visit procedures. More frequent evaluation may be undertaken for an individual subject to monitor safety at the discretion of the Investigator. Data for all unscheduled visits should be recorded in the electronic case report form (eCRF).

Assessments can be completed over multiple, non-consecutive days instead of 1 full day, at the discretion of the Investigator.

All ophthalmic assessments will be performed on both the TE and CE.

The primary endpoint will be assessed at 18 months of treatment. Available data on other efficacy and safety parameters will also be reported at that time point. All efficacy and safety parameters will continue to be followed up until Month 24 -For subjects completing the study, the Sponsor plans on providing access to study drug and/or continued follow up after the EOS visit, in an open-label extension study.

4.2.2 Emergency Unmasking Procedure

In the event of a medical emergency, when knowledge of treatment assignment is needed for immediate medical management of the subject's health, the Investigator can obtain unmasked treatment assignment through the centralized Interactive Web Response System (IWRS) at any time. Instructions on how to unmask subjects will be provided in the eCRF completion guidelines. Thorough documentation of the rationale for unmasking is required along with prompt notification to the Medical Monitor that unmasking has taken place, however this should not delay the unmasking.

4.2.3 Stopping Criteria

4.2.3.1 Stopping Criteria for Individual Subjects

The Investigator may also discontinue a subject from study treatment for other reasons Reference is made to Section 9.4.1 for required follow-up by the Investigator in case of ongoing (serious) AEs at the time of study treatment discontinuation. Any subject discontinued from study treatment is to have the reason recorded in the eCRF.

If a subject is discontinued from the study, his/her subject number cannot be reused.

4.2.3.2 Subject Withdrawal

Subjects are free to withdraw from the study at any time. However, subjects will be encouraged to remain in the study for safety follow-up whenever possible through the EOS visit. A subject who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator should make every attempt to encourage the subject to remain in the study for observation (at least) through the Month 24 Visit (see also Section 9.4.1). The Investigator should follow up on AEs outside of the clinical study to ensure subject safety; however, no data on such events will be collected for study purposes.

4.2.4 Discontinuation of the Study

4.2.4.1 Efficacy

The final inferential analyses will be performed at the planned primary time point at Month 18. Analyses at other (earlier or later) time points will be considered as exploratory. Hence, there are no planned inferential interim analyses (i.e., for either a futility or efficacy claim) and therefore no associated stopping rules.

4.2.4.2 Safety

The DMC and Medical Monitor will evaluate the safety and tolerability data at pre-specified time points (defined in the DMC charter, Section 9.1) and on an ad hoc basis as needed (Section 4.2.3), leading to a recommendation (by the DMC) and subsequently a decision (by the Sponsor) if the study should continue or cease, or if any modifications should be made as to how subjects are treated or managed. Reference is also made to Section 13.3.

5.0 SELECTION OF STUDY POPULATION

5.1 Study Population

Subjects with a diagnosis of RP due to mutations in exon 13 of the *USH2A* gene who meet all eligibility criteria will be eligible for participation in this study.

5.2 Selection of Subjects

Screening of subjects will be performed within 12 weeks prior to dosing. Screening will take place over at least 2 days. The treatment visit (Day 1) should be performed as soon as possible after Screening, where feasible.

Subjects will be evaluated against all eligibility criteria as presented in the SOE

If a subject would not be eligible in the opinion of the Sponsor's Medical Monitor, after

discussion with the Investigator, it may be decided that the subject cannot participate in the study.

Results of assessments for all eligibility criteria must be available and reviewed prior to the subject's dose of study treatment.

5.3 Eligibility Criteria

5.3.1 Inclusion Criteria Relating to Study Initiation

The subject is eligible for the study and thus eligible to receive ultevursen or sham-procedure in the TE if all the following inclusion criteria apply at Screening/Day 1:

1. An adult (≥ 18 years) willing and able to provide informed consent for participation prior to performing any study related procedures, and suitable verbal, auditory, written and/or tactile sign language communication as to allow informed consent to be obtained, in the opinion of the Investigator.
   OR
   A minor (12 to < 18 years) with a parent or legal guardian willing and able to provide written permission for the subject's participation prior to performing any study related procedures and pediatric subjects able to provide age appropriate assent for study participation. The lower age limit for pediatric populations is subject to local regulatory and ethics committee requirements (e.g., 16 to <18 for Norway).
2. An adult willing to comply with the protocol, follow study instructions, attend study visits as required and willing and able to complete all study assessments.
   OR
   A minor able to complete all study assessments and comply with the protocol, and has a parent or caregiver willing and able to follow study instructions, and attend study visits with the subject as required.
3. Clinical presentation consistent with RP with Usher syndrome type 2 or non-syndromic form of RP (NSRP), based on ophthalmic, audiologic, and vestibular examinations.
4. A molecular diagnosis of homozygosity or compound heterozygosity for 1 or more pathogenic exon 13 mutations in the *USH2A* gene, based on genetic analysis at screening.
5. BCVA between ≥30 and ≤68 letters (approximate Snellen equivalent 20/250 – 20/50) in the TE, using the mean BCVA reading at Screening (see Section 8.1) and based on ETDRS. Subjects with a mean BCVA between >68 and ≤73 letters will be allowed with documented historic evidence of a BCVA equivalent decline of >5 letters in both eyes (i.e., >1 line decline using Snellen or >0.1 LogMAR) anytime within the last 18 months relative to Screening.
6. BCVA between ≥30 and ≤73 letters (approximate Snellen equivalent 20/250 – 20/40) in the CE, using the mean BCVA reading at Screening (see Section 8.1) and based on the ETDRS.
7. A difference in mean BCVA readings at Screening between the TE and CE of ≤10 letters (based on ETDRS). BCVA differences between eyes that are greater than 10 letters may be allowed however, the Investigator should discuss the case with the Medical Monitor.

8. Stable BCVA in the TE and CE, defined as 2 separate BCVA measurements at Screening that fall within ≤ 5 letters (based on the ETDRS) for each respective eye. See Section 8.1 of the protocol.
9. A visible EZ layer on SD-OCT in the TE, as determined by the Investigator.
10. No limitations to SD-OCT image collection that would prevent high quality, reliable images from being obtained in both eyes, as determined by the Investigator.
11. Reliable BCVA, perimetry, and other measurements in both eyes, as described in the Study Reference Manual and Imaging Manual and determined by the Investigator.
12. No visually significant ocular media opacities and adequate pupillary dilation to permit good quality retinal imaging in both eyes, as assessed by the Investigator.

