PROTOCOL: TIGEM3-UshTher-NHS

TITLE:	A Multicentre, Prospective, Longitudinal, Observational Natural History Study to Evaluate Disease Progression in Subjects with Usher Syndrome type 1B (USH1B)
DRUG:	N/A
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Fondazione Telethon
PRINCIPAL/ COORDINATING INVESTIGATOR:	Francesca Simonelli University of Campania Luigi Vanvitelli Naples, Italy
PROTOCOL HISTORY:	16 March 2018 Version 1.1

SIGNATURE PAGE

CLINICAL PROTOCOL NUMBER: TIGEM3-UshTher-NHS

Principal Investigator at Administration Site:

STUDY TITLE
A Multicentre, Prospective, Longitudinal, Observational Natural History Study to Evaluate Disease Progression in Subjects with Usher Syndrome type 1B (USH1B)

Sponsor: Fondazione Telethon

Sponsor Address: Via Varese 16B, 00185 Rome, Italy

Sponsor's Representative: Dr. Stefano Zancan

On behalf of the Sponsor I agree to this protocol:

_____ _____
Sponsor signature Date

Investigator Name:
Investigator Address:

My signature below confirms that I have read and approved this protocol, and assures that this clinical study will be conducted according to all of the requirements in this protocol, the Declaration of Helsinki (1991), ICH Guideline for Good Clinical Practice and all applicable regulatory requirements.

_____ _____
Principal Investigator signature **Date:**

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STUDY SYNOPSIS

Protocol number: TIGEM3-UshTher-NHS	**Disease under study:** Usher Sydrome type 1B
Title of the study: A Multicentre Longitudinal, Observational Natural History Study to Evaluate Disease Progression in Subjects with Usher Syndrome type 1B (USH1B)	
Number of subjects (total): Approximately 50 subjects are planned to be enrolled in the recruitment period.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Italy, Spain and The Netherland	
Study period (planned): 2018-2021	**Clinical phase:** NA

Objectives:

Primary: The primary objective of this study is to evaluate the natural progression of disease over time in USHIB patients using visual field testing and best corrected visual acuity.

Secondary: The secondary objectives of this study are to evaluate the progression of disease over time in USHIB patients through additional assessments:

- Microperimetry (only in selected centres)
- Fundus autofluorescence (FAF)
- Optical Coherence Tomography (OCT)
- Full-field Electroretinogram (ERG),
- Multifocal Electroretinogram,
- Vision-related function and quality of life, as measured by the 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25)

Rationale:

This natural history study is being conducted to understand the progression of disease in USH1B patients as measured by visual acuity and visual field testing and a number of other vision-related assessments.

Investigational product, dose, and mode of administration: N/A

Methodology:

This is a multicenter longitudinal, observational study designed to evaluate the rate of progression in USH1B subjects by visual acuity and visual field measurements and a number of other vision-related assessments.

Inclusion and exclusion criteria:

Inclusion Criteria:

The study population consists of 50 subjects with clinical and genetic diagnosis of USH1 due to *MYO7A* mutations showing Retinitis Pigmentosa.

Male and female subjects of any ethnic group are eligible for participation in this study, providing they meet the following criteria:

1. Must be willing to adhere to protocol for long-term follow-up as evidenced by written informed consent or parental permission and subject assent.
2. Subjects diagnosed with USH1.
3. Molecular diagnosis of USH1B due to *MYO7A* mutations (homozygotes or compound heterozygotes).
4. Age eight years old or older at the time of baseline.
5. Visual acuity ≥ 20/640 in at least one eye

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Unable or unwilling to meet requirements of the study.
2. Unable to communicate with suitable verbal/auditory and/or tactile sign language (in the opinion of the investigator)
3. Participation in a clinical study with an investigational drug in the past six months.
4. Pre-existing eye conditions that would interfere with the interpretation of study endpoints (for example, glaucoma, corneal or significant lenticular opacities, cystoid macular oedema, macular hole).
5. Complicating systemic diseases in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (for example, radiation treatment of the orbit; leukemia with CNS/optic nerve involvement). Also excluded would be subjects with immuno- compromising diseases, as there could be susceptibility to opportunistic infection [such as cytomegalovirus (CMV) retinitis].
6. Subjects with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (e.g. macular edema or proliferative changes).
7. Prior ocular surgery within three months.
8. Any other condition that would not allow the potential subject to complete follow-up examinations during the course of the study and, in the opinion of the investigator, makes the potential subject unsuitable for the study.

