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Study Title:

SMART Study: Scotopic Microperimetric Assessment of Rod Function in Stargardt Disease

JHM IRB - eForm A – Protocol

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1. Abstract

- a. Provide no more than a one-page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Stargardt disease [1] is responsible for 7% of all retinal dystrophies and affects 1 in 10,000 people. The typical onset occurs during the first two decades of life, which makes it the most common form of juvenile macular degeneration with an estimated incidence of 10 – 12.5 per 100,000. STGD has been associated with considerable clinical and genetic heterogeneity, nearly two thirds of the cases are caused by several mutations in the ABCA4 gene [2, 3] with predominantly autosomal recessive inheritance [4]. A minor percentage have been associated with mutations in the ELOVL4 and PROM1 genes [5, 6] and was linked to autosomal dominant Stargardt-like phenotypes [7], which usually have later onset [8].

In STGD, the visual acuity impairment is accompanied by atrophic-appearing lesions in the macula and presence of yellow-white lesions at the level of the retinal pigment epithelium (RPE), also known as “fundus flecks”. Histologically, these fundus flecks are characterized by sub-retinal deposition of lipofuscin-like material mainly formed from the abnormal photoreceptors’ visual cycle [9-12]. Multiple lines of evidence indicate that the toxic effect of lipofuscin accumulation in the RPE is responsible for the RPE cells death [13-15]. Following the RPE loss, photoreceptor cells (rods and cones) degenerate rapidly [16] as their maintenance is largely dependent on RPE cells.

It was surprising that first reports of ABCA4 expression found its presence in rod but not in cone photoreceptors [17]. Such findings contradicted the STGD most common clinical manifestations, which are primarily related to cones dysfunction. Only few years later, it was shown by immunofluorescence microscopy and Western blot analysis that ABCA4 is also expressed in the fovea, and so, both cones and rods express the defective gene [18]. Studies with electroretinography (ERG) confirmed the findings of ABCA4 expression in both types of photoreceptors by showing abnormal electro-activity of cone and rods. For example, Scholl and collaborators have found that L and M-cone driven ERG exhibit phase and amplitude alterations in STGD [19]. Others studies with ERG have also demonstrated ERG rod dysfunction [20], although important variability in the degree of cone and rods dysfunction are frequently seen across STGD patients. The association between clinical phenotype and ERG phenotype has been previously attempted by some investigators [20]. A study conducted by Simonelli et al has shown reasonable correlation between clinical appearance and full-field ERG findings, however, such association was not supported by a later study with a larger cohort of patients [21].

Moreover, the marked phenotype (clinical appearance) variability, variable autosomal traits and large amount of mutations involving the ABCA4 gene make the correlation between gene mutations and phenotype a challenge for retina physicians. Furthermore, the differential impairment of rods and cones activity during the natural course of STGD is yet to be fully understood. It is possible that rod photoreceptors show the earliest functional decline, show regional variability of dysfunction and different rate of progression as compared to cones dysfunction. Such aspects may play important role in possible therapeutic targeting, clinical trial planning and outcomes interpretations. Whereas ERG is capable of detecting the differential rod and cone’s electrical activities, it cannot be precisely correlated with focal anatomical changes and distinguish macular lesions.

A relatively novel technology, the automated fundus related perimetry technology (also known as microperimetry-MP), constitutes a surplus tool to assess retinal function, in this case sensitivity, with the advantage of precisely correlating the retinal sensitivity to the anatomical changes seen in scanning laser ophthalmoscope (SLO) images and autofluorescence images. In the last 5 years, many studies using MP have reported cross-sectional findings of retinal sensitivity impairment in STGD [22-25]. The majority of these findings were based on the evaluation of microperimetric mesopic response (cones and rods response combined) without any consideration to differential activity and impairment of the two types of photoreceptors during the natural course of the disease.

More recently, Crossland and colleagues followed by Birch and colleagues have described and validated protocols to measure rod sensitivity using a modified MP-1 [26, 27], which may allow, for the first time, the precise evaluation of rod function and its correlation with morphologic damage in the natural history of STGD.

Ultimately, the understanding of the differential impairment of the cone and rods photoreceptors, through microperimetry findings, may establish consistent and reliable parameters to monitor patients and investigate potential treatments for STGD, which thus far, has not been available for patients with ABCA4-related retinal disease.

2. Objectives (include all primary and secondary objectives)

Through a multicenter prospective cohort study on the natural history of STGD (the ProgStar Study), this ancillary study has the main objective of investigating the rod photoreceptors' sensitivity during the natural course of the disease.

The primary objective is:

- To assess the yearly rate of progression of STGD using macular sensitivity under scotopic testing conditions.

The secondary objectives are:

- To correlate scotopic microperimetric changes with anatomical status/progression as determined by visual acuity, ERG, optical coherence tomography (OCT) and autofluorescence images.
- To determine the variability of the test.
- To determine the earliest functional deficits in STGD
- To establish the best microperimetric parameters to monitor patients with STGD.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Device: NIDEK MP-1S (NIDEK Technologies Srl, Italy; holding company, NIDEK Co., Ltd. Japan)

In 2002, Nishida and colleagues described for the first time an automated measuring system for fundus perimetry [28]. The MP-1 microperimeter produced by NIDEK Technologies was the first commercial microperimeter garnished with a true eye-track system, replacing the manual correction for eye movements which allowed accurate quantification of sensitivity and spatial location of the points tested [29, 30].