5.3.2 Exclusion Criteria Relating to Study Initiation

The subject is ineligible for the study if any of the following criteria apply at Screening/Day 1:

1. Presence of additional non-exon 13 *USH2A* pathogenic mutation(s) on the *USH2A* allele carrying the exon 13 mutation in subjects who have mono-allelic exon-13 mutations.
2. Presence of non-exon 13 *USH2A* pathogenic mutation(s) on both *USH2A* alleles in subjects who have biallelic exon 13 mutations.
3. Presence of pathogenic mutations in genes (other than the *USH2A* gene) associated with Usher syndrome Type 2 or NSRP, or other inherited retinal degenerative diseases or syndromes.
   Note: The confirmed presence of homozygous or compound heterozygous known disease-causing mutations in other genes involved in recessive retinal dystrophies (RD), or the confirmed presence of known disease-causing mutations in genes involved in dominant or X-linked retinal dystrophies is exclusionary.
4. Presence of any significant ocular (in either eye) or non-ocular disease/disorder (or medication and/or laboratory test abnormalities) which, in the opinion of the Investigator and with concurrence of the Medical Monitor, may either put the subject at risk because of participation in the study, may influence the results of the study, or the subject's ability to participate in the study. This includes but is not limited to a subject who has uncontrolled cystoid macular edema (CME). CME is permissible if stable for 3 months (with or without treatment). Past CME is permissible if resolved for more than 1 month.
5. History or presence of ocular herpetic diseases (including herpes simplex virus, varicella zoster or cytomegalovirus) in either eye.
6. Presence of any suspected or active ocular or periocular infection in either eye.
7. Presence of any of the following lens opacities in either eye based on the age-related eye diseases study (AREDS) lens grading scale: cortical opacity ≥ +2, posterior subcapsular opacity ≥ +2, or a nuclear sclerosis ≥ +2, and which are: 1) clinically significant in the opinion of the Investigator, 2) would adequately prevent clinical and photographic evaluation of the retina.
8. History of amblyopia in either eye that resulted in significant vision loss, in the opinion of the Investigator.

9. Receipt within 3 months prior to Screening of any intraocular or periocular surgery (including refractive surgery), or an IVT injection other or planned intraocular surgery or procedure in either eye during the course of the study. For YAG laser treatment of a posterior capsular opacity, receipt within 1 month prior to Screening or planned procedure in either eye during the course of the study.
10. Current treatment or treatment within the past 12 months with therapies known to influence the immune system (including but not limited to steroid implants, cytostatics, interferons, tumor necrosis factor (TNF)-binding proteins, drugs acting on immunophilins, or antibodies with known impact on the immune system). Subjects that have been treated with systemic steroids within the past 12 months or that require intermittent use of topical steroids may be considered for inclusion following approval by the Medical Monitor.
11. A history of glaucoma or an IOP greater than 21 mmHg in either eye that is not controlled with medication or surgery. IOP measurements between 21 and 24 mmHg may be allowed however, the Investigator should discuss the case with the Medical Monitor.
12. Use of any investigational drug or device within 90 days or 5 half-lives preceding the first dose of study medication, whichever is longer, or plans to participate in another study of an investigational drug or device during the course of the study.
13. Any prior treatment with genetic or stem-cell therapy for ocular or non-ocular disease.
14. History of malignancy within 2 years prior to Screening, except adequately treated squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
15. Known hypersensitivity to antisense oligonucleotides or any constituents of the injection.
16. Pregnant and breastfeeding subjects. Females of childbearing potential and males must comply with using highly effective methods of contraception as defined in Section 6.2.2. Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the criteria in the protocol (see Section 6.2.2).

6.0 STUDY DRUG AND CONCOMITANT THERAPIES

6.1 Study Drug

6.1.1 Study Drug Description and Supply

The ultevursen study drug is a solution for IVT injection.

Please refer to the Pharmacy Manual and Study Reference Manual for additional details.

6.1.2 Placebo

No placebo is used.

6.1.3 Study Drug Shipment and Storage

Please refer to the Pharmacy Manual for details on shipment, storage, handling and dose preparation. For administration, please refer to the Study Reference Manual.

6.1.4 Study Drug Accountability and Reconciliation

The Investigator must designate a research pharmacist or other staff member to maintain an inventory record of drugs received and dispensed. Additional details on study drug accountability are provided in the Pharmacy Manual and the Study Reference Manual.

Forms are provided to facilitate the inventory control. These forms must be used unless the Investigator (or designee) has previously established a system that complies with local regulations and is approved by the Sponsor. The study drug must be dispensed only at the institution(s) specified on form Food and Drug Administration (FDA) 1572 or Statement of Investigator (as applicable).

Upon completion or termination of the study and after inventory by a Sponsor representative (monitor), it will be determined if unopened study drug vials are to be sent to the Sponsor in the original containers or are to be destroyed at the study center.

6.1.5 Dosage and Administration

Two dose regimens of ultevursen will be tested:

1. 180 µg loading dose, 60 µg maintenance dose (180/60 µg)

2. 60 µg loading dose, 60 µg maintenance dose (60/60 µg)

The physician administering study treatment will be unmasked to assignment of study drug or sham-procedure but will be masked to the dose of study drug. Treatment assignment will be through the centralized IWRS for the study. The physician performing the clinical assessments will be masked. All subjects will be masked to study treatment assignment.

Subjects will receive ultevursen via IVT injection or will undergo a sham-procedure. Administration of ultevursen and the sham-procedure will only be performed by qualified ophthalmologists in an in-clinic setting. No other medications should be mixed with ultevursen.

Reference is made to the Study Reference Manual and Pharmacy Manual for detailed instructions on the IVT injection and the sham-procedure.

