Foundation Fighting Blindness (FFB) Consortium

Rate of Progression of PCDH15-Related Retinal Degeneration in Usher Syndrome 1F (RUSH1F)

Funded by: Foundation Fighting Blindness and Usher 1F Collaborative

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Key Roles and Signature Page

Rate of Progression of PCDH15-Related Retinal Degeneration in Usher Syndrome 1F (RUSH1F)

Protocol Identifying Number: RUSH1F

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACMG	American College of Medical Genetics
ADRP	Autosomal dominant retinitis pigmentosa
AE	Adverse Event
ANCOVA	Analysis of covariance
BCVA	Best corrected visual acuity
BRVT	Berkeley Rudimentary Vision Test
CC	Coordinating Center
CFR	Code of Federal Regulations
CGA	Central Genetics Auditor
CI	Confidence interval
CME	Cystoid macular edema
CSF	Contrast Sensitivity Function
DHA	Docosahexaenoic acid
EC	Ethics Committee
ERG	Electroretinogram
ETDRS	Early Treatment of Diabetic Retinopathy Study
EVA	Electronic Visual Acuity
EZ	Ellipsoid Zone
FAF	Fundus Autofluorescence
FFB	Foundation Fighting Blindness
FST	Full-field stimulus threshold
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Committee of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IOP	Intraocular Pressure
IRB	Institutional Review Board
IS/OS	Inner Segment/ Outer Segment
LLVA	Low Luminance Visual Acuity
LPV-FVQ II	L.V. Prasad Functional Vision Questionnaire
MRDQ	Michigan Retinal Degeneration Questionnaire
MP	Microperimetry
N	Number or sample size
OD	Right Eye
OS	Left Eye

ABBREVIATION	DEFINITION
OU	Both eyes
PI	Principal investigator
PRO	Patient-reported outcomes
PROMIS®-29	Patient-Reported Outcomes Measurement Information System
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
RP	Retinitis pigmentosa
SAE	Serious adverse event
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SP	Static perimetry
TALEN	Transcription activator-like effector nuclease
VA	Visual acuity
VF	Visual Field
VPA	Valproic Acid

PROTOCOL SUMMARY

ITEM	DESCRIPTION
Title	Rate of Progression of PCDH15-Related Retinal Degeneration in Usher Syndrome 1 (RUSH1F)
Précis	This natural history study of patients with PCDH15 disease-causing variants will accelerate the development of outcome measures for clinical trials. Sensitive, reliable outcome measures of retinal degeneration will greatly facilitate development of treatments for retinitis pigmentosa due to PCDH15 disease-causing variants. Together these approaches are expected to have an impact on understanding PCDH15-related retinal degeneration, developing experimental treatment protocols, and assessing their effectiveness. The goals and expected impact of this natural history study are to: 1. Describe the natural history of retinal degeneration in patients with bi-allelic disease-causing variants in the PCDH15 gene 2. Contribute to the identification of sensitive structural and functional outcome measures to use for future multicenter clinical trials of PCDH15-related retinal degeneration 3. Contribute to the identification of populations for future clinical trials of investigative treatments for PCDH15-related retinal degeneration
Objectives	1. Characterize the natural history of retinal degeneration associated with bi-allelic disease-causing variants in the PCDH15 gene over 4 years, as measured using functional, structural, and patient-reported outcome measures 2. Explore whether structural outcome measures can be validated as surrogates for functional outcomes in individuals with bi-allelic disease-causing variants in the PCDH15 gene 3. Explore possible risk factors (genotype, phenotype, environmental, and comorbidities) for progression of the outcome measures at 4 years in individuals with bi-allelic disease-causing variants in the PCDH15 gene 4. Explore variability and symmetry of left and right eye outcomes over 4 years in individuals with bi-allelic disease-causing variants in the PCDH15 gene
Study Design	Multicenter, longitudinal, prospective natural history study. Participants will be assigned to one of two Vision Cohorts based on visual acuity (VA) and kinetic visual fields (VF).
Number of Clinical Sites	Approximately 10
Endpoint	Functional Outcomes: • VF sensitivity as measured by static perimetry with quantitative, topographic analysis (Hill of Vision) and assessed by a central reading center • Early Treatment of Diabetic Retinopathy Study (ETDRS) Best-corrected visual acuity (BCVA) letter score as measured on the Electronic Visual Acuity (EVA) system or ETDRS charts. Berkeley Rudimentary Vision Test (BRVT) will be used for patients unable to see letters • Mean retinal sensitivity as measured by fundus-guided microperimetry (MP) and assessed by a central reading center at selected sites with requisite equipment • Full-field retinal sensitivity as measured by full-field stimulus threshold (FST) testing to blue, white and red stimuli

ITEM	DESCRIPTION
	• Best corrected low luminance visual acuity (LLVA) letter score • Contrast sensitivity function (CSF) as measured by the CSV-1000E VectorVision chart Structural Outcomes: • Ellipsoid zone (EZ) area as measured by spectral domain optical coherence tomography (SD-OCT) and assessed by a central reading center • Explore qualitative categorization of Fundus Autofluorescence (FAF) pattern assessed by a central reading center • Explore quantitative measures of FAF as assessed by a central reading cen Patient Reported Outcomes (PRO): • <u>Adults (18 years or older)</u> ○ Michigan Retinal Degeneration Questionnaire (MRDQ) ▪ The MRDQ is a patient reported outcomes instrument for Inherited Retinal Degeneration with 59 questions and contains seven domains which are; central vision, color vision, contrast sensitivity, photosensitivity, scotopic function, mesopic and photopic peripheral vision. ○ Patient-Reported Outcomes Measurement Information System (PROMIS-29) ▪ The PROMIS®-29 questionnaire contains items from seven PRO domains: depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities. The seven domains cover the most relevant areas of self-reported health for most people with chronic illness. There is also one 11-point rating scale for pain intensity. • <u>Children (less than 18 years)</u> ○ L. V. Prasad-Functional Vision Questionnaire (LVP-FVQ II) ▪ The LVP-FVQ-II is a self-reported questionnaire with 23 questions that will be administered to minor participants to assess self-reported functional vision problems.
Population	Key Eligibility Criteria: The entire list of eligibility criteria is in protocol section 2.3.1 and must be reviewed at the Screening Visit. All eligibility criteria must be met to enroll into the genetic screening phase A key subset of those eligibility criteria includes the following. • Age ≥ 8 years of age • Clinical diagnosis of retinal dystrophy • Must meet one of the Genetic Screening Criteria: ➢ <u>Screening Group A</u>: At least 2 disease-causing variants in the PCDH15 gene which are homozygous or heterozygous in trans, based on a report from a clinically certified lab (or a report from a research lab that has been pre-approved by the study Genetics Committee)

<table>
<tr><th>ITEM</th><th>DESCRIPTION</th></tr>
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<u>Screening Group B:</u> Only 1 disease-causing variant in the PCDH15 gene, based on a report from a clinically certified lab (or a report from a research lab which has been pre-approved by the study Genetics Committee)
<u>Screening Group C</u>: At least 2 disease-causing variants in the PCDH15 gene which are unknown phase, based on a report from a clinically certified lab (or a report from a research lab which has b pre-approved by the study Genetics Committee)

Participants eligible upon initial screening will continue to the genetic screening phase. Following the genetic screening phase, to be eligible to enroll in the study cohort, the following must be documented:

<u>Final Study Cohort Criteria:</u> At least 2 disease-causing variants in the PCDH15 gene which are homozygous or heterozygous in trans, based on a report from a clinically certified lab (or a report from a research lab that ha been pre-approved by the study Genetics Committee), and confirmed by a Central Genetics Auditor (CGA).

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<tr><td>Sample Size</td><td>
Recruitment will be tracked within Vision Cohort defined as follows. Sample size rationale is detailed in protocol section 6.1.

Vision Cohort 1: ~25 participants with the better eye Screening Visit visual acuity ETDRS letter score of 54 or more [approximate Snellen equivalent 20/80 or better] <u>and</u> visual field diameter 10 degrees or more in every meridian of the central field
Vision Cohort 2: ~15 participants with the better eye Screening Visit visual acuity ETDRS letter score of 15 to 53 [approximate Snellen equivalent 20/100 to 20/400] <u>or</u> (visual acuity ETDRS letter score of 54 or more [approximate Snellen equivalent 20/80 or better] <u>and</u> visual field diameter less than 10 degrees in any meridian of the central field)

The better eye is defined as the eye with better Screening Visit ETDRS VA. If both eyes have the same VA (defined as the same Snellen equivalent), then determination will be made at investigator discretion as the eye with better fixation or clearer ocular media to permit highest quality retinal imaging.