Subjects will not be excluded based on their gender, race or ethnicity.

Maximum duration of subject involvement in the study:

- Planned duration of enrollment period: 18 months
- Planned duration of assessment period: 24 months

Statistical analysis:

Continuous variables at each scheduled visit will be summarized using descriptive statistics (n, mean, quartiles, standard deviation, minimum and maximum). For categorical variables, tabular summaries will consist of presenting the number and percentage in each category, including missing category, if applicable. The annual rate of progression of each endpoint will be estimated by means of regression models for the analysis of longitudinal data, as appropriate.

Table 1: Study Schedule of Events

Evaluation[a]	Baseline	1 year follow-up	2 year follow-up
Informed Consent[b]	•		
Eligibility Criteria	•		
Demographics	•		
Medical History/Review of Systems[c]	•		
NEI VFQ-25=25-Item National Eye Institute Visual Functioning Questionnaire [d]	•	•	•
Concurret Medical Conditions \ Disease progression	•	•	•
Pregnancy or nursering status	•	•	•
Medication/Nutritional Supplements/Therapies/Procedures	•	•	•
Ophthalmic examination[e]	•	•	•
Refraction and Best corrected visual acuity	•	•	•
Visual Field Assessments (Kinetic and Static)	•	•	•
Microperimetry	•	•	•
Fundus Photography*	•	•	•
Fundus autofluorescence*	•	•	•
Optical Coherence Tomography*	•	•	•
Multifocal electroretinogram[f**]	•	•	•
Full field electroretinogram[g**]	•	•	•

Notes:

a It may take approximately 2 days to complete all required assessments.

b Informed consent will be obtained

c Includes family history, vision-related medical history, vision-related family history and abstracting of all previous available tests and examination.

d The NEI VFQ-25 will be administered at the start of the scheduled visit so that any interaction between physician and subject will not influence the subject's responses to the questionnaires.

e Clinical ophthalmic examination will include slit lamp examination, direct and/or indirect ophthalmoscopy, and cataract grading.

f To be performed only in patients with stable fixation

g If a patient has a non-detectible ERG response at previous visit, ERG assessments will not be performed at subsequent study visits.

* to be performed without dilation in pregnant subjects

** to be not performed in pregnant subjects

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

With an overall prevalence of 1 in 6000 (Kimberling, Hildebrand et al. 2010), the autosomal recessive Usher syndrome (USH) is the most common combination of genetic deafness and blindness due to Retinitis Pigmentosa (RP) (Gregory-Evans, Pennesi et al. 2013). USH type I which accounts for approximately 40% of all USH cases (Rosenberg, Haim et al. 1997) is the most severe form with the RP onset in childhood (Gregory-Evans, Pennesi et al. 2013). USH type IB (USHIB) accounts for 35-50% of USHI [(Ouyang, Yan et al. 2005), 1 in 30-42000 individuals] and is caused by mutations in *MYO7A*. While hearing loss in USH can be counteracted by cochlear implantation, RP remains untreatable.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Drug development in non-syndromic and syndromic RP has proved to be challenging, also due to the difficulty in applying endpoints commonly used in ophthalmology clinical trials. For instance, BCVA, which is used as a registration endpoint in many ophthalmologic clinical trials, may be not a viable endpoint for use in this slowly progressing disease. In addition, due to the slow progression of RP and the large amount of variability inherent to visual function assessments, some assessments have insufficient sensitivity for quantifying clinically meaningful changes in photoreceptor loss in a time frame desirable for clinical trials.
This natural history study (NHS) is being conducted to understand the progression of disease in USH1B patients as measured by a number of vision-related assessments. Disease progression will be evaluated as change over time in these measures, and associations between the endpoints will be examined.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of this study is to evaluate the natural progression of disease over time in USHIB patients using best corrected visual acuity and visual field testing.