6.2 Concomitant Medications and Auxiliary Therapy

The medications usually used in ophthalmology care are permitted, including but not limited to: topical anesthetic agents, carbonic anhydrase inhibitors (intravenous, oral, topical), alpha agonists ophthalmic drops, rho kinase inhibitor ophthalmic drops, beta blocker ophthalmic solutions, prostaglandin analog ophthalmic solutions, ophthalmic solutions/gels of corticosteroids, non-steroidal anti-inflammatory ophthalmic drops, antibiotics and antiseptics, topical agents for pupillary dilatation, artificial tears and anti-allergic ophthalmic solutions, in accordance with the approved Label or Summary of Product Characteristics of the products. Use of topical steroids should be initiated only when other treatments have been deemed ineffective/unsafe for the subject.

The concomitant medications recommended for IVT injection are detailed in the Study Reference Manual.

There are no medicinal products classified as auxiliary in this clinical trial.

6.2.1 Prohibited Concomitant Medications

The use of any investigational drug or device within 90 days or 5 half-lives of the drug at Day 1, whichever is longer, or plans to participate in another clinical study during the study period is prohibited. Medications that are known to be toxic to the lens, retina, or optic nerve are prohibited. These may include, but are not limited to: systemic/intraocular steroids, amiodarone, deferoxamine, chloroquine/hydroxychloroquine sulfate, tamoxifen, phenothiazines, and ethambutol, pentosan polysulfate, etc. Topical steroids are not prohibited but should only be used following consultation with the Medical Monitor (see Section 6.2).

During the study, use of any new medication or change in the dose of a medication that may have side effects on vision will need to be reviewed and approved by the Medical Monitor.

6.2.2 Adequate Forms of Birth Control

Women of childbearing potential (WOCBP; i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile) and fertile male subjects (i.e., after puberty unless permanently sterile) must either practice true abstinence in accordance with their preferred and usual lifestyle,

. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A man is considered fertile unless permanently sterile by bilateral orchiectomy or has undergone vasectomy and received medical assessment of surgical success.

Highly effective methods of birth control include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (provided that the partner is the sole sexual partner and has received medical assessment of the surgical success)
- Sexual abstinence: sexual abstinence must be true abstinence which is the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception

Double barrier methods (a combination of condom with cap, diaphragm, or sponge with spermicide) are not considered highly effective.

Women of non-childbearing potential (i.e., not fertile, before menarche, postmenopausal, or permanently sterilized) may be included without the use of adequate birth control, provided they meet the criteria in the protocol.

Birth control measures must be employed during the time of participation (beginning at the Screening Visit) in this study and must be continued

A man who is fertile should use a condom during treatment and until

7.0 STUDY VISITS

All study visits, assessments and procedures should be completed as indicated per the SOE

7.1 Visit and Assessment Windows

For those procedures for which a specific time point post dose is required (e.g., systemic exposure blood draws), the protocol refers to nominal times. Actual times for such assessments are to be recorded in the source documentation and in the eCRFs, and if any time points are

missed, the reasons are also to be recorded. For more details, please refer to the case report form completion guidelines.

Visits and/or assessments can be completed over multiple, non-consecutive days.

All efforts should be made to prevent missing data. Therefore, deviations from the treatment cycle (and subsequent assessments) may be justified in some cases (e.g., if an AE makes treatment impossible at the schedule dosing day). In exceptional cases, e.g., related to the significant restrictions in site activities or subject's ability to travel to sites for visits as occurring related to the COVID-19 pandemic, extensions of the visit window or alterations in the SOE can be approved by the Medical Monitor. Such extensions of the visit window will be documented as protocol deviations. Still, sites should make every reasonable effort to complete scheduled visits within the time windows defined in this protocol.

7.2 Screening

Prior to or at the first Screening visit a sample for gene sequencing analysis will be obtained (see Section 8.5 for further details). In case the sample for gene sequencing analysis will be obtained prior to the first Screening visit, a separate Informed Consent Form (ICF) and/or assent is available for this purpose (see Section 12.2).

During the screening period, subjects will be assessed according to the eligibility criteria and specified assessments conducted, as presented in the SOE Subjects who have been identified as screen failure may be rescreened if, in the opinion of the Investigator, there is a reasonable chance that the subject may become eligible at a later timepoint. If the decision is taken to rescreen a subject, the subject will need to be re-consented and will obtain a new subject number.

For all subjects, screening should be conducted in a stepwise manner so that eligibility is confirmed first by less intensive assessments. More intensive assessments are to be conducted once eligibility by other criteria have been confirmed to minimize risk and burden.

7.3 Dosing and Follow-up Visits

The timing of dosing and follow-up visits is outlined in the SOE Study treatment will be administered by unmasked qualified ophthalmologists.

All follow-up study visits, assessments and procedures should be completed as indicated per the SOE All efforts should be taken to prevent missing data. Deviations from the treatment cycle (and subsequent assessments) may be justified in some cases (e.g., if an AE makes treatment impossible at the scheduled dosing day [see also Section 7.1]). Subjects will be assessed for safety, tolerability, and efficacy at follow-up visits with all ophthalmic assessments performed on both the TE and CE.

7.4 End of Study Visit & Roll Over to Open Label Extension Study

8.0 STUDY ASSESSMENT PROCEDURES

All clinical assessments (including all efficacy and safety assessments) will be performed by masked staff. Clinical monitoring during and right after administration of study treatment will be performed by an unmasked IVT physician (see also Section 4.2.1.3).

Eligible subjects must complete all Screening examinations. If a subject is unable to complete a specific assessment, this should be recorded in the eCRF and the subject's ability reassessed at the next specified visit. All attempts at performing assessments should be recorded in the eCRF. Any assessment may be repeated if the results are considered unreliable or of unacceptable quality by the Investigator.

8.1 Efficacy

Efficacy assessments include BCVA, LLVA, SD-OCT, microperimetry, FST and PROs. A central reading center, utilizing evaluators masked to treatment assignment, will assess microperimetry, FST, and SD-OCT. See the Study Reference Manual and Imaging Procedure Manual for further information on these assessments.

Subject's assessment of disease severity will be assessed by PGI-S, and assessment of any improvement or decline in clinical status will be assessed by PGI-C.