The visual field (VF) is defined as a clinically determined kinetic VF-e performed within the last 18 months prior to or including the Screening Visit
<table>
<tr><th></th><th>VF diameter ≥10° in every meridian</th><th>VF diameter <10° in any meridian</th></tr>
<tr><td>20/80 or better</td><td>Vision Cohort 1</td><td>Vision Cohort 2</td></tr>
<tr><td>20/100-20/400</td><td>Vision Cohort 2</td><td>Vision Cohort 2</td></tr>
</table>
<u>Initial recruitment goals will be as follows:</u>
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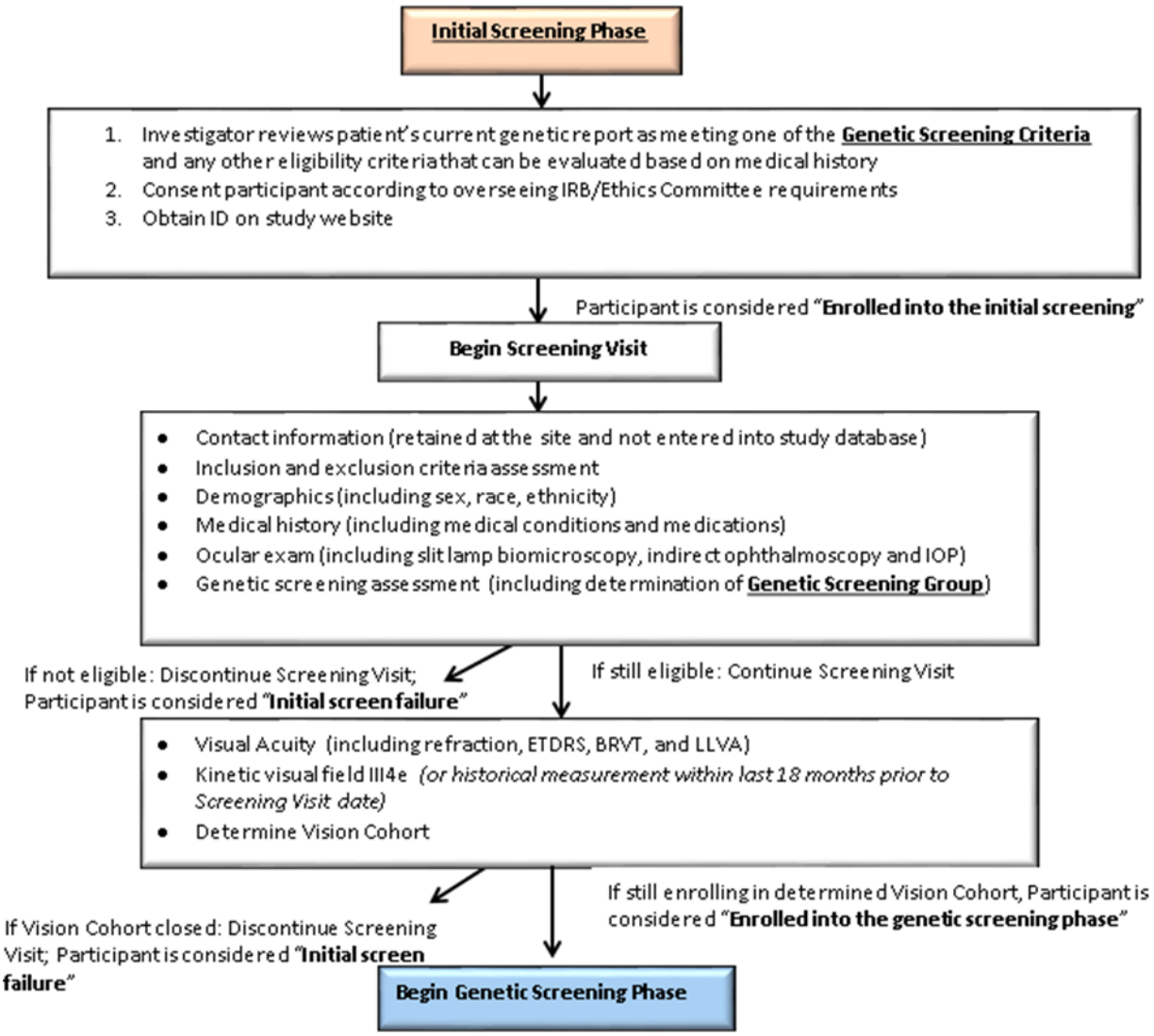
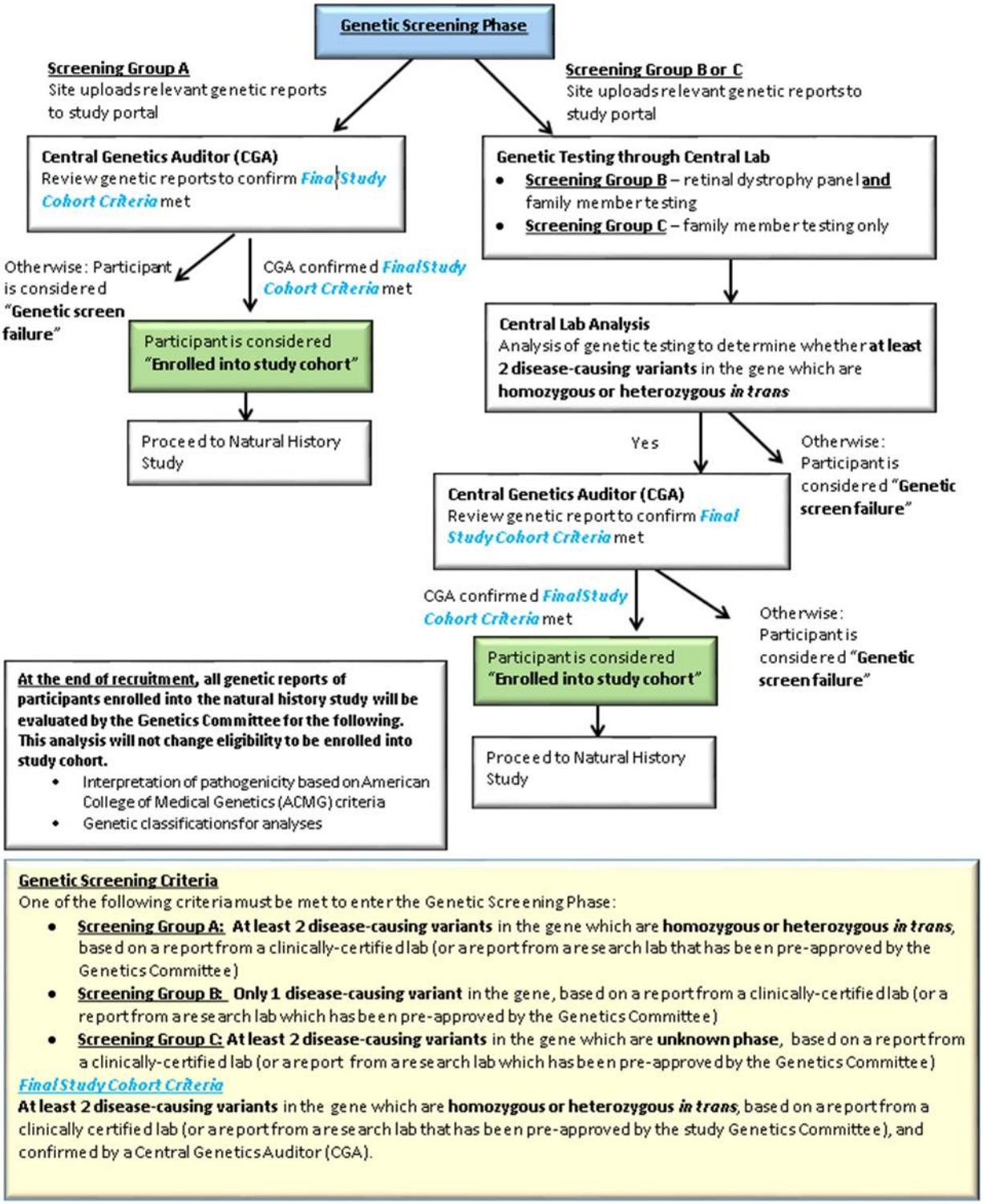
ITEM	DESCRIPTION
	• 40 participants enrolled into the study cohort (Vision Cohorts 1 and 2, combined) If recruitment is not at a rate to meet the initial goals, an interim assessment of feasibility may be made by the FFB Consortium Executive Committee. At a minimum of 20 participants enrolled in Vision Cohorts 1 and 2 combined will be targeted.
Participant Duration	From the time of screening until the 48-month visit: Approximately 51 Months • Screening – Baseline Visit (~ 3 months) • Baseline Visit – 48-month Follow-up Visit (~ 48 months)
Protocol Overview/Synopsis	1. Investigator reviews patient's current genetic report as meeting one of the Genetic Screening Criteria and any other eligibility criteria that can be evaluated based on medical history 2. Consent participant according to overseeing Institutional Review Board (IRB)/Ethics Committee (EC) requirements 3. Obtain ID on study website to enroll into initial screening 4. Complete a Screening Visit to determine eligibility, Vision Cohort and Genetic Screening Group. Participants meeting criteria to continue will enroll into the genetic screening phase (See flow chart in next section for details) 5. Complete genetic screening according to the requirements for the given Genetic Screening Group. Participants meeting criteria to continue will enroll into the study cohort. (See flow chart in next section for details) 6. Participants who enroll into the study cohort will return to the clinic within 90 days of the Screening Visit date to start baseline testing, and no later than 30 days after receiving confirmation of meeting final study cohort criteria from the CGA 7. All participants who enroll into the study cohort will return to the clinic at 12, 24, 36 and 48 months from the baseline visit start date for follow-up visits. 8. After the 48-month follow-up visit, participation in the study will be completed

SCHEMATIC OF STUDY DESIGN




Genetic Screening Phase
Screening Group A
Site uploads relevant genetic reports to study portal
Screening Group B or C
Site uploads relevant genetic reports to study portal
Central Genetics Auditor (CGA)
Review genetic reports to confirm Final Study Cohort Criteria met
Genetic Testing through Central Lab
Screening Group B – retinal dystrophy panel and family member testing
Screening Group C – family member testing only
Otherwise: Participant is considered "Genetic screen failure"
CGA confirmed Final Study Cohort Criteria met
Participant is considered "Enrolled into study cohort"
Proceed to Natural History Study
Central Lab Analysis
Analysis of genetic testing to determine whether at least 2 disease-causing variants in the gene which are homozygous or heterozygous in trans
Yes
Otherwise: Participant is considered "Genetic screen failure"
Central Genetics Auditor (CGA)
Review genetic report to confirm Final Study Cohort Criteria met
CGA confirmed Final Study Cohort Criteria met
Otherwise: Participant is considered "Genetic screen failure"
Participant is considered "Enrolled into study cohort"
Proceed to Natural History Study
At the end of recruitment, all genetic reports of participants enrolled into the natural history study will be evaluated by the Genetics Committee for the following. This analysis will not change eligibility to be enrolled into study cohort.
Interpretation of pathogenicity based on American College of Medical Genetics (ACMG) criteria
Genetic classifications for analyses
Genetic Screening Criteria
One of the following criteria must be met to enter the Genetic Screening Phase:
Screening Group A: At least 2 disease-causing variants in the gene which are homozygous or heterozygous in trans, based on a report from a clinically-certified lab (or a report from a research lab that has been pre-approved by the Genetics Committee)
Screening Group B: Only 1 disease-causing variant in the gene, based on a report from a clinically-certified lab (or a report from a research lab which has been pre-approved by the Genetics Committee)
Screening Group C: At least 2 disease-causing variants in the gene which are unknown phase, based on a report from a clinically-certified lab (or a report from a research lab which has been pre-approved by the Genetics Committee)
Final Study Cohort Criteria
At least 2 disease-causing variants in the gene which are homozygous or heterozygous in trans, based on a report from a clinically certified lab (or a report from a research lab that has been pre-approved by the study Genetics Committee), and confirmed by a Central Genetics Auditor (CGA).

SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Schedule

Visit	Screening	Baseline	12M	24M	36M	48M
Visit Target Windows	(up to Day -90) [a]	(Day 0) [b]	Wk 52 ± 4 [c]	Wk 104± 4 [c]	Wk 156±4 [c]	Wk 208±4 [c]
Participant-Level Procedures						
Informed Consent	X					
Demographics/Screening Medical History (including pre-existing conditions, patient-reported daily activities and medications)	X					
Concomitant Medications/Adverse Events		X	X	X	X	X
Patient Reported Outcomes (Adults: NEI VFQ-25 and PROMIS® 29; Children: LPV-VFQ II)		X		X		X
Audiology History		X				
Pre-cochlear implant audiogram		X				
Ocular Procedures- All testing performed in each eye						
Complete Ophthalmic Exam [e]	X		X	X	X	X
Visual acuity (including refraction, ETDRS, BRVT if needed, LLVA if needed)	X	X [h]	X	X	X	X
Contrast Sensitivity (VectorVision CSV-1000E)		X	X	X	X	X
SD-OCT with measurement of EZ area (Heidelberg Spectralis)		X	X	X	X	X
Axial Length and Corneal Curvature measurements		X				
Near Infrared Reflectance Photos (Heidelberg Spectralis with 55degree lens) [i]		X				
Fundus Autofluorescence (Optos, where available)		X	X	X	X	X
Full-field Stimulus Threshold (Diagnosys Espion)		X	X	X	X	X
Static perimetry (Octopus 900 Pro)		X [d]	X	X	X	X
Fundus guided microperimetry (MAIA)		X [d]	X	X	X	X
Kinetic VF III4e for Vision Cohort definition only	X [f]					

a. All Screening Visit testing must be completed on the same day
b. Baseline Visit date (defined as the start date of all Baseline testing) must be no later than 30 days after receiving confirmation of meeting final study cohort criteria from the CGA (and if possible, within 90 days of the Screening Visit date). All Baseline testing should be completed within 7 days of the Baseline Visit date, except PROs as specified.
c. All Follow up visit testing must be completed on the same day, except PROs as specified.
d. For static perimetry and microperimetry, all Vision Cohort 1 and 2 participants will complete two tests at the Baseline visit. The results will be compared according to the visual field criteria to determine if a third test is needed.
e. Ophthalmic exam includes slit lamp biomicroscopy, indirect ophthalmoscopy and intraocular pressure (IOP). IOP measurements will be taken prior to pupil dilation and will take place at approximately the same time of the day at each visit and with the same equipment
f. Kinetic VF III4e performed within the last 18 months prior to or including the Screening Visit date for Vision Cohort determination only
g. May be completed in person or remotely any time within 6 months of the Baseline visit or any time within the allowable window of the associated visit window (not required to be the same day as the rest of the visit).
h. If the Baseline visit date is more than 90 days after the Screening Visit date, all Visual acuity procedures must also be completed
i. Required for all sites except with the exception of any site with equivalent equipment approved by the reading center and operations committee

Chapter 1: Background Information

1.1 Introduction

Usher syndrome (USH), is a neurosensory disease that impacts vision and hearing, inherited in an autosomal recessive way. It is characterized by the combination of hearing impairment up to deafness and retinal dystrophy (retinitis pigmentosa, RP), in some cases vestibular and olfactory deficits.[1,2] The three main clinical subtypes known are USH1, USH2 and USH3. USH type 1 (USH1) patients are born completely deaf. These patients experience other complications such as delayed sitting and walking age due to vestibular problems. RP with night blindness is typically diagnosed by 10 years of age. In USH2 patients, hearing impairment is less pronounced, and the patients do not experience balance deficits. In most cases, this subtype does not progress over time. Night blindness normally occurs later than in USH1.[3] USH3 accounts for 2% of patients and found mostly in Finland and Ashkenazi Jews. In this type, the hearing impairment is progressive, and a balance defect may be present.[4,5]

USH1F is a subtype of USH1 caused by allelic mutations of the USH1F gene, also called protocadherin 15 (PCDH15). This gene has been localized in the ear hair cell stereocilia and outer segments of primates' retinal photoreceptors; strong PCDH15 activity has been described in cones, but also diffusely in rods through the whole photoreceptor layer.[6] The majority of PCDH15 mutations leading to USH1F are localized in the ectodomains of the protein, but not in the transmembrane domain or the cytoplasmic domain, the latter two being probably important outside of the hearing and visual system. It is assumed that PCDH15 might have a role in the morphogenesis and cohesion of stereocilia bundles and retinal photoreceptor cell maintenance or function. Protocadherin 15 deficiency leads to functionally impaired cones and rods with abnormally shaped outer segments.[6,7]

PCDH15 has been linked to congenital deafness or its syndromic form USH1F.[6,8] Additionally, digenic inheritance of Usher syndrome USH1D/F has been described in patients with heterozygous mutations in both CDH23 and PCDH15 genes.[9] The prevalence of USH1 is around 1- 9 /100,000; the prevalence of USH1F is not precisely known due to its rarity but might be around 10 % of all USH1 patients.[2,10]

The current knowledge about the natural course of USH1F is limited, as no systematic observational trials of the retinal phenotype have been published. The phenotype and fast time course of the retinal degeneration in USH1F is comparable with the phenotype of USH1 in general, which is characterized by profound pre-lingual deafness, vestibular ataxia, and childhood onset of retinitis pigmentosa.[11,12]

A large cohort of 268 USH patients in a multicenter European study TREATRUSH (https://cordis.europa.eu/project/rcn/95259_en.html) was conducted to understand the genotype-phenotype correlations of USH and enabled some insight into the subgroups of phenotypes of USH1. The analyses from this study indicated decay of visual fields and visual acuity as a function of the patients' age corresponds to the changes of the USH1 cohort in general.[12]

Hearing loss is treatable with cochlear implants in many patients with USH1F. However, the therapy for treating the retinal phenotype is still in preclinical research. Gene replacement

therapy, similar as the first approved AAV (adeno associated virus) mediated subretinal gene therapy for RPE65 retinitis pigmentosa, is not possible in USH1F due to the large size of the PCDH15 gene.

Gene-based therapies such as viral vectors, gene editing or mini genes and suppression of several PCDH15 mutations by aminoglycosides have been examined. Aminoglycosides can influence the translation of mRNA into protein by inhibiting ribosomal proofreading, thus, leading to read-through of nonsense mutations. A partial read-through of PCDH15 nonsense mutations leading to various levels of the full-length protein was shown by aminoglycosides in vitro and ex vivo.[13] However, more preclinical and clinical research is needed to determine whether these approaches can restore vision in patients with USH1F or slowdown the degeneration process leading to blindness.

The clinical research in therapy trials for other types of syndromic or non-syndromic RP shows that valid readouts are one of the most important aspects of clinical trials. Morphological readouts have improved with high resolution retinal imaging such as spectral domain OCT (SD-OCT) and became standard in clinical follow-ups and clinical trials due to its objectivity and lower variability than psychophysical functional tests.[14,15]

For functional tests of the retina, psychophysical examinations of visual fields and best corrected visual acuity (BCVA) as well as contrast vision (or low luminance BCVA) are commonly used but describing only foveal cone vision. Further, fundus guided mesopic microperimetry has been used widely in clinical trials of inherited retinal degenerations. However, due to the mesopic range of the stimuli, the method is not sensitive enough to test rod vision.[17] Additionally, in retinal degeneration with increasing dark-adapted rod thresholds, the mesopic testing is not able to distinguish between the degenerating rod system and the healthy or degenerating cone system.

With respect to the knowledge of the progression of the cone and rod degeneration and future therapy approaches, a clear differentiation of the rod and cone function is desirable. Routinely used objective readouts of the photoreceptors such as scotopic and photopic full-field electroretinography (ERG) are usually non-recordable already in early stages of the retinal degeneration, including RP in USH1 patients.[18] Therefore, the full-field ERG is not a practical follow-up readout for the natural course of USH1 or therapy interventions. A psychophysical test of the dark-adapted thresholds, FST (full-field stimulus threshold) with chromatic stimuli is better suited to describe the deterioration of the retinal progression even in late stages of RP.[17,18]

Although these scotopic readouts are widely used, they do not possess the ability to show the local retinotopy of the rod system. A method which can evaluate the local rod function is dark adapted chromatic perimetry (DAC). This method has also earlier been applied in patients with RP.[19,20] A novel, shortened protocol for application in RP trials has been proposed recently with duration of around 7 minutes, intervisit repeatability of 7.6 ± 2.8 dB for cyan and 5.9 ± 1.7 dB for red stimuli and ability to detect the local rod rescue after gene therapy.[22]

Further, novel diagnostic development has been introduced, enabling objective, retinotopically correct evaluation of the rod and cone system by analyzing the pupil response to local stimuli.[23] The chromatic pupil campimetry, although not broadly available, is a tool for

evaluation of the function of both photoreceptors separately in an objective way, with a superior intervisit repeatability compared to DA.[22]

In respect to the promising therapy approaches in RP, including the retinal phenotypes of USH1, clinically acceptable tests of the local rod and cone function, supporting the morphological evaluations such as OCT are needed. Only understanding the dynamic of the cone and rod degeneration over time in a retinotopically correct manner can enable us to understand the natural history of the disease and to evaluate eventual therapy safety and efficacy in the future

1.2 Scientific Rationale for Study Design

A prospective natural history study is the gold standard for tracking the course of disease. The knowledge of the course of patients with PCDH15 mutations will guide the planning of future controlled treatment trials. Identifying the most sensitive and reliable outcome measures of retinal degeneration will greatly facilitate development of treatments with maximum efficiency. Together, these approaches are expected to have an impact on understanding PCDH15-related retinal degeneration, developing investigational treatment protocols, and assessing their effectiveness.