2.2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the progression of disease over time in USHIB patients through additional assessments:

- Microperimetry (only in selected centres)
- Fundus autofluorescence (FAF)
- Optical Coherence Tomography (OCT)
- Full-field Electroretinogram (ERG),
- Multifocal Electroretinogram,
- Vision-related function and quality of life, as measured by the 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25).

3 STUDY DESIGN

3.1 Study Design

This is a multicentre longitudinal, observational study designed to evaluate disease progression in in subjects with USHB1 by several vision-related assessments.
After informed consent (and assent, if applicable) is obtained from the subject or his/her parent(s) or legally authorized guardian(s), initial eligibility will be based on a confirmed clinical and molecular diagnosis of USH1B.

Subjects will be assessed using the following schedule:

- Baseline visit
- 1 year follow-up visit
- 2 year follow-up visit

This is an observational study; no treatment for USH1B with an investigational medicinal product will be provided. Subjects who are eligible to enroll into this study are not obligated to participate. Once enrolled, subjects may withdraw at any time and for any reason without prejudice to any future medical care or research opportunities. A subject's participation in this observational study does not guarantee participation in future interventional studies.
The evaluation performed in the course of this study are part of the standard clinical care of USHIB patients. The study does not require any additional test or administration of any drugs.

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 24 months.
Recruitment period is 18 months.
The study will be completed in approximately 3.5 years.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. The Study Completion Date is used to ascertain timing for posting and reporting of study results.

3.3 Sites and Regions

The study is planned to be conducted at 3 sites: the Eye Clinic of the University of Campania Luigi Vanvitelli, Naples, Italy, as Coordinating Centre, the Instituto de Investigacion Sanitaria de la Fundacion Jimenez Diaz, Madrid, Spain and the Stichting Oogziekenhuis Rotterdam, Rotterdam, The Netherland.

4 STUDY POPULATION

It is expected that approximately 50 patients may be recruited into the study during the recruitment period.
Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

Male and female subjects of any ethnic group are eligible for participation in this study, providing they meet the following criteria:

1. Must be willing to adhere to protocol for long-term follow-up as evidenced by written informed consent or parental permission and subject assent.
2. Subjects diagnosed with USH1.
3. Molecular diagnosis of USH1B due to *MYO7A* mutations (homozygotes or compound heterozygotes).
4. Age eight years old or older at the time of baseline.
5. Visual acuity ≥ 20/640 in at least one eye

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Unable or unwilling to meet requirements of the study.
2. Unable to communicate with suitable verbal/auditory and/or tactile sign language (in the opinion of the investigator)
3. Participation in a clinical study with an investigational drug in the past six months.
4. Pre-existing ocular conditions that would interfere with the interpretation of study endpoints (for example, glaucoma, corneal or significant lenticular opacities, moderate / severe cystoid macular oedema, macular hole) in both eyes.
5. Complicating systemic diseases in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (for example, radiation treatment of the orbit; leukemia with CNS/optic nerve involvement).
6. Subjects with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (e.g. macular edema or proliferative changes).
7. Prior ocular surgery within three months.
8. Any other condition that would not allow the potential subject to complete follow-up examinations during the course of the study and, in the opinion of the investigator, makes the potential subject unsuitable for the study.

Subjects will not be excluded based on their gender, race or ethnicity.

4.3 Reproductive Potential

Pregnant or nursering patient will not be excluded. Subjects who become pregnant while on study may continue participation in the study. Pregnancy information, including outcome, as reported by the patient will be recorded . Pregnant and nursing subjects will undergo study assessments without instillation of ocular drops for the duration of their pregnancy and nursing. All study assessments which cannot be done without ocular drops will be omitted while the subject is pregnant and nursing.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety).

Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents.

Subjects who withdraw or are discontinued from participation in the study may be replaced at the discretion of the sponsor.

4.4.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document.

Reasons for discontinuation include but are not limited to:

- Protocol deviation
- Withdrawal by subject/parent/guardian
- Lost to follow-up
- Physician decision
- Unwilling or unable to comply with protocol
- Study terminated by sponsor
- Site terminated by sponsor
- Other (must be specified by investigator)

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point before withdrawing him\ her from the study.