8.2 Safety

Safety assessments to monitor for AEs include ophthalmic examinations, laboratory evaluations, and SD-OCTs. Assessments will be conducted as indicated by the SOE

8.2.1 Adverse Events

Information regarding occurrence of AEs will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment, and relationship to study drug will be recorded. Refer to Section 9.0 for further details.

8.2.2 Laboratory Evaluations

All laboratory evaluations will be conducted at a central laboratory. Reference ranges for all laboratory parameters are provided in the Laboratory Manual. See Appendix 2 for a list of laboratory tests to be conducted.

Serum chemistries will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphorus, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γGT), C-reactive protein (CRP), alkaline phosphatase (ALP), total and direct bilirubin, lactic dehydrogenase (LDH), albumin, and total protein. Estimated glomerular filtration rate (eGFR) is to be calculated using the Chronic Kidney Disease Epidemiology- Collaboration Creatinine Equation 2009 calculation for adult subjects and the Bedside Schwartz equation, according to the recommendation from National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases, for pediatric subjects.

Hematology will include a complete blood count (CBC): CBC with absolute differential (hematocrit, hemoglobin, white blood cell count [WBCs], red blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count).

Coagulation panel: prothrombin time and International Normalized Ratio (INR).

Approximately 80 mL of blood will be drawn over the course of the entire study for laboratory evaluations, systemic exposure and immunogenicity.

For female subjects of childbearing potential, a pregnancy test will be performed as indicated by the SOE -and is recommended at any visit that may warrant a pregnancy test.

Eligibility of the subject to participate in the study is based in part on safety signals that may be indicated by laboratory values.

Repeat laboratory tests are permitted to confirm potentially spurious values or false positive results, at the discretion of the Investigator. Repeat analysis results for any laboratory assessments that are eligibility criteria should be discussed with the Medical Monitor prior to subject inclusion.

8.2.3 Ophthalmic Examinations

Ophthalmic examinations include slit lamp biomicroscopy, intraocular pressure, and dilated fundus examination and will be performed as indicated per the SOE

Further details on the procedures for ophthalmic examinations are in the Study Reference Manual.

8.2.4 Spectral Domain Optical Coherence Tomography

Changes in SD-OCT findings,

All SD-OCT scans should be performed in accordance with the procedures outlined in the Imaging Procedure Manual.

8.3 Systemic Exposure

Blood samples for systemic exposure analysis of ultevursen will be collected from all subjects as indicated per the SOE (see Section 8.2.2

8.4 Immunogenicity

Blood samples for assessment of immunogenicity will be taken as indicated per the SOE (see Section 8.2.2 and stored for potential later quantification.

8.5 Gene Sequencing

A genotyping report is required for eligibility.

Separate informed consent may need to be obtained per local requirements. A blood or saliva sample for genotyping and gene sequencing should be obtained at or prior to the Screening Visit. In case the sample for gene sequencing analysis will be obtained prior to the first Screening Visit, a separate ICF and/or assent is available for this purpose (see Section 12.2).

9.0 ASSESSMENT OF SAFETY, ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All subjects who receive study treatment will be assessed for safety.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor regarding any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The Investigator is responsible for appropriate medical care of subjects during the study and may add unscheduled visits, additional exams/tests for safety purposes.

9.1 Data Monitoring Committee

An independent DMC will provide safety oversight for the study. A DMC operational charter will be finalized, and an initial organizational meeting held prior to screening of the first subject.

Reference is also made to Sections 4.2.3 and 4.2.4.

9.2 Definitions of Adverse Event, Serious Adverse Event, and Suspected Unexpected Serious Adverse Event

9.2.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related or not. Adverse events can include any unfavorable, noxious, unintended sign, symptom, or disease temporally associated with use of a study drug or other protocol-imposed intervention, regardless of attribution. Adverse events may be spontaneously reported

by the subject, discovered by Investigator questioning, or detected through laboratory test, or other means.

Adverse events include:

- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period (as specified in Section 9.4.1)
- Adverse events not previously observed in the subject that emerge during the protocol-specified AE reporting period (as specified in Section 9.4.1)
- Complications that occur as a result of protocol-mandated interventions
- Adverse events that occur prior to study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as blood draws, sedation prior to IVT injection)

9.2.2 Serious Adverse Events

An AE is considered "serious" if, in the view of Investigator, it results in any of the following outcomes:

- Death
- Life-threatening AE. This definition implies that the subject, in the view of the Investigator, is at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongs existing hospitalization, except for planned hospitalization
- Persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Congenital anomaly or birth defect. This serious criterion applies if a congenital anomaly/birth defect is diagnosed in a child born to a female subject, or a female partner of a male subject exposed to the study drug
- Other important medical events. Medical and scientific judgment should determine whether an AE should be classified as serious in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above.

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs. Surgery for lens opacity removal (lens replacement) is not considered a serious AE as it does not require the subject be admitted to a hospital unit based on the nature of the surgery. Even in the

case where the subject may be hospitalized for convenience, or a subject is too frail to make the commute back and forth to the surgical center, it is still not a Serious AE. The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache) (see Section 9.3.1). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and serious adverse events (SAEs) on the AE eCRF and SAE form.

9.2.3 Suspected Unexpected Serious Adverse Reaction Definition

In order to be qualified as a suspected unexpected serious adverse reaction (SUSAR), the AE must meet 3 criteria: the event is serious, there is a certain degree of probability that the event is a reaction to the study drug being researched and the nature and severity of the reaction are not in agreement with the product information (i.e., the reaction is unexpected as per the reference safety information). All SUSARs will be reported as required to the Competent Authorities and to the Ethics Committee (EC)/Institutional Review Boards (IRBs) of the countries and centers concerned.

9.2.4 Adverse Events of Special Interest

9.3 Assessment of Adverse Events

The Investigator is responsible for assessing the severity and causality of AEs.

9.3.1 Assessment of Severity (Intensity) of Adverse Events

On the AE eCRF, the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- MILD: Awareness of sign, symptom, or event, but easily tolerated. Does not interfere with subject's usual function.
- MODERATE: Discomfort enough to cause interference to some extent with subject's usual function and may warrant intervention.
- SEVERE: Incapacitating and interferes significantly with subject's usual function and warrants intervention.

As described previously in Section 9.2.2, note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event and may not meet the regulatory definition of serious. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as a serious AE unless it met one of the regulatory criteria for SAEs, listed above in Section 9.2.2.