The goals and expected impact of this natural history study are to:

- Describe the natural history of retinal degeneration in patients with biallelic mutations in the PCDH15 gene
- Contribute to the identification of sensitive structural and functional outcome measures to use for future multicenter clinical trials in PCDH15-related retinal degeneration
- Contribute to the identification of populations for future clinical trials of investigative treatments for PCDH15-related retinal degeneration

1.3 Study Objectives

1. Characterize the natural history of retinal degeneration associated with biallelic pathogenic mutations in the PCDH15 gene over 4 years, as measured using functional, structural, and patient-reported outcome measures
2. Explore whether structural outcome measures can be validated as surrogates for functional outcomes in individuals with biallelic pathogenic mutations in the PCDH15 gene
3. Explore possible risk factors (genotype, phenotype, environmental, and comorbidities) for progression of the outcome measures at 4 years in individuals with biallelic pathogenic mutations in the PCDH15 gene
4. Explore variability and symmetry of left and right eye outcomes over 4 years in individuals with biallelic pathogenic mutations in the PCDH15 gene

1.4 General Considerations

The study is being conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP). Employing a prospective longitudinal study design is advantageous because it reflects a systematic method of data collection. This study design incorporates several strategies to minimize bias, detailed below, using considerations from "Rare Diseases: Natural

History Studies for Drug Development: Guidance for Industry, Draft Guidance.[24] These are considered standard for treatment trials and will enhance the translation of the data from this study to a treatment trial.

- Establishing standardized testing procedures and specific required equipment for all investigators, leading to greater consistency and precision in the information collected
- Training and certification of study staff who will perform the following procedures related to the primary outcomes (SP, OCT, MP, FAF) by a Reading Center. The Reading Center will grade test results in a uniform manner independently from study sites
- Use of standard, consistent definitions of pre-existing medical conditions, medications and treatments, and adverse events (AEs) across all clinical sites
- A consistent schedule of follow-up visits for all participants with established visit time frames
- A coordinating center (CC) is responsible for monitoring the conduct of the study to ensure adherence to protocol

Chapter 2: Study Enrollment and Screening Visit

2.1 Participant Recruitment and Enrollment

Study participants will be recruited from approximately 10 clinical sites worldwide. All eligible participants will be included without regard to gender, race, or ethnicity. Potential eligibility will be assessed during a routine examination by an investigator prior to obtaining informed consent, as part of usual care, through referrals from other providers or self-referral.

2.1.1 Participant Recruitment Goals and Strategy

Recruitment will be tracked within two Vision Cohorts as defined as follows. Sample size rationale is detailed in section 6.1.

- **Vision Cohort 1**: ~25 participants with the ***better eye*** Screening Visit visual acuity ETDRS letter score of 54 or more [approximate Snellen equivalent 20/80 or better] **and** ***visual field*** diameter 10 degrees or more in every meridian of the central field
- **Vision Cohort 2:** ~15 participants with the ***better eye*** Screening Visit visual acuity ETDRS letter score of 19-53 [approximate Snellen equivalent 20/100 - 20/400] **or** (visual acuity ETDRS letter score of 54 or more [approximate Snellen equivalent 20/80 or better] **and** ***visual field*** diameter less than 10 degrees in any meridian of the central field)

The better eye is defined as the eye with better Screening Visit ETDRS VA. If both eyes have the same VA (defined as the same Snellen equivalent), then the determination will be made at investigator discretion as the eye with better fixation or clearer ocular media to permit highest quality retinal imaging.

The visual field (VF) is defined as the clinically determined kinetic VF III4e performed within the last 18 months prior to or including the Screening Visit date.

	VF diameter ≥10° in every meridian	VF diameter <10° in any meridian
20/80 or better	Vision Cohort 1	Vision Cohort 2
20/100-20/400	Vision Cohort 2	Vision Cohort 2

The Foundation Fighting Blindness (FFB) Consortium Executive Committee will review recruitment progress and feasibility at regular intervals. Initial recruitment goals will be as follows:

- 40 participants enrolled into the study cohort (Cohorts 1 and 2, combined)
- If recruitment is not at a rate to meet the initial goals, an interim assessment of feasibility may be made by the FFB Consortium Executive Committee. A minimum of 20 participants enrolled in Vision Cohort 1 and Vision Cohort 2 combined will be targeted.

Participants will not be counted as enrolled into the study cohort until initial screening and genetic screening have been confirmed as a success (sections 2.3 and 2.4). This means that more participants will be screened than noted above, the number and reasons for screen failures will be tracked. It is also possible that some participants will have completed Screening Visit and will be awaiting genetic confirmation at the time the enrolled numbers reach goals above, therefore, the final enrolled numbers may be larger. To limit over-enrollment, clinical sites will be notified as the recruitment goals near completion, efforts will be made to accurately predict numbers in the genetic screening queue and consent and screening of participants which could contribute to over-enrollment in a given Vision Cohort may be paused

2.2 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine care examination by an investigator prior to obtaining informed consent, as part of usual care referral from another physician, or self-referral. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained using consent documentation approved by the overseeing IRB/EC.

The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form (ICF) to read. Potential study participants with severe vision impairment may be presented with a Short Form to be read aloud by a clinical staff member if they prefer, following the overseeing IRB/EC requirements. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

A participant is considered enrolled into the initial screening when the ICF has been signed and a participant ID has been obtained from the study website.

An immediate family member(s) of study participants may be asked to participate in family member genetic testing as part of the genetic screening phase. In these cases, family member(s) will be asked to provide a saliva sample (described in section 2.4). An electronic consent form will be reviewed and signed by the family member(s) in order to obtain permission to collect a saliva sample.

2.3 Screening Visit

After the ICF has been signed, potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of ophthalmic tests as described below, and genetic testing, if applicable. The Screening Visit date will be the date the Screening Visit testing procedures started. All Screening Visit testing procedures will be completed on this date.

2.3.1 Eligibility Criteria

To be eligible to **enroll into the genetic screening phase,** a study participant must meet all the inclusion criteria and none of the exclusion criteria at the Screening Visit.

2.3.1.1 Participant Criteria

Participant Inclusion Criteria

Participants must meet all the following inclusion criteria at the Screening Visit in order to be eligible to enroll into the genetic screening phase

1. Willing to participate in the study and able to communicate consent during the consent process
2. Ability to return for all study visits over 48 months
3. Age ≥ 8 years
4. Not planning to enroll in an experimental clinical trial for the treatment of PCDH15 for the duration of this study
5. Must meet one of the Genetic Screening Criteria, defined below:
   - Screening Group A: At **least** 2 disease-causing variants in the PCDH15 gene which are homozygous or heterozygous in trans, based on a report from a clinically certified lab (or a report from a research lab that has been pre-approved by the Genetics Committee)
   - Screening Group B: Only 1 disease-causing variant in the PCDH15 gene, based on a report from a clinically certified lab (or a report from a research lab which has been pre-approved by the Genetics Committee)
   - Screening Group C: At **least** 2 disease-causing variants in the PCDH15 gene which are unknown phase, based on a report from a clinically certified lab (or a report from a research lab which has been pre-approved by the Genetics Committee)

Note pertaining to all Screening Groups: if a participant has a variant(s) of unknown significance, he/she would still qualify if there is at least 1 disease-causing variant(s) on the PCDH15 gene.

Participant Exclusion Criteria

Participants must not meet any of the following exclusion criteria at the Screening Visit in order to be eligible to enroll into the genetic screening phase

1. Mutations in genes that cause autosomal dominant retinitis pigmentosa (ADRP), X-linked retinitis pigmentosa (RP), or presence of biallelic mutations in autosomal recessive RP/retinal dystrophy genes other than PCDH15
2. Expected to enter experimental treatment trial at any time during this study
3. History of more than 1 year of cumulative treatment, at any time, with an agent associated with pigmentary retinopathy (including hydroxychloroquine, chloroquine, thioridazine, and deferoxamine)

Note: Pregnant women are not being specifically excluded from participation.

2.3.1.2 Ocular Criteria

Ocular Inclusion Criteria

Both eyes must meet all the following at the Screening Visit for a participant to be eligible to enroll into the genetic screening phase

1. Clinical diagnosis of retinal dystrophy
2. Clear ocular media and adequate pupil dilation to permit good quality photographic imaging

Ocular Exclusion Criteria

If either eye has any of the following at the Screening Visit, the participant is not eligible to enroll into the genetic screening phase

1. Current vitreous hemorrhage
2. Current or any history of tractional or rhegmatogenous retinal detachment
3. Current or any history of (e.g., prior to cataract or refractive surgery) spherical equivalent of the refractive error worse than -8 Diopters of myopia
4. History of intraocular surgery (e.g., cataract surgery, vitrectomy, penetrating keratoplasty, or LASIK) within the last 3 months
5. Current or any history of confirmed diagnosis of glaucoma (e.g., based on glaucomatous VF changes or nerve changes, or history of glaucoma filtering surgery)
6. Current or any history of retinal vascular occlusion or proliferative diabetic retinopathy
7. History or current evidence of ocular disease that, in the opinion of the investigator, may confound assessment of visual function
8. History or evidence of active treatment for retinitis pigmentosa that could affect the progression of retinal degeneration, including:
    a. Any use of ocular stem cell or gene therapy
    b. Any treatment with ocriplasmin
    c. Treatment with an ophthalmic oligonucleotide within the last 9 months (last treatment date is less than 9 months prior to Screening Visit date)
    d. Treatment with any other product within five times the expected half-life of the product (time from last treatment date to Screening Visit date is at least 5 times the half-life of the given product)
    e. Treatment with Ozurdex (dexamethasone), Iluvien or Yutiq (fluocinolone acetonide) intravitreal implant

2.3.2 Screening Data Collection and Testing

The study design schematic at the beginning of the protocol shows the flow of the Screening Visit. The following procedures will be performed at the Screening Visit. The testing procedures are detailed in the RUSH1F Clinical Site Manual of Procedures. An overview of the equipment and technician requirements for all testing is in section 3.4. All ocular testing will be performed in each eye, right eye (OD) first and then left eye (OS).