5 PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment (medications/nutritional supplements/therapies/procedures) includes all treatment (pharmacologic and non-pharmacologic) received within 90 days prior to obtaining IC. Prior treatment information must be recorded.

5.2 Concomitant Treatment

Concomitant treatment (medications/nutritional supplements/therapies/procedures) refers to all treatment taken between the dates of obtaining IC and the final protocol-defined assessment. Concomitant treatment information must be recorded.

5.2.1 Permitted Treatment

Treatments not specifically listed in Section 5.2.2 are permitted.

5.2.2 Not recommended Treatment

The patient is asked to notify the investigator in case he\she takes any of the following not recommended mediciation in the course of the study:

:

- Plaquenil
- Thioridazine
- Clofazimine
- Deferoxamine
- Phenothiazine
- Chlorpromazine
- Cisplatin
- Valproic acid
- Any other drugs with known visual side effects

6 INVESTIGATIONAL PRODUCT

Not applicable. This is a natural history study, and no investigational product will be administered.

7 STUDY PROCEDURES

7.1 Study Schedule

See Table 1 for study procedures.

The 1 year and 2 year follow-up visit assessments may be performed within a ± 30-day window.

7.1.2 Baseline visit

The following procedures will be performed:

- Obtaining written IC (and assent if applicable) by subject, and/or the subject's parent(s) or legally authorized guardian(s)
- Assessment of eligibility according to the inclusion/exclusion criteria
- Collection of medical history, including subject's ocular history, previous medications, and previous test and examination
- NEI VFQ-25 plus its additional items
- Concurret Medical Conditions
- Pregnancy or nursering status
- Concomitant treatment (medications/nutritional supplements/therapies/procedures)
- Refraction and BCVA
- Visual field assessments (kinetic and static)
- Clinical ophthalmic examination
- Microperimetry
- Fundus Photography
- Fundus autofluorescence
- Optical Coherence Tomography
- Confirmation of eligibility according to the inclusion/exclusion criteria
- Multifocal electroretinogram
- Full field electroretinogram

7.1.3 1 year and 2 year follow-up visit

The following procedures will be performed:

- NEI VFQ-25 plus its additional items
- Concurret Medical Conditions \ Disease progression
- Pregnancy or nursering status
- Concomitant treatment (medications/nutritional supplements/therapies/procedures)
- Refraction and BCVA
- Visual field assessments (kinetic and static)

- Clinical ophthalmic examination
- Microperimetry
- Fundus Photography
- Fundus autofluorescence
- Optical Coherence Tomography
- Multifocal electroretinogram
- Full field electroretinogram

7.1.4 Additional Care of Subjects after the Study

No after care is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

7.2.1.1 Demographics

Subject demographic information including sex, age, race, and ethnicity will be collected.

7.2.1.2 Medical history

Medical history, including subject's ocular history, previous medications, and previous test and examination will be collected at baseline.

On this visit, if the patient has been previously visited at the clinical centre, the available historical data on visual related assessments as described in section 7.2.2 will be collected and will form the retrospective data.

7.2.1.3 Concurret Medical Conditions

Any clinically significant medical condition will be recorded.

Deafness severity or grade will also be recorded

7.2.2 Measures of Disease Progression

The study procedures described in this section must be performed by trained site personnel.

7.2.2.1 Refraction and Best Corrected Visual Acuity

Visual acuity with manifest refraction will be assessed in both eyes using a standardized ETDRS protocol. Following complete refraction of both eyes by a trained refractionist, BCVA measurements will be obtained for each eye. Subjects will be allowed as much time as necessary and will be encouraged to read each letter. If they are unsure about a letter, they will be asked to guess. Details are provided in the Technical Manual of Procedures.

7.2.2.2 Visual Field Assessments

Visual field measurements will be made in both eyes using the Octopus 900 (Haag-Streit International) with the semiautomatic kinetic perimetry module and a full field static perimetry protocol as defined in the Technical Manual of Procedures. Visual field measurements will be

evaluated by the Coordinating center.