Any change in severity should be noted in the eCRF, e.g., a change from mild to severe or a change from severe to moderate should be noted with the start and stop dates for each intensity.

9.3.2 Assessment of the Relationship of Adverse Events to Study Drug

The Investigator will make a causality assessment about the relationship of each AE to study drug. Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the study drug, presence of characteristic clinical or pathological phenomena, underlying conditions in the study population, exclusion of other causes, and/or absence of alternative explanations. To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

Not Related: The AE has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after dose of study drug).

Related: An AE that is related to the study drug or its administration (i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or

expected response pattern to the suspected intervention, that could not be reasonably explained by the known characteristics of the subject's clinical state).

For all AEs and SAEs, Investigators will make separate assessments of causality about the relationship of the event to study drug and to study procedures (i.e., IVT injection).

Note: The Investigator's assessment of causality for individual AE reports is part of the study documentation process and will be recorded in the subject's medical record, AE eCRF, and SAE form if applicable. Adverse events recorded without the Investigator's assessment of the relationship to study drug will be followed up until causality is assigned.

9.3.3 Assessment of the Outcome of Adverse Events

The Investigator will record the outcome of AEs and SAEs using the following criteria:

- **Recovered/resolved:** The subject has fully recovered from the event, with no residual effects observable.
- **Recovered/resolved with sequelae:** The subject has recovered from the event, but with residual sequelae effects observable.
- **Not recovered/resolved:** Effects of the event are still present.
- **Recovering/resolving:** The subject has improved but has not fully recovered from the event.
- **Fatal:** The death is related to the event.
- **Unknown:** The outcome of the event is unknown to the reporter (e.g., subject was lost to follow-up).

9.4 Reporting of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the subject's medical record, AE eCRF, and/or SAE form, and reported to the Sponsor in accordance with protocol instructions. The AE eCRF can be used to report both AEs and SAEs. If necessary, e.g., in case of failure of the Electronic Data Capture (EDC) system or for logistical reasons, a paper AESI/SAE/Special Situation reporting form may be used instead.

9.4.1 Adverse Event Reporting Period

After signing of the Informed Consent all significant medical conditions including signs/symptoms of the underlying disease and known pre-existing medical conditions found during the screening period and up to initiation of dosing will be captured as medical history. Any event/condition, including those related to participation in the study or study procedures, those not related to underlying disease or pre-existing medical conditions already part of medical

history, and occurring before first dose of study treatment will be captured as a non-treatment emergent AE.

Any event/condition noted once the subject receives their dose of study drug will be captured as a treatment emergent AE. All AEs and SAEs regardless of attribution will be collected until at least 90 days following the last administration of study drug or the subject's EOS visit, whichever is later. At the last scheduled visit, the Investigator should instruct each subject to report to the Investigator any subsequent AEs/SAEs that the subject's personal physician believes could be related to prior study treatment.

SAEs unrelated to study treatment and non-serious AEs are to be followed until the last scheduled study visit (EOS visit), with the outcome at that point of time to be recorded in the eCRF. SAEs related to study treatment (Serious Adverse Drug Reactions) are to be followed until resolution or until they return to baseline, stabilize, or the subject is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF and SAE form (if applicable) and in the subject's medical record to facilitate source data verification. For some SAEs, the Sponsor or its designee may follow up by telephone, facsimile, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

9.4.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

9.4.3 Recording Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF and/or AESI/SAE/Special Situation reporting form. Colloquialisms and abbreviations should be avoided. Serious AEs must also be recorded on the AE eCRF or AESI/SAE/Special Situation reporting form. Only 1 medical concept should be recorded in the event field on the AE eCRF and AESI/SAE/Special Situation reporting form (if applicable).

a. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should also be entered as separate AEs. For example, if severe diarrhea is known to have resulted in dehydration, both diarrhea and dehydration should be entered as AEs on the eCRF, and if also serious, as SAE on AE eCFR and AESI/SAE/Special Situation reporting form (if applicable).

b Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe or occurs more frequently, it should be recorded again on the AE eCRF with the increased severity grading.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded individually on the AE eCRF.

c. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded as AEs on the eCRF and SAE form (if applicable).

If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs on the eCRF and SAE form (if applicable), unless their severity, seriousness, or etiology changes.

d. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 9.4.1), regardless of attribution, will be recorded on the AE eCRF and SAE form and reported to the Sponsor within 24 hours of event knowledge.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept. For example, if death resulted from respiratory failure, the AE recorded should be “Respiratory Failure”, and the outcome of the AE would be “Death”. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “unexplained death” on the AE eCRF and SAE form.

e. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical History eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE eCRF and SAE form (if applicable), it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

f. Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

g. Pregnancy

If a female subject or a female partner of a male subject becomes pregnant during study participation of the female subject or the male partner, a Pregnancy Report form should be completed and faxed to the Sponsor within 24 hours of learning of the pregnancy, using the fax numbers listed in the Study Reference Manual.

Abortion, whether therapeutic or spontaneous, will also be reported on a Pregnancy Report form and faxed to the Sponsor. Refer to the Study Reference Manual for forms and complementary reporting information. If the abortion meets seriousness criteria (see Section 9.2.2, Serious Adverse Event Definition), this information will be captured on the AE eCRF and SAE form (if applicable).

Pregnancy should be followed up until after delivery, and any events to 3 months post-partum or termination of the pregnancy. Any congenital anomaly/birth defect in a child born to a female subject or to a female partner of a male subject exposed to the study drug should be recorded and reported as an SAE.

h. Special Situations Reporting

Medication errors and uses outside what is foreseen in the protocol, including overdose and occupational exposure must be reported to the Sponsor within 24 hours from awareness on an paper AESI/SAE/Special Situation reporting form (if applicable) for tracking purposes and will be considered a protocol deviation. Overdose is defined as any study drug dose administered above the intended dose for the cohort assignment. Additional instructions for reporting special situation information will be provided by the Sponsor at the time of notification.