Participants meeting criteria to continue will be enrolled into the genetic screening phase (section 2.4). Otherwise, the participant will be an initial screen failure (section 2.3.3). The below information will be collected at the Screening Visit:

1. Contact information (retained at the clinical site and not entered in the study database)
2. Inclusion and exclusion criteria assessment (criteria in sections 2.3.1.1 and 2.3.1.2)
3. Demographics (including sex, race, ethnicity)
4. A medical history will be elicited from the study participant and extracted from available medical records, including patient-reported daily activities, pre-existing medical conditions and medications
5. Complete ophthalmic exam. Exam will include slit lamp biomicroscopy, indirect ophthalmoscopy, and intraocular pressure (IOP). IOP measurements will be taken prior to pupil dilation
6. Genetic screening assessment (including number and phase of mutations in the PCDH15 gene, history of consanguinity, and collection of the source genetic report(s) available at the clinical site)
   - This includes an assessment that the participant meets the Genetic Screening Criteria described in section 2.3.1.1. If the participant does not meet the criteria for one of the Genetic Screening Groups, then the remainder of procedures and testing are not required. Participant will be discontinued as an initial screen failure per section 2.3.3
7. Visual acuity (including refraction, ETDRS, BRVT if needed, LLVA if needed)
   - The VA letter score will determine whether LLVA or BRVT will be performed. The criteria are defined in the RUSH1F Clinical Site Manual of Procedures
8. Kinetic VF III4e (or historical measurement performed within the last 18 months prior to or including the Screening Visit date) Vision Cohort determination, based on eye with better visual acuity and kinetic VF above (criteria in section 2.1.1)
   - If the participant's determined Vision Cohort is closed for enrollment, the remainder of procedures and testing are not required. Participant will be discontinued as an initial screen failure per section 2.3.3

2.3.3 Initial Screen Failures

Participants who do not meet criteria to continue as noted above will be discontinued as an initial screen failure. The Screening Visit Form will still be completed, entering "Not Done" for testing not finished. A Final Status Form will be completed, and the reason for screen failure will be noted.

2.4 Genetic Screening Phase

Participants passing the initial screening and enrolling into the Genetic Screening Phase will complete the following genetic testing and/or review procedures according to their Screening Group (defined in section 2.3.1.1). The study design schematic at the beginning of the protocol also summarizes the flow of the Genetic Screening Phase. More detailed procedures are specified in the RUSH1F Clinical Site Manual of Procedures.

- All genetic reports noted below to be uploaded to the study website by the clinical site or Central Lab may be available to and reviewed by CC, associated clinical site, Central

Lab, CGA, Genetics Committee, and investigators involved in oversight of the study (which include the study chair, Operations Committee, FFB Consortium Executive Committee). All reports will be de-identified prior to uploading

Screening Group A

- The clinical site will upload supporting genetic documentation (including genetic reports) onto the study website
- A CGA will review the genetic documentation provided by the clinical site to verify the genetic screening data entry and appropriate documentation of the final study cohort criteria (section 2.5) of at **least** 2 disease-causing variants in the PCDH15 gene which are homozygous or heterozygous in trans. Additional documentation may be requested as needed to verify the final study cohort criteria and all genetic screening assessments
  - If final study cohort criteria are verified, participant will be considered enrolled into the study cohort
  - Otherwise the participant will be a genetic screen failure (section 2.4.1)

Screening Group B or C

- The clinical site will upload supporting genetic documentation (including genetic reports) onto the study website
- Participants will be asked to provide a saliva sample, and approach at least 1 first-degree relative to provide a saliva sample for additional genetic testing. The first-degree relative(s) will be provided with information on how to provide informed consent and how to complete the saliva kit.
- The participant's and first degree relative(s)'s samples will be shipped to and analyzed by the Central Lab to conduct retinal dystrophy panel genetic testing and determine the presence and number of disease-causing variants on the PCDH15 gene (Screening Group B only), and the phase of the alleles from the family member testing (Screening Groups B and C). The Central Lab will provide these assessments and genetic report(s), which will be uploaded to the study website
  - If the Central Lab determines there are at least 2 disease-causing variants in the PCDH15 gene which are homozygous or heterozygous in trans, the participant's reports will move forward to CGA review
  - Otherwise the participant will be a genetic screen failure (section 2.4.1)
- A CGA will review the reports provided by the clinical site and the Central Lab to verify the genetic screening data entry and appropriate documentation of the final study cohort criteria (section 2.5) of at **least** 2 disease-causing variants in the PCDH15 gene which are homozygous or heterozygous in trans. Additional documentation may be requested as needed to verify the final study cohort criteria and all genetic screening assessments
  - If final study cohort criteria are verified, the participant will be considered enrolled into the study cohort
  - Otherwise the participant will be a genetic screen failure (section 2.4.1)

2.4.1 Genetic Screen Failures

Participants who do not meet criteria to continue as noted above will be discontinued as a genetic screen failure. A Final Status Form will be completed, and the reason for screen failure will be noted.

2.4.2 Genetics Committee Review

A Genetics Committee will review the genetic documentation of participants with verified final study cohort criteria and enrolled into the study cohort for interpretation/evaluation of whether the PCDH15 mutations are causative of the disease (i.e., pathogenic, likely pathogenic). Details of the process are described in the RUSH1F Monitoring Plan. Cases that are not confirmed as disease causing will remain in the study and will not be considered ineligible, however their data may be analyzed separately from those with pathogenic mutations.

2.5 Participants Enrolled into the Natural History Study

All participants meeting initial screening and eligibility criteria (section 2.3.1) who complete the Genetic Screening Phase (section 2.4) and meet the final study cohort criteria (defined below) will be considered enrolled into the study cohort and will complete the natural history study.

- Final Study Cohort Criteria: At **least** 2 disease causing variants in the PCDH15 gene which are homozygous or heterozygous in trans, based on a report from a clinically certified lab (or a report from a research lab that has been approved by the study genetics committee), and confirmed by a CGA.

Chapter 3: Natural History Study Procedures

3.1 Baseline Visit

Participants meeting criteria to enter the natural history study (section 2.5) will return for a Baseline Visit date within thirty (30) days after receiving confirmation of meeting **final study cohort criteria** from the CGA. The Baseline Visit date will be documented as the date testing procedures began. All Baseline Visit testing procedures will be completed within seven (7) days of the Baseline Visit date, except PROs as specified below.

The testing procedures that are performed at the Screening Visit will serve as baseline measures for the study and will not be completed again at the Baseline Visit. The only exception will be if the Baseline Visit date is more than ninety (90) days after the Screening Visit date. The visual acuity testing will need to be repeated (including refraction, ETDRS, LLV if A needed, BRVT if needed) if the baseline visit is completed more than ninety (90) days from the screening visit.

3.2 Baseline Testing Procedures

The following procedures will be performed at the Baseline Visit. The testing procedures are detailed in the RUSH1F Clinical Site Manual of Procedures. An overview of the equipment and certification requirements for all testing is in section 3.4. All ocular testing will be performed in each eye, OD first and then OS.

1. Medical updates, including new/changed adverse events, ocular procedures, and medications
2. Audiology history
    a. Participant-reported audiology history will be collected on the Audiology History Information Form. This includes history of hearing loss, newborn screening hearing, hearing aid use, cochlear implant use, history of ear infections, history of ear surgery and balance disorders.
3. Audiogram (request the most recent pre-cochlear implant audiogram)
    a. The most recent available audiogram prior to cochlear implant will be collected on each participant including air conduction threshold and bone conduction threshold. The Audiogram Results Form will be completed using the most recent audiogram. The historical audiogram will be sent to the central study audiologist reviewer, to confirm correct interpretation for the Results Form.
4. Patient Reported Outcomes (Adults: MRDQ and PROMIS®-29; Children: LPV-FVQ II)
    a. The PROs may be completed in person or remotely (phone or other remote methods) any time within 6 months of the Baseline Visit (not required to be the same day as the rest of the Baseline Visit)
5. Contrast sensitivity
6. SD-OCT
7. Axial Length and Corneal Curvature measurements
8. Near Infrared Reflectance Photos

9. Full-field Stimulus Threshold
10. Fundus Autofluorescence (on Optos, ***where available***)
11. Static perimetry
    a. Two tests will be performed. The clinical site will compare the certified technician-determined mean sensitivity from test 1 versus test 2
        - If the absolute value of the difference between the two tests is ≤ 2.4 dB, then the participant passes static perimetry reliability criteria and a third test is not needed
        - If the absolute value of the difference between the two tests is > 2.4 dB then the participant does not pass static perimetry reliability criteria, and a third test is needed
12. Fundus-guided microperimetry
    a. Two tests will be performed. The clinical site will compare the certified technician-determined mean sensitivity from test 1 versus test 2
        - If the absolute value of the difference between the two tests divided by the average between them is $\leq 50\%$ OR the absolute value of the difference between the two tests is ≤ 0.5 dB, then the participant passes microperimetry reliability criteria and a third test is not needed
        - If the absolute value of the difference between the two tests divided by the average between them is $> 50\%$ AND the absolute value of the difference between the two tests is > 0.5 dB, then the participant does not pass microperimetry reliability criteria and a third test is needed

3.3 Follow-up Visits

The Baseline Visit date is considered study day 0, from which follow-up visit windows are timed. The Follow-up Visit date will be the date the Follow-up Visit testing procedures started. All Follow-up Visit testing procedures will be completed on the same date other than the PROs required at the 24 Month and 48 Month Visits, which can be completed ± 6 weeks of the visits.

Follow up visits will be conducted at:

Visit	Target	Target Window	Allowable Window
12 Month Visit	52 Weeks	± 4 Weeks	± 6 Weeks
24 Month Visit	104 Weeks	± 4 Weeks	± 6 Weeks
36 Month Visit	156 Weeks	± 4 Weeks	± 6 Weeks
48 Month Visit	208 Weeks	± 4 Weeks	± 6 Weeks

Visits will be scheduled in the target window. If circumstances do not permit this, visits may be scheduled to extend out to the allowable window without being considered a protocol deviation.

The reason for scheduling outside the target window must be documented on the visit form. Visits that occur out of the allowable window will be used for analysis but will be documented as protocol deviations. Details regarding when to consider a visit missed are specified in the RUSH1F Clinical Site Manual of Procedures.

3.3.1 Follow-up Visit Testing Procedures

The following procedures will be performed at the Follow-up Visits as noted below. The testing procedures are detailed in the RUSH1F Clinical Site Manual of Procedures. An overview of the equipment and certification requirements for all testing is in section 3.4. All ocular testing will be performed in each eye, OD first and then OS.

The following will be performed at the 12 Month, 24 Month, 36 Month, and 48 Month Visits unless otherwise noted.