7.2.2.3 Clinical ophthalmic examination

Clinical ophthalmic examination includes:

External Ocular Examination: to assess the motility of the extraocular muscles and the appearance and function of the eyelids before the instillation of any dilating or anesthetic eye drops;

Slit Lamp Examination (SLE) (biomicroscopy), to assess eyelids, lashes, conjunctiva, cornea, lens, iris and anterior chamber. SLE must be performed before the instillation of any dilating or anesthetic eye drops or the fluorescein agent.

Intraocular Pressure (IOP) measurement, performed using either Goldmann applanation tonometry or a handheld applanation tonometer (e.g. Tonopen) after instillation of a topical anesthetic.

Dilated Fundus Ophthalmoscopy, performed after dilation of the pupil, in order to assess the retina, macula, choroid and optic nerve head.

7.2.2.4 Microperimetry

Microperimetry will be performed using the MP-1 or Maia to more accurately access the central visual field by tracking fundus movements while the patient looks steadily at the fixation target.

7.2.2.5 Fundus photography

Non-stereo images of macula and eight non-stereoscopic photographic fields surrounding the macula will be taken through a dilated pupil to document the appearance of the posterior pole.

7.2.2.6 Fundus autofluorescence

Infrared reflectance and FAF (blue) imaging covering 30° degree and centred on the macula will be obtained using the Spectralis (Heidelberg Engineering) or other sponsor-approved FAF machine. Details are provided in the Technical Manual of Procedures

7.2.2.7 Ocular Coherence Tomography

A volume scan capturing a 30 x 25 degree region of the posterior pole of the retina of both eyes will be obtained using the Spectralis (Heidelberg Engineering) or other sponsor-approved OCT machine. Details are provided in the Technical Manual of Procedures.

7.2.2.8 Multifocal electroretinogram

Multifocal electroretinograms will be performed in both eyes (monocular stimulation) using a Reticom (Roland Consultant) or Espion D15 (Diagnosis) equipment according to the International Society for Clinical Electrophysiology of Vision standards(Hood, Bach et al. 2012). Details are provided in the Technical Manual of Procedures.

7.2.2.9 Electroretinography

Full field electroretinograms will be performed in both eyes using a Reticom (Roland Consultant) or Espion D15 (Diagnosis) equipment according to the International Society for Clinical Electrophysiology of Vision standards(McCulloch, Marmor et al. 2015). Scotopic and photopic assessments will be performed as follows:

- Dark-adapted (40 minutes)
- Rod response (0.01 ERG)
- Maximal combined rod/cone response (3 ERG)
- Light-adapted (10 minutes)
- Cone response (3 ERG)
- Response to flicker (30 Hz flicker ERG)

Details are provided in the Technical Manual of Procedures.

If a patient has a non-detectible ERG response to all stimuli at previous visit (or as assessed by medical history), ERG assessments will not be performed at subsequent study visits.

7.3 Patient Reported Outcomes

Patient reported outcome assessments will not be administered to subjects less than 16 years old.

25-ITEM NATIONAL EYE INSTITUTE VISUAL FUNCTIONING QUESTIONNAIRE AND ITS ADDITIONAL ITEMS

Vision-related function and QOL will be assessed using the NEI VFQ-25 and its additional items, a valid and reliable questionnaire developed to measure the influence of visual impairment on QOL due to chronic eye diseases/conditions (Mangione, Lee et al. 2001). The questionnaire will be administered by an interviewer (interviewer-administered format) during the scheduled visits so that any interaction between subject and physician will not influence the subject's responses to the questionnaire. On average, it takes approximately 10 minutes to administer.

The NEI VFQ-25 includes 25 items plus 1 general health item and an appendix of 13 supplementary items (additional items) that are used to expand the scales. These additional items enhance the reliability of the specific scales and are likely to improve responsiveness of the sub-scale to changes over time. The NEI VFQ-25 and its additional items result in 11 vision-related constructs/scales (37 items) assessing global vision, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral vision, limitations with color vision, and ocular pain and a general health scale (2 items).There is limited information on the performance of the NEI VFQ-25 in subjects with Usher Syndrome; therefore the SF-12v2 and PGI-S (see below) will also be assessed to establish the psychometric properties (validity, reliability, and sensitivity) of the NEI VFQ-25 and its additional items in this patient population.