9.5 AESIs and Serious Adverse Events Notification

For all AESI and SAEs, regardless of suspected causality, a completed AESI/SAE/Special Situation reporting form must be sent within 24 hours of discovery of the event immediately (without undue delay) to:

DRUG SAFETY

See Study Reference Manual

Any fatal or life-threatening (i.e., imminent risk of death) event that is attributed by the Investigator to the study drug must be immediately telephoned to:

DRUG SAFETY

Phone: See Study Reference Manual for phone number

followed by submission of written case details on an AESI/SAE/Special Situation reporting form within 24 hours.

Serious AEs occurring any time after study participation that are considered by the Investigator to be possibly related to study drug must also be reported. The following are important points to remember when completing the SAE form:

- If complete information is not available, at a minimum, subject identifier, suspect drug, study center identifier, event or outcome, and Investigator assessment of causal relationship to study drug should be provided.
- A rationale for the causality assessment of an SAE should always be included, so that a better understanding of the event can be compiled.
- Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event should be submitted by revising the SAE form as soon as the information becomes available. Copies of source documents, with subject identifiers redacted, should be submitted only when they are written in English. If source documents are not in English, the Investigator must summarize the source documents, providing a complete English narrative that includes a description of the events as it evolved, the results of all diagnostic procedures performed, treatments administered, and outcome of the event. A query regarding a follow-up report should be answered within 5 working days from receipt of the query.
- Appropriate diagnostic tests and therapeutic measures are to be performed as necessary and reported on the SAE form.
- All SAEs must be reported to the IRB/EC, if applicable. See the International Council for Harmonisation (ICH) GCP E6 (R2), Section 4.11.1 (ICH 2016).

9.6 Expedited Reporting of Suspected Unexpected Serious Adverse Reactions

The Sponsor or designee will fulfil reporting obligations as defined in the Safety Management Plan (SMP). The SMP details the responsibilities, processes and timelines for expedited reporting and aggregate periodic reporting to relevant recipients (e.g. Competent Authorities, Central ECs/Central IRB, Investigators etc.) across sites within the study. The SMP ensures a systematic approach to safety monitoring and promotes early issue detection to help mitigate any safety risks in clinical trial subjects.

- The Sponsor or its designee is responsible for notifying the study centers of all expedited SAEs that occur during any clinical studies that are using the study drug. The Sponsor or its designee shall also notify Central ECs and Central IRB of SUSARs or significant risks to subjects, per country requirements. All SUSARs will be reported as required to the Competent Authorities of all involved participating countries.
- The Investigator will notify local IRB/EC of SUSARs or significant risks to subjects, per local country requirements. The Investigator must keep copies of all AE information, including correspondence with the Sponsor or local IRB/EC on file.
- The Sponsor will inform Investigators of any emerging safety issues as soon as possible, and at least prior to any planned dosing, following which the Investigator will subsequently inform participants.
- All studies that are conducted within any European country will comply with the European Clinical Trial Directive 2005/28/EC, the Clinical Trial Directive 2001/20/EC, and the Detailed Guidance CT-3 (2011/C 172/01) and Regulation 536/2014.

10.0 STATISTICAL METHODOLOGY

10.1 General Considerations

A comprehensive SAP specifies the statistical methodology, and table, listing and figure (TLF) formats for all aspects of the planned analyses. The SAP supports the completion of the Clinical Study Report (CSR) for this protocol. All AEs will be considered in determining the safety profile of ultevursen. Exploratory analyses not necessarily identified in the SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in the SAP will be clearly identified in the CSR, in accordance with applicable Standard Operating Procedures of the Sponsor.

10.2 Determination of Sample Size

This is a Phase 2/3 study designed to evaluate efficacy, safety, and tolerability of ultevursen in subjects with RP due to mutations in exon 13 of the *USH2A* gene

10.3 Randomization and Masking

Subjects, treating physicians and study staff are masked. The physician administering study treatment will be unmasked to assignment of study drug or sham-procedure but will be masked to the dose of study drug.

The randomization procedure used to assign study treatment to eligible subjects will be through a centralized IWRS, utilizing the randomization schedule generated by the designated unmasked statistician. Subjects will be sequentially assigned according to a computer generated randomization list in the appropriate randomization ratio to 1 of 3 treatment groups and the TE will be treated accordingly (see Section 10.2 and Section 4.2). Subjects will be stratified at randomization based on clinical presentation (i.e., syndromic/non-syndromic RP).

10.4 Replacement of Subjects

10.5 Analysis Populations

All Screened Subjects: All subjects who provided informed consent to participate in the study.

Intent to Treat Population: All subjects who were randomized.

Safety Population: All subjects who were randomized and received at least one dose of study treatment.

Full Analysis Set (FAS) Population: All subjects who received at least one dose of study treatment and had at least 1 baseline BCVA observation or measurement.

Per Protocol Efficacy Population: All subjects in the FAS Population with the exception of subjects with major protocol deviations. The list of major protocol deviations selected for exclusion from this population will be completed prior to database lock.

Systemic Exposure Set: All subjects who received ultevursen and have at least one pharmacokinetic sample taken.

10.6 Subject Disposition, Demographics and Baseline Disease Characteristics

Subject disposition will be summarized for All Screened Subjects population by dose group.

The number and percentage of subjects who receive ultevursen or the sham-procedure will be tabulated by the number of doses and the treatment group.

Subject demographics and baseline characteristics will be summarized for each treatment group and for all subjects combined. Subject characteristics at baseline include age, race, body weight, and height. Baseline disease characteristics include ophthalmic examinations, measurements and tests, as previously described.

10.7 Treatment Compliance

All doses are observed and administered by study staff. Treatment compliance will be determined by source records documenting treatment observations and summarized.

10.8 Efficacy Analyses

The efficacy evaluations will include evaluations of the endpoints listed in Section 4.1.

Descriptive statistics of clinical efficacy will be tabulated by dose group, and if appropriate, for dose groups combined.

All continuous endpoints will be summarized using the following descriptive statistics: number of subjects, mean, standard deviation, standard error, median, minimum, maximum and 95% confidence intervals for the mean. Categorical endpoints will be summarized using the following: number of subjects, frequency, percentages and 95% confidence intervals. If data appear highly skewed, natural log or other transformation may be used to compute summary statistics.

Continuous efficacy endpoints will be summarized and may be analyzed using appropriate parametric and/or nonparametric inference tests.