1. Medical updates, including new/changed AEs, ocular procedures, and medications
2. Patient Reported Outcomes at 24-Month and 48-Month visits only (Adults: MRDQ and PROMIS®-29; Children: LPV-FVQ II)
    a. The PROs may be completed in person or remotely (phone or other remote methods) any time within the Allowable Window of the associated visit, (not required to be the same day as the rest of the Follow up Visit).
3. Complete ophthalmic exam. Exam will include slit-lamp biomicroscopy, indirect ophthalmoscopy, and intraocular pressure (IOP). IOP measurements will be taken prior to pupil dilation
4. Visual acuity (including refraction, ETDRS, BRVT if needed, LLVA if needed)
    a. The visual acuity letter score will determine whether LLVA or BRVT will be performed. The criteria are defined in the RUSH1F Clinical Site Manual of Procedures
5. Contrast sensitivity
6. SD-OCT
7. Full-field Stimulus Threshold
8. Fundus Autofluorescence (on Optos, ***where available***)
9. Static perimetry
10. Fundus guided Microperimetry

3.3.2 Unscheduled Visits

Testing procedures at unscheduled visits are at investigator discretion. However, it is recommended that procedures performed during these visits follow the standard protocol for each procedure and be performed by certified personnel. Unscheduled visits will be recorded on the FFBC Consortium's study website. Study images taken during unscheduled visits do not require submission to the study website.

3.4 Personnel and Equipment Requirements for Study Procedures

The testing procedures are detailed in the RUSH1F Clinical Site Manual of Procedures. An overview of the equipment and certification requirements for all testing is as follows.

Study Procedures	Equipment Required (if applicable)	Who can Perform
Investigator taking overall responsibility for a visit oversees that consent process was performed in accordance with IRB/EC requirements, signs off on all eCRFs for a participant, eCRF edits, and protocol deviations	N/A	Certified investigator
Coordinator taking responsibility for the visit oversees the data entry aspect of the visit, addresses protocol queries and signs off on deviations	N/A	Certified coordinator
Informed consent: explanation/review of study with the potential participant and/or signature of ICF	N/A	Certified investigator/coordinator as permitted by the IRB/EC
Signature of Informed Consent Form	N/A	Certified investigator/coordinator as permitted by the IRB/EC
Data entry on study website	Computer and internet connection	Certified coordinator (or certified investigator with additional study website certification)
Sample collection and shipping	Study will provide necessary materials – detailed in RUSH1F Clinical Site Manual of Procedures	Certified coordinator
Collect information regarding medical history, demographics, adverse events, medications	N/A	Certified investigator/coordinator
Patient Reported Outcomes	Study will provide necessary materials – detailed in RUSH1F Clinical Site Manual of Procedures	Certified investigator/coordinator
Ocular Exam (including slit lamp biomicroscopy, indirect ophthalmoscopy and intraocular pressure (IOP)	Any equipment is acceptable	Certified investigator
Visual Acuity - Refraction	N/A	Clinical site personnel certified for refraction
Visual Acuity - ETDRS	EVA system (preferred) otherwise ETDRS charts	Clinical site personnel certified for ETDRS

Visual Acuity - LLVA	EVA system (preferred) otherwise ETDRS charts 2.0 neutral density filter to be provided by study	Clinical site personnel certified for performing ETDRS is also certified to perform LLVA
Visual Acuity - BRVT	BRVT charts provided by study	Clinical site personnel certified for BRVT
Contrast Sensitivity	VectorVision CSV-1000E provided by study	Clinical site personnel performing this testing do not require a study-specific certification but must be trained and delegated by the PI per the SSDL
SD-OCT	Heidelberg Spectralis	Clinical site personnel certified for SD-OCT
Fundus Autofluorescence (on Optos)	Optos (where available)	Clinical site personnel certified for Fundus Autofluorescence on Optos
Axial Length and Corneal Curvatur	Any equipment is acceptable	Clinical site personnel performing this testing do not require a study-specific certification but must be trained and delegated by the PI per the SSDL
Near Infrared Reflectance Photos	Heidelberg Spectralis (with 55degree lens*)	Clinical site personnel certified for Near Infrared Photos
FST	Diagnosys Espion	Clinical site personnel performing this testing do not require a study-specific certification but must be trained and delegated by the PI per the SSDL
Static Perimetry	Octopus 900 Pro (GATE Protocol)	Clinical site personnel certified for SP
Fundus-guided Microperimetry	MAIA	Clinical site personnel certified for MP
Kinetic Perimetry (historical)	Any equipment is acceptable	(Historical) Does not need to be performed by study certified personnel or recorded in the RUSH1F Study Staff Delegation Log

*Required for all sites except with the exception of any site with equivalent equipment approved by the reading center and operations committee.

Chapter 4: Unanticipated Problems and Adverse Event Reporting

4.1 Unanticipated Problems

Site investigators will promptly report to the CC all unanticipated problems meeting the criteria below via the Unanticipated Problems eCRF. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB/EC approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm)

Sites will follow the overseeing IRB's Unanticipated Problem reporting requirements as applicable. The CC also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the CC or at another participating entity such as a laboratory.

4.2 Adverse Events

4.2.1 Definition

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of AEs in the Integrated Addendum to ICH E6 (R2)[21]).

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a SAE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening)
- Is a congenital anomaly or birth defect
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above)

4.2.2 Reportable Adverse Events

For this protocol, a reportable AE includes all events meeting the definition of AE as above.

All AEs—whether volunteered by the participant, discovered by study personnel during questioning, or detected through examination, laboratory test, or other means—will be reported on an AE form online.

The purpose of AE collection for the RUSH1F study will be to provide historical controls for future clinical trials. As a no greater than minimal risk study, AEs do not require any specific reporting to regulatory or oversight bodies. Each Principal Investigator is responsible for abiding by any other reporting requirements specific to his/her IRB or equivalent ethics oversight committee.

4.2.3 Relationship of Adverse Event to Study Procedure

The study investigator will assess the relationship of any AE to be related or unrelated to a study procedure by determining if there is a reasonable possibility that the AE may have been caused by the procedure.

To ensure consistency of AE causality assessments, investigators will apply the following general guideline when determining whether an AE is related:

Yes:

There is a plausible temporal relationship between the onset of the AE and a study procedure, and the AE cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to a study procedure; and/or the AE abates or resolves upon discontinuation of a study procedure and, if applicable, reappears upon re-challenge.

No:

Evidence exists that the AE has an etiology other than a study procedure (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to a study procedure.

4.2.4 Severity (Intensity) of Adverse Event

The severity (intensity) of an AE will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. Thus a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

1. MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities
2. MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities but is usually ameliorated by simple therapeutic measures and participant is able to continue in study
3. SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study drug, and generally requires systemic drug therapy or other treatment

4.3 Pregnancy Reporting

If a pregnancy occurs, the participant will remain in the study. The occurrence of pregnancy will be reported to the Coordinating Center within seven (7) days of the site's discovery of the pregnancy (including at screening) and the Pregnancy Notification form will be completed within seven (7) calendar days. Sites will collect concomitant medications throughout the pregnancy. If an Adverse Event occurs as a result of the pregnancy, then the site will record the Adverse Event on the Adverse Event form.

Chapter 5: Miscellaneous Considerations

5.1 Treatments During the Study

5.1.1 Treatment for PCDH15-Related Retinal Degeneration

Participants **enrolled into the final study cohort** will be asked to not enroll into experimental treatment trials of underlying conditions related to PCDH15 mutations during the 4-year study duration. Should a participant enroll into a treatment trial during participation, the Executive Committee will decide as to their continuance in RUSH1F.

5.1.2 Treatment for Cystoid Macular Edema

Participants **enrolled into the final study cohort,** who need to receive treatment for CME during the study, may continue treatment.

5.1.3 Intraocular Surgical Procedures

Participants enrolled into the final study cohort who have intraocular surgery during the study will have follow-up visits timed either before the surgery date or at least 3 months after the surgery date. Clinical sites will make reasonable efforts to schedule the participant's follow-up visit as close to the visit target window as possible.

5.2 Risks and Benefits

5.2.1 Risks and Discomforts

Most examination procedures are considered part of standard care for retinal degenerations. This study will be capturing some information about participants that include identifiable, personal information, like date of birth (will be collected if permitted by site's regulatory bodies). The study has procedures in place to protect that information. However, there is a chance that a loss of that protection could occur. This would be a loss of confidentiality. There are special efforts being made to ensure that this does not happen. Otherwise, there are no known risks or discomforts beyond those involved in standard clinical care for patients with retinal degeneration involved in participation in this study, which involves systematically collecting information in a prospective fashion.

The sections below summarize the risks and discomforts that may be involved in the usual care of the patient during the period of prospective data collection.

- Risks associated with testing VA, KP, SP, Optos FAF, near infrared reflectance photos, and PRO may include boredom and frustration, but no lasting adverse effects are associated with these noninvasive tests
- Dilating eye drops will be used as part of the ophthalmic examination and before the SD-OCT, FST, and MP. Dilating eye drops may sting, cause light sensitivity, or an allergic reaction. There is a small risk of inducing a narrow angle glaucoma attack from the pupil dilation. However, all participants will have had prior pupil dilation usually on multiple occasions and therefore the risk is extremely small. If glaucoma occurs, treatment is available

- IOP Examination: In rare instances, the cornea may be scratched during measurement of intra-ocular pressure or use of a contact lens electrode. An abrasion like this may be painful, but it heals quickly with no lasting effects. If a participant experiences a corneal abrasion, a tear ointment may be administered, and an eye patch or gauze may be placed over the eye
- The risks of genetic testing include emotional and psychological stress when patients may learn they have a genetic disease that could be passed along to their children, if information relating to the family, such as adoption and paternity, could be determined from these tests. All the genetic testing information will be kept in confidential laboratory documents and medical records. If data gathered through genetic testing is accidentally released or stolen, it is possible that the information could become available to an insurer, an employer, a relative, or someone else. There are discrimination protections in US Federal Law and many State laws, however there is still a small chance that participants could be harmed if a release occurred

5.2.2 Benefits

Study participants are not expected to benefit directly from participation in this study. Subjects participating in this study may benefit from close attention from the study personnel and PI. The risks of participating in the study are outweighed by the benefits including increased attention from the study personnel and the ability to contribute to increased understanding of the natural history of PCDH15-related retinal degeneration and contribute to future development of treatments

5.3 Collection of Pre-Existing Conditions and Medications

Pre-Existing Condition: Any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the study (e.g., prior myocardial infarction or stroke) will be recorded.