Questionnaire will be provided in the patient language and administrated with the help of a sign language interpreter, as required / recommended by national law or local procedures

8 DATA MANAGEMENT AND STATISTICAL METHODS

8.1 Data Collection and source data

The investigators' authorized site personnel must enter the information required by the protocol in the Clinical Record Form (CRF)

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All key data must be recorded in the subject's medical records.
Original source data will include, but are not limited to subject's medical file, including all visual assessments.

All data sent to the sponsor must be endorsed by the investigator.

A study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

Essential documents must be maintained according to ICH GCP requirements .

8.2 Statistical Analysis Process

Continuous variables at each scheduled visit will be summarized using descriptive statistics (n, mean, quartiles, standard deviation, minimum and maximum). For categorical variables, tabular summaries will consist of presenting the number and percentage in each category, including missing category, if applicable. The annual rate of progression of each endpoint will be estimated by means of regression models for the analysis of longitudinal data, as appropriate.
The main analysis will be done on data collected prospectively, but a secondary analysis will be performed considering also the retrospective data recovered in patients medical history.

8.3 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

One interim analysis is planned when all patients recruited within in the first six months will have the 1-year follow-up visit. Data will be reviewed and a longitudinal analysis exploring the annual rate of progression of the main endpoints will be performed to help future clinical development planning.

8.4 Sample Size Calculation and Power Considerations

No formal sample size computation was performed. Approximately 50 subjects will be enrolled in this study.

8.5 Study Population

The **Enrolled Set** will consist of all subjects who have signed an informed consent and study procedures have begun.

All safety and disease progression data will be assessed using the Enrolled Set.

9 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, the International Conference on Harmonisation (ICH), European Union (EU) Directive 2001/20/EC and its updates, and local ethical and legal requirements.

9.1 Sponsor's Responsibilities

9.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required.

9.1.2 Indemnity/Liability and Insurance

No insurance policy is in place for this study, being an observational one.

9.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

9.2 Investigator's Responsibilities

9.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

9.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met all of the protocol-defined eligibility criteria.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, or investigator, according to national provisions and will be documented in the investigator agreement.

9.2.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.
The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, European Medicines Agency [EMA]) or an auditor.

9.3 Ethical Considerations

9.3.1 Informed Consent

It is the responsibility of the investigator to obtain written IC and assent, where applicable, from all study subjects prior to any study-related procedures. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject IC form after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and subject's rights and responsibilities. A copy of the IC and assent documentation (ie, a complete set of subject information sheets and fully executed

signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form and assent form where applicable which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB's/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

9.3.2 Institutional Review Board or Ethics Committee

The study will be submitted by the investigator to the competent Ethics Committee to seek EC approval to the study.
A copy of the IRB's/EC's written favorable opinion/approval of the study must be provided to the sponsor prior to the start of the study

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all IC documents and amendments to the protocol unless there is a subject safety issue.

The sponsor will provide a summary of the clinical study report to the EC and will inform the EC in case of early termination of the study

9.4 Privacy and Confidentiality

Subject will be assigned a unique alphanumeric code and all subject data will be identified by that code. Only the cinical centre staff wll have access to the patient identity.

The patients' data may, in addition, be reviewed by the sponsor delegated staff, the monitor and others, including auditors and third parties involved in the UshtTer Consorium; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

The results of studies, containing subjects' unique identifying numbers and relevant medical records, may be transferred to and used in other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

9.5 Study Results/Publication Policy

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements,

letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication.

Since the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenterstudy publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

10 REFERENCES

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11 APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	31 Jan 2018	Global
Version 1.1	16 March 2018	Spain, Netherland

SUMMARY OF CHANGES FROM PREVIOUS VERSION

In the section 4.1.1 Reasons for Discontinuation Adverse Event was removed from the list of reason for Discontinuation, as not applicable for an observational study.
Since the current study is an observational study, the therapy listed in the paragraph 5.2.2 should be nonrecommended instead of prohibited.
In the section 7.2.2.4 Microperimetry, the use of Maia instrumentation was included.

APPENDIX 2 SCALES AND ASSESSMENTS

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment	Version Number
25-Item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) and its Additional Items	NEI VFQ-25

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above, and a new master file containing the revised scale/assessment will be provided to the site.