10.9 Safety Analyses

10.9.1 Treatment Emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as an event that was not present prior to administration of the first dose of study treatment and present after the first administration or if it represents the exacerbation of an event that was present prior to the first administration.

Adverse events noted during the study will be coded to system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The overall incidence of TEAEs will be summarized by treatment group and classified by SOC and PT. Deaths, AE severity, serious AEs, relationship to study treatment and study discontinuation due to AE will also be tabulated by treatment group. An AE will be considered related to study treatment if the Investigator indicated the event is at least "possibly" related or if the relationship is missing. Adverse events with missing start dates, but with stop dates overlapping into the treatment period will be counted as treatment emergent. All AEs will be listed in subject listings and summarized by numbers and percentages of subjects by treatment group.

10.9.2 Other Safety Assessments

Other safety assessments, such as ophthalmic examinations and SD-OCT will be summarized and listed as specified in the SAP.

10.10 18-Month Primary Analysis and 24-Month/EOS Analysis

<u>18-Month Primary Analysis</u>

After all randomized subjects have completed their Month 18 visit or discontinued the study prior to this visit, the primary analysis will be conducted, i.e., analysis of the primary and secondary efficacy endpoints at Month 18. Follow-up data beyond 18 months, and available data from other endpoints will be analyzed as well.

24-Month /EOS Analysis

Follow-up data collected post the 18-month treatment period will be presented based on an analysis to be performed after the database is locked once all subjects have reached Month 24.

10.11 Multiplicity Considerations

10.12 Subgroup Analyses

10.13 Systemic Exposure Analyses

Systemic exposure analyses will be performed as outlined in the SAP.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Collection

The Investigator will prepare and maintain adequate and accurate source documents (including medical records) designed to record all observations and other pertinent data for each subject treated with the study treatment. Study center staff at each study center will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee) but will be identified by a study center number and subject number, which will be completed in the Screening and Enrollment Log. This number will be used for the duration of their participation in the study. The subject Screening number cannot be re-used if a subject withdraws consent or is a screening fail.

Study center staff will be trained and authorized to use the system in compliance with the Code of Federal Regulations (CFR) 21CFR Part 11, International Council for Harmonisation (ICH) - Good Clinical Practice (GCP) and local regulations, before recording data on eCRFs. All corrections to eCRFs will be made by authorized users, and the changes will be automatically logged in the audit trail of the system (time and date stamps and the user entering or updating

data). Electronic CRFs should be completed for every subject screened or enrolled in the study. At the study's conclusion, a Portable Document Format file will be created for each study center containing their subjects' data submitted on eCRFs. A copy of the eCRF will remain at the study center at the completion of the study.

The Investigator is responsible for all information collected on subjects enrolled in this study and shall ensure that the eCRFs are accurate, complete and completed in a timely fashion. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. The Investigator will ensure that the eCRFs are accurate, complete, and completed in a timely fashion. The Investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are retained according to storage guidelines (Section 13.4). Separate source records are required to support all eCRF entries. The eCRF is not to be used to document data without prior written or electronic records. The Investigator will electronically sign and date in the required places in the eCRF. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF and agrees with the content.

11.2 Data Quality Control

To ensure the quality of clinical data across all subjects and study centers, a clinical data management review will be performed on subject data. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and ICH GCP. To resolve any questions arising from the clinical data management review process, data queries will be sent to the study center. Corrections or updates to the data resulting from queries should be made on the eCRF. All changes will be automatically documented in the software's audit trail, including the reason for change.

11.3 Monitoring

A Sponsor representative (monitor) will contact the Investigator(s) at periodic intervals by telephone or on-site visit for the purpose of monitoring the facilities and assessing the progress of the study. Electronic CRFs and subject records will be reviewed at on-site visits at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy, and consistency of the data, and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRF.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits, including delays in completing eCRFs, are resolved.

Monitoring of study center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the

protocol, ICH GCP, and applicable regulatory requirements. Study drug dispensing and accountability will also be assessed.

11.4 Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/EC may perform audits or inspections at the study center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the study center.

12.0 ETHICAL AND REGULATORY OBLIGATIONS

12.1 Ethical Considerations

The Investigator agrees to conduct this study in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP. The Investigator will conduct all aspects of this study in compliance with the protocol, ICH GCP and applicable regulatory requirements.

12.2 Informed Consent

Before the start of required study procedures, the Investigator or his/her associate must obtain informed consent from each study participant (or the subject's legal representative) in accordance with ICH GCP, and country authority requirements. Age-appropriate assent and permission from a minor subject's parent or legal guardian is required for pediatric subjects. The subject or his/her legal representative must sign the current version of the written, IRB/EC-approved Informed Consent Form in the presence of a witness and be given a copy. The Investigator will ensure that a copy of the signed consent is kept with the subject's records.

In accordance with ICH GCP and country authority requirements, an IRB/EC must review and approve this protocol and the ICF prior to initiation of the study.

12.3 Ethics and Regulatory Review

An IRB/EC should approve the final study protocol, including the final version of the ICF, assent forms and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable IRB/EC, and to the study center staff.

The opinion of the IRB/EC should be given in writing. The Investigator should submit the written approval to Sponsor before enrollment of any subject into the study.

The IRB/EC should approve all advertising used to recruit subjects for the study.

The Sponsor should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/EC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The Sponsor will handle the distribution of any of these documents to the national regulatory authorities.

The Sponsor will provide Regulatory Authorities, IRB/ECs and Investigators with safety updates/reports according to local requirements.

Each Investigator is responsible for providing the IRB/EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study drug. The Sponsor will provide this information to the Investigator so that he/she can meet these reporting requirements.

12.4 Subject Confidentiality

The Investigator and the Sponsor must ensure that the subject's confidentiality is maintained, in accordance with GCP and local regulations. On the eCRFs or other documents submitted to the Sponsor, subjects should be identified by their age and subject number only. Documents that are not for submission to the Sponsor (e.g., signed ICF), should be kept in strict confidence by the Investigator.