Medications: All medication for the treatment of chronic pre-existing conditions, medical conditions, and/or AEs that the participant is currently taking at screening and during the study will be recorded. Nutraceuticals and preventative treatment also will be recorded.

5.4 Participant Compensation

Participant compensation will be specified in the ICF.

5.5 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

5.6 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the FFB Consortium CC, the Jaeb Center for Health Research in Tampa, FL, USA. De-identified participant information may also be provided to research sites involved in the study.

Chapter 6: Statistical Considerations

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

6.1 Sample Size

The sample size evaluation focuses on objective 1 of the study, to characterize the natural history of retinal degeneration associated with biallelic pathogenic mutations in the PCDH15 gene over 4 years on both the structural and functional outcomes of interest. Calculations to address objective 3, explore possible risk factors associated with progression, are summarized. A justification of the selected sample size using percent change for the outcomes of interest is outlined. The precision of the between-eye correlation is also provided.

6.1.1 Sample Size Considerations for Evaluating Percent Change from Baseline to 4 Years (All Outcomes)

Longitudinal changes on all outcome parameters being collected will be of interest. Change from baseline to 4 years will be evaluated for sample size purposes. The power/sample size calculations may be used to consider percent change on any outcome measure from baseline to 4 years.

Both eyes of a participant will be assessed for the main outcomes of interest. Thus, if there are N participants, 2N eyes will be available for analysis. However, outcome measures from 2 eyes of a person are typically strongly correlated ($r \geq 0.5$). The contribution of information in this case is (2/(1+r)) instead of 2. Values for the multiplier to the number of participants to obtain an effective sample size are given below:

r	Effective N
0.0	2.00
0.1	1.82
0.2	1.67
0.3	1.54
0.4	1.43
0.5	1.33
0.6	1.25
0.7	1.18
0.8	1.11
0.9	1.05
1.0	1.00

One objective is to estimate the correlation between eyes for the outcome measures; therefore, the value of the correlation is not known at the time of study design. We assume here a correlation of 0.8. This assumption is conservative in that it requires a higher number of participants that other plausible values of r.

The primary way sample size is evaluated is by considering the precision around the point estimates for the outcome measures of interest. Table 1 (including the table of specific values corresponding to the graph) provides the half width of the 95% confidence interval (CI) for the estimated mean percent change for combinations of the standard deviation (SD) of the distribution of percent change and sample size. The larger the SD, the wider the CI, meaning the range of possible true values grows.

Table 1. Sample size versus half width of 95% confidence interval for the mean percent change for varying standard deviation values

	Effective Sample Size (N of participants)				
	n=11 (10)	n= 22 (20)	n= 33 (30)	n= 44 (40)	n=55 (50)
SD=20%	12%	8%	7%	6%	5%
SD=30%	18%	13%	10%	9%	8%
SD=40%	24%	17%	14%	12%	11%
SD=50%	30%	21%	17%	15%	13%

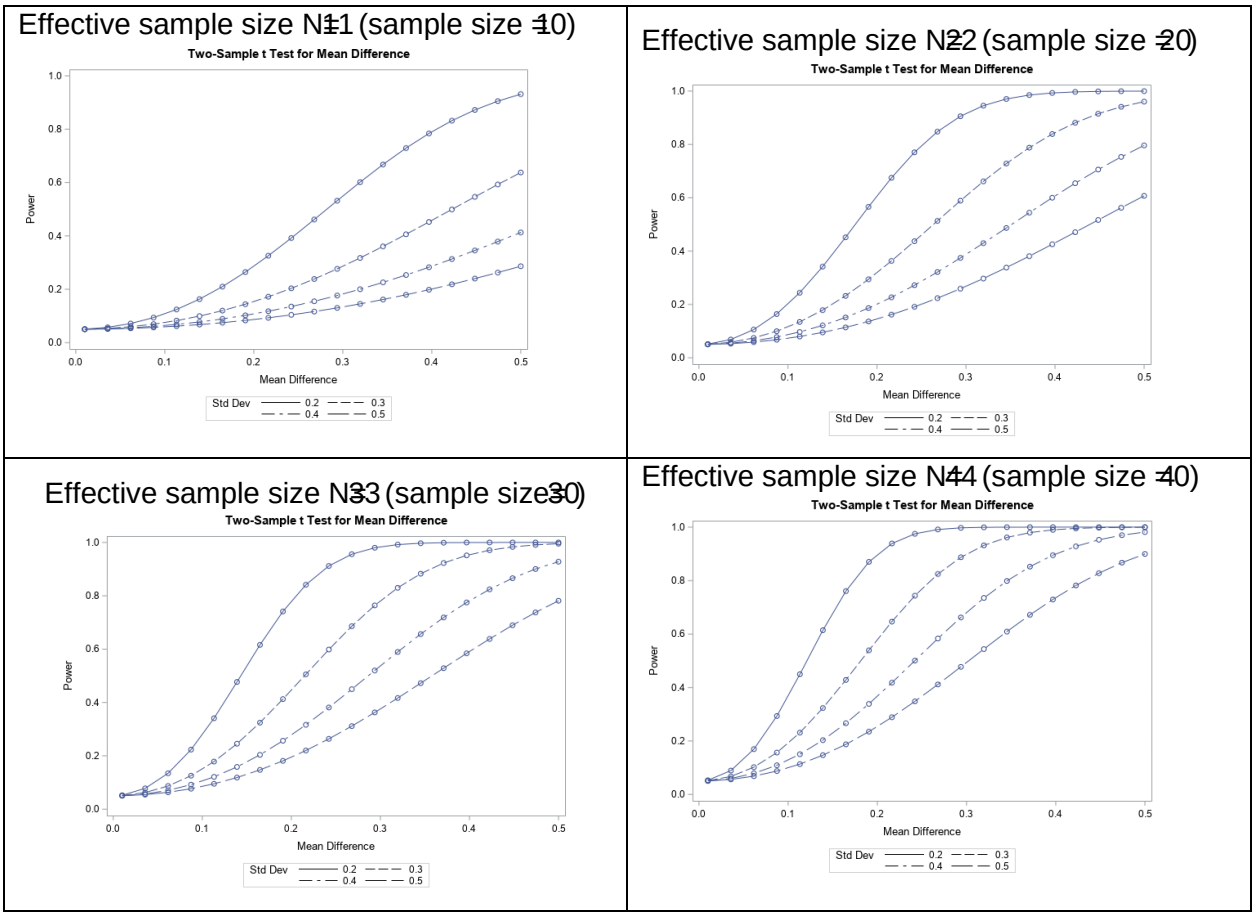
Note: Shaded columns correspond to the range of sample sizes feasible based on preliminary patient counts and financial constraints

6.1.2 Sample Size Considerations for Comparing Percent Change from Baseline to 4 Years within Subgroups of Interest (All Outcomes)

Another important objective for this natural history study will be to explore the association of possible risk factors with progression of various functional outcome variables (objective 3). Figure 1 considers various expected SDs of the distribution of percent change from baseline to 4 years per eye and evaluates the power to detect varying differences in average percent change from baseline to 4 years, comparing subgroups of various equally distributed sizes. If subgroups are not equally sized the detectable difference (with the same power) will be larger. Testing will be performed with a Type I (α) error rate of 0.05.

Note: within subgroup point estimates and CIs will also be important. Table 1 above can be applied to potential subgroup sample sizes as well to consider the precision that would be observed.

Figure 1. Power to conclude there is a difference given varying true difference values, population standard deviation, and sample size



Power to conclude there is a difference, when true difference in mean percent change is x-axis value. Assuming various sample size (subgroups close to equal distribution).

For example, with an effective sample size 22 and an effective sample size of 11 in each group, to have power of 80% or more, the true difference needs to be approximately 1.25 SDs (a mean difference of 25% if the SD of the percent change over 4 years 20%). If the effective sample size is 33, the true difference needs to be approximately 1.0 SD (a mean difference of 20% if the SD of the percent change over 4 years is 20%). If the effective sample size is 44, the true difference needs to be approximately 0.86 SDs (a mean difference 17% if the SD of the percent change over 4 years is 20%). Such mean differences are considered large.

6.1.3 Sample Size Considerations for Precision of the Estimate of the Correlation between Eyes

The intraclass correlation coefficient is used to assess the strength of correlation between eyes. When both eyes have the same mean for the outcome measure, the intraclass correlation coefficient is equal to the standard Pearson correlation coefficient (r). The distribution of r is not symmetric; therefore, CIs for the estimated correlation coefficient are not symmetric. A transformation of r ($z = 0.5 * \ln((1+r)/1-r)$) is used to create a variable that is asymptotically

distributed N (0, 1/(sqrt(N-3))) under the null hypothesis that r=0. The table below provides the 95% CI for different estimates of r from the observed data.

Table 2. 95% Confidence Intervals for an Observed Value of r

	N of patients				
r	n= 10	n= 20	n= 30	n= 40	n=50
0.3	(-0.41,0.78)	(-0.16,0.66)	(-0.07,0.60)	(-0.01,0.56)	(0.02,0.53)
0.4	(-0.31,0.82)	(-0.05,0.72)	(0.05,0.66)	(0.10,0.63)	(0.14,0.61)
0.5	(-0.19,0.86)	(0.07,0.77)	(0.17,0.73)	(0.22,0.70)	(0.26,0.68)
0.6	(-0.05,0.89)	(0.21,0.82)	(0.31,0.79)	(0.35,0.77)	(0.39,0.75)
0.7	(0.13,0.92)	(0.37,0.87)	(0.45,0.85)	(0.50,0.83)	(0.52,0.82)
0.8	(0.34,0.95)	(0.55,0.92)	(0.62,0.90)	(0.65,0.89)	(0.67,0.88)
0.9	(0.62,0.98)	(0.76,0.96)	(0.80,0.95)	(0.82,0.95)	(0.83,0.94)

Note: Shaded columns correspond to the range of sample sizes feasible based on preliminary patient counts and financial constraints

6.1.4 Final Sample Size Justification

Longitudinal changes in all outcome parameters being collected will be of interest for objectives 1 and 3. Information on rates of decline for PCDH15, and for inherited retinal degenerations in general, is very limited.