The Investigator and the Sponsor will ensure that all clinical trial information shall be recorded, processed, handled, and stored, in such a way that it can be accurately reported, interpreted and verified while the confidentiality, integrity and availability of records and the personal data of the subjects remain protected in accordance with the applicable (local) laws on personal data protection. Measures taken to ensure all of the above include, but are not limited to, encryption, anonymization, multifactor authentication, Intrusion Protection, segregation of authentication.

In compliance with applicable regulations, it is required that the Investigator and institution permit authorized representatives of the Sponsor, the United States (US) Food and Drug Administration (FDA), other regulatory authorities (e.g., European Union/European Economic Area Member State inspector), and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any or all records and reports that are important to the evaluation of this study. The Investigator is obligated to inform and obtain the

consent of the subject to permit named representatives to have access to the study-related records without violating the confidentiality of the subject.

The sponsor will notify the Member States concerned about a serious data security breach at the time of the breach without undue delay but not later than 7 days of becoming aware of that breach. Measures that will be implemented to mitigate the possible adverse effects of a serious data security breach include, but are not limited to, back-ups including remote location, high availability systems for critical environments, and a security incident response plan.

13.0 STUDY ADMINISTRATION

13.1 Investigator's Brochure

Before the study begins, the Investigator will receive the ultevursen IB describing all known nonclinical data, contraindications, warnings, precautions, and adverse reactions associated with the administration of the study drug. If such information is revised while the study is in progress, the IB will be amended or revised, and the Sponsor will provide the most current version to the Investigator.

13.2 Protocol Amendments

If there are any substantial changes to the study protocol, these changes will be documented in a protocol amendment and in a new version of the protocol. The Sponsor will inform the Investigator in writing of any amendment to the protocol. The Investigator must submit the protocol modifications and any ICF modifications to the IRB/EC, and approval must be obtained before the modifications are implemented. The Investigator must send a copy of the approval letter from the IRB/EC to the Sponsor for review. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. In this case, as soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the sponsor, IRB/EC and if applicable the regulatory authority.

13.3 Study Termination and Procedure

Both the Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Investigator should notify the IRB/EC in writing of the study's completion or early termination and send a copy of the notification to the Sponsor.

If the Sponsor, Medical Monitor or designee, study center monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that a study center should be terminated, this action may be taken after appropriate consultation. Termination may occur in accordance with the clauses contained in the study center's executed clinical study agreement. The Sponsor reserves the right to discontinue the

study prior to enrollment of the intended number of subjects but intends only to exercise this right for valid scientific reasons.

If the clinical development of ultevursen is discontinued, the Sponsor shall immediately inform all Investigators/institutions and regulatory authorities. Study termination and follow-up will be performed in compliance with the conditions set forth in the ICH Guidelines S7A (ICH 2000) and local regulatory requirements.

13.4 Study Documentation and Storage

The Sponsor will provide the Investigator with records of drug shipments, eCRFs, and other forms as necessary. The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include, but are not limited to:

- Subject files containing ICFs and supporting originals of source documentation.
- Study files containing the protocol with all amendments, IB, copies of pre-study documentation, and all correspondence to and from the IRB/EC, applicable country authorities, and the Sponsor.
- Records of drug accountability and all drug-related documentation.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Upon the request of the Sponsor, designees, or the regulatory authorities, the Investigator will make all study records available for inspection, including source documents. This information will be treated as confidential.

No study document is to be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

13.5 Use of Information

All personal data pertaining to the subjects in this study and in any subsequent reports will be kept confidential. Subjects will be identified only by their month and year of birth and a subject number. It is the responsibility of the Investigator to keep a subject listing for cross-referencing.

The sponsor will notify the Member States concerned about a serious data security breach at the time of the breach without undue delay but not later than 7 days of becoming aware of that breach. Measures that will be implemented to mitigate the possible adverse effects of a serious data security breach include, but are not limited to, back-ups including remote location, high availability systems for critical environments, and a security incident response plan.

The Investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the development of the study drug. This information may be disclosed to other clinical Investigators, to the US FDA, and to other government agencies.

The Sponsor will ensure that personal data transfers and bodily materials transfer comply with Data Protection Laws of the EU, i.e., the General Data Protection Regulation 2016/679. To that end, all parties/vendors involved in this study will have been assessed and qualified by the Sponsor to ensure data privacy protection is at an adequate level. Appropriate contractual arrangements (Standard Contractual Clauses) will be in place and sufficient supplement technical measures will be implemented by the parties involved in the study.

13.6 End of Study and Final Report

The end of the study is defined as the date of the last visit of the last subject in the study globally.

The Investigator or delegate must notify the IRB/EC upon study completion or termination in compliance with local regulations.

The Sponsor or its designee will provide a final report and/or synopsis to the Investigators, the IRB/EC and Regulatory Authorities in accordance with local requirements.

13.7 Financing and Insurance

Financing and Insurance are addressed separately in the Clinical Study Agreement.

13.8 Publication Policy

Publication policy is addressed separately in the Clinical Study Agreement.

Reporting of clinical study results will be performed in accordance with local Competent Authority regulatory requirements and obligations (e.g., trial data uploaded to EudraCT database within one year following end of the trial).

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15.0 PROTOCOL SUMMARY OF CHANGES

16.0 APPENDICES

16.2 Appendix 2: Clinical Laboratory Tests

Chemistry	Hematology
Sodium	Hematocrit
Potassium	Hemoglobin
Chloride	Red blood cells
Bicarbonate	White blood cells (WBCs)
Blood urea nitrogen (BUN)	Neutrophils
Creatinine	Lymphocytes
Glucose	Monocytes
Calcium	Eosinophils
Phosphorus	Basophils
Albumin	Platelets
Total protein	
Alkaline phosphatase (ALP)	
Aspartate aminotransferase (AST)	
Alanine aminotransferase (ALT)	
Gamma-glutamyl transferase (γGT)	
Total and direct bilirubin	
Lactic dehydrogenase (LDH)	
Creatinine clearance (eGFR by CKD-EPI or Bedside Schwartz)*	
C-reactive protein (CRP)	
Other Tests	**Coagulation**
Pregnancy testing	INR
	Prothrombin time

* Estimated glomerular filtration rate (eGFR) is to be calculated using the CKD-Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation 2009 calculation for calculation for adult subjects and Bedside Schwartz equation, according to the recommendation from National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases, for pediatric subjects.