Data to consider for evaluating sample size:

- Valproic Acid Protocol (VPA) Data (a phase II multiple site, randomized, placebo controlled trial of oral valproic acid for ADRP) [Placebo group N=44; data can be accessed at https://public.jaeb.org/ffb/stdy]
  - Percent Change from Baseline to 1 year, Mean (SD):
    - -0.3% (16%) OD
    - -4.9% (17%) OS
- Natural history of 15 participants with EYS mutations (McGuigan/Jacobson, 2017)
  - -5.7% per year for VA [8 participants]
  - -5.8% for Inner Segment/Outer Segment (IS/OS) extent
- Natural history of 12 participants with EYS mutations (Miyata/Yoshimura, 2016)
  - -5.2 ±3.1% for IS/OS extent

Assumptions made:

- Expect average annual decline in the PCDH15 eyes will be 5% per year or 20% by 4 years
- True SD of percent change at 4 years is like VPA 1-year SD of approximately 20%

If 30 patients or 33 effective eyes are recruited: With an effective sample size of 33, the half width of a 95% CI around the point estimate for mean percent change would be 7%. A comparison of two equal-sized subgroups would have about 80% power to conclude there is a difference if the true difference is 20%.

If 40 patients or 44 effective eyes are recruited: With an effective sample size of 44, the half width of a 95% CI around the point estimate for mean percent change would be 6%. A comparison of two equal-sized subgroups would have about 80% power to conclude there is a difference if the true difference is 17%.

For objective 4 of evaluating variability and symmetry, a sample size of 30 participants for Vision Cohorts 1 and 2 will have a 95% CI of (0.17,0.73) when observed r equals to 0.5, and (0.62,0.90) when observed r equals to 0.8. A sample size of 40 participants for Vision Cohorts 1 and 2 will have a 95% CI of (0.22,0.70) when observed r equals to 0.5, and (0.65,0.89) when observed r equals to 0.8.

Recruitment is anticipated to take 10 months from the time of study launch.

6.2 Data Analysis

The analysis plans below are written with respect to the majority of outcomes of interest. Analyses will include data on both eyes for each participant, and confidence intervals will adjust for correlation between 2 eyes of the same participant.

6.2.1 Primary Objectives Analyses

The primary objectives of the natural history study and brief analysis plan for each are as follows.

1. Characterize the natural history of retinal degeneration associated with biallelic disease causing variants in the PCDH15 gene over 4 years, as measured using functional, structural, and patient-reported outcome measures
    a. Analysis plan for functional and structural measures: The distribution of each outcome at each visit will be summarized (including tabulating categorically, as well as means, SDs, medians, quartiles, ranges; both the absolute change and percent change will be evaluated; tests performed multiple times will be analyzed using average of all available tests). To determine the average annual rate of progression in the population for each outcome, a repeated measure least squares regression model will be fit using all available outcome data at baseline and all annual visits. Multiple imputation will be used to impute the outcome values for all missing time points (including participants who discontinue follow up prior to 48 months). Secondary analyses using binary definitions of outcome measures will also be explored in time to event analyses; Kaplan-Meier estimates with 95% confidence intervals will be calculated
    b. Analysis plan for PRO measures: The scoring of each questionnaire will be completed according to the procedures for each instrument and is detailed further in a separate statistical analysis plan. Baseline scores will be cross tabulated with categorical (severity of disease) versions of the outcome measures of interest at baseline. Changes in scores will be cross tabulated with binary (progression of disease) versions of the outcome measures of interest at the 24- and 48-month

visits. A generalized linear model adjusted for baseline differences will be explored.

2. Explore whether structural outcome measures can be validated as surrogates for functional outcomes in individuals with biallelic pathogenic mutations in the *PCDH15* gene
    a. Analysis plan: Scatterplots and Spearman correlation coefficients of changes in SD-OCT EZ area versus VF progression from baseline to each visit will be evaluated.
3. Explore possible risk factors (genotype, phenotype, environmental, and comorbidities) for progression of the outcome measures at 4 years in individuals with biallelic pathogenic mutations in the *PCDH15* gene
    - Analysis plan: The distribution of each outcome in terms of both absolute change and percent change from baseline to 4 years will be summarized (including tabulating categorically, as well as means, standard deviations, medians, quartiles), stratified by categorical levels of each potential risk factor of interest (listed below). Potential risk factors to evaluate include:
        - Phenotypic:
            - Clinical diagnosis
            - Age of onset of initial vision symptoms
            - Gender
            - Race/ethnicity
            - Visual acuity
            - Lens Status (phakic/pseudophakic/aphakic)
            - SD-OCT (as factors related to SP Hill Of Vision (HOV))
                - Presence of cysts
                - Central subfield thickness
            - MP
                - Mean retinal sensitivity
            - SP (as factors related to SD-OCT EZ area)
                - Volume of 30 degrees HOV
                - Mean sensitivity
                - Full field HOV
        - Genotypic:
            - Characterizations of the variants on the *PCDH15* protein
        - Environmental factors
            - Smoking status at baseline
            - Vitamin A use at baseline
            - Docosahexaenoic acid (DHA) use at baseline
            - Lutein use at baseline

4. Evaluate variability of repeat perimetry testing and symmetry of left and right eye outcomes over 4 years in individuals with biallelic pathogenic mutations in CDH15 gene

    a. Analysis plan for variability of repeat perimetry testing at baseline: Scatterplots and Spearman correlation coefficients for pairs (first versus second) of testing values for each repeated perimetry test. Bland-Altman plots of difference versus the mean value will be inspected. The intraclass correlation coefficient of the values and the within-person variance will be estimated.
    b. Analysis plan for the symmetry of left eye versus right eye: At baseline and each subsequent testing time, the symmetry of the test result values from the left and right eyes will be assessed and the symmetry of the change from baseline from the left and right eyes will be assessed for each follow-up visit. Bland-Altman plots of the inter-eye difference versus the mean value will be inspected. The intraclass correlation coefficient of the values will be estimated.

6.2.2 Interim Data Analysis

No formal interim analysis or "stopping guidelines" are planned for determining early stopping according to statistical rules, as no intervention is being studied and thus early efficacy and safety signals are not applicable.

Interim analyses will be planned for other reasons, including to evaluate data at baseline and annual visits for reporting in preliminary manuscripts, as well as monitoring data for recruitment and retention benchmarks, and quality assurance throughout the duration of the study. The FFB Consortium Executive Committee will review and oversee these data and their use in reporting.

Chapter 7: Data Collection and Monitoring

7.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in the eCRFs, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results which are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRF (e.g., office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.) and provided to the coordinating center for review.

The Central Lab will generate genetic reports from the retinal dystrophy genetic panel testing and/or family member testing analysis as applicable. These reports will be uploaded to the FFB Consortium study website and made available to the clinical site.

The CGA will review the genetic lab report(s) submitted by the clinical site during genetic screening against the genetic eCRF data to ensure that the data entered by the clinical site are consistent with the source(s) provided prior to the Baseline visit. The CGA will document his/her verification of these genetic data on the FFB Consortium study website and the clinical site will be notified of the results of the review.

In addition to providing interpretation/evaluation of whether or not PCDH15 mutations are causative of the disease on the FFB Consortium study website (see section 2.4.2), the Genetics Committee will review and provide approval for the use of genetic reports from research labs to be used for determining participant eligibility.

Reading Centers will conduct grading of the study data collected for MSP, SD-OCT, Optos FAF, and SP using the FFB Consortium study website. The Reading Center will conduct quality review only of the first ERG obtained from each clinical site using the FFB Consortium study website. These data will remain in the study database and will not be provided to the clinical site.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

7.2 Study Records Retention

Study documents will be retained for a minimum of six (6) years from the date on which the CC receives IRB approval to close the study. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the CC. It is the responsibility of the CC to inform the investigator when study documents no longer need to be retained.

7.3 Quality Assurance and Monitoring

Designated personnel from the CC will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the

applicable regulatory requirements as well as to ensure that the rights and well-being of trial participants are protected and that the reported trial data are accurate, complete, and verifiable.

Consistent with the Integrated Addendum to ICH E6 (R2)[24], a risk-based monitoring (RBM) plan will be developed and revised as needed during the study. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM plan may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of IRB/EC coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Communications with site staff
- Participant retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- AE reporting

CC representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

7.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI and study staff delegated to study responsibilities are responsible for knowing and adhering to their IRB/EC requirements.

Chapter 8: Ethics/Protection of Human Participants

8.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in Title 45 Code of Federal Regulations (CFR) Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

8.2 Institutional Review Boards and Ethics Committees

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the IRB or EC for review and approval. Approval of both the protocol and ICF(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB or EC before the changes are implemented to the study. All changes to the consent form will be IRB or EC approved; a determination will be made regarding whether previously consented participants need to be re-consented.

8.3 Informed Consent Process

8.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. All consent forms will be IRB- or EC-approved and in the case of written consent, the participant will be given the opportunity to carefully read and review the document. For any form of consent presented (written or verbal), the investigator or his/her designee (as approved by the IRB/EC) will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Participants will be asked to carefully consider the consent form presented to them and have any questions answered prior to signing.

Participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants must sign the ICF prior to any procedures being done specifically for the study. Participants may withdraw consent at any time throughout the course of the trial. A copy of the ICF will be given to participants for their records. The rights and welfare of participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

8.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, the funder(s) and their agents. This confidentiality is extended to cover genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The CC, other authorized vendors or representatives of the funder, representatives of the IRBs/ECs, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the FFB Consortium CC, located at the Jaeb Center for Health Research in Tampa, Florida. This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, a unique study identification number will identify individual participants and their research data. The study data entry and study management systems used by clinical sites and the FFB Consortium CC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the FFB Consortium CC.

8.4 Stored Specimens

With the participant's approval and as approved by the IRB/ECs, deidentified biological samples collected for genetic testing in screening groups B and C will be stored at Blueprint Genetics until the FFB Study Team notifies them in writing to destroy the samples. We expect the samples to be destroyed one (1) year after the end of the study.

Chapter 9: References

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