The device is composed of an infrared fundus camera, which acquires real-time fundus images in up to 45 deg of view (768 × 576 pixels resolution). A liquid crystal display (LCD) with set luminance of 1.27cd/m² (4abs) presents the fixation target and the stimuli, which is generated and controlled by a computer [31]. At the end of the exam, a conventional fundus camera captures a standard full color image. The built-in software superimposes the visual field map onto the retinal image, providing the spatial correlation between the anatomic landmarks and visual sensitivity maps [30, 32, 33]. The perimeter software also allows customization of the test parameters, the overlay of the fixation test results onto the fundus image, re-test of the same area scanned in a previous visit and automated comparison between exams.

The MP-1 received FDA 510(k) clearance in September 28 of 2006 (510k No. K023719) and was classified as a class II device. It has been approved for color retinography, fixation exam, fundus-related MP and visual rehabilitation.

Normative data has been published by Springer and co-authors [34] and Midena and collaborators [35] facilitating the interpretation of results obtained in diseased individuals. In addition, Chen and colleagues contributed with information regarding the test-retest variability of MP in patients with macular retinopathy as measured by the MP-1 [36]. In 2011, Crossland and colleagues validated for the first time a protocol for MP evaluation under scotopic conditions [26]. Fixation patterns have also been described in patients with various macular diseases using the MP-1 microperimeter [31, 37-40].

Physicians interested in the study of psychophysical parameters rapidly incorporated the technology employed in the MP-1, contributing vast literature over the last decade. Moreover, macular sensitivity and fixation stability have become measures to evaluate patients in clinical routine. Also, low vision rehabilitation could be enhanced with training sessions for fixation relocation [40].

MP has been shown to be a good tool to enhance the understanding of functional impairment in STGD. The information gathered from this proposed study should provide guidance and support to the identification of the most appropriate clinical outcome measures for anticipated clinical trials.

4. Study Procedures

This study will assess the scotopic macular sensitivity determined by rod cells using controlled fundus perimetry under dark-adapted conditions. This test will be performed in addition to the standard of clinical care tests required in the IRB approved prospective ProgStar-02 Study (JHU IRB NA# 00081134). Only one eye will be enrolled in the SMART study. In case both eyes are eligible and are enrolled in the ProgStar-02 study, the

principal investigator (PI) will choose one eye (study eye - SE) to participate in the SMART study. The following SE selection criteria are recommended, although the final decision will be at the PI's discretion:

→ Recommended SE selection criteria:

- a) The eye that has the smaller lesion within the range defined in the ProgStar-02 protocol
- b) The eye that has the better vision in terms of best-corrected visual acuity (BCVA)
- c) The eye that has the better fixation stability, which is defined by the smaller bivariate contour ellipse area (BCEA).

- a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care). Study duration and number of study visits required of research participants.

This is a prospective longitudinal observational study. The study shall utilize up to 12 clinical sites to collect prospective longitudinal observations on up to 70 participants. To qualify for this study, participants be enrolled in the IRB approved ProgStar Study. The scotopic MP will be the sole non-standard of care procedure executed at each visits.

The study will collect data every 6 months over a 24 months period. Therefore, 5 visits will take place during the study (baseline, months 6, 12, 18 and 24). If enrollment and prospective evaluation of an eligible patient in the ProgStar-02 study started significantly earlier than the start of the SMART study, then it is possible that only 18 months of follow-up will be available. The last ProgStar-02 visit should also be the last SMART study visit. Each visit, all patients will undergo microperimetric examination under scotopic condition in addition to the standard of care procedures included in the ProgStar Study protocol, which are described below:

- best-corrected visual acuity,
- complete ophthalmic exam (including dilated fundoscopy),
- autofluorescence imaging,
- MP and
- spectral-domain optical coherence tomography (SD-OCT) will be performed).

The ProgStar study results will be sent by the participating centers to the Dana Center for of Preventative Ophthalmology of the Wilmer Eye Institute, the Johns Hopkins University, Baltimore, for evaluation, with exception of the results of MP, autofluorescence and optical coherence tomography, which will be sent to a central reading center at the Doheny Eye Institute, Los Angeles, California.

This is a natural history study. There will be no treatments being investigated in this trial.

- b. Blinding, including justification for blinding or not blinding the trial, if applicable. N/A
- c. Justification of why participants will not receive routine care or will have current therapy stopped. N/A
- d. Justification for inclusion of a placebo or non-treatment group. N/A
- e. Definition of treatment failure or participant removal criteria. N/A
- f. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely. N/A

5. Inclusion/Exclusion Criteria

Inclusion criteria:

- A mandatory inclusion criteria for the index ancillary study is being a participant of the IRB approved ProgStar Study (JHU IRB NA# 00081134). In the ProgStar Study, the study participants are required to meet the following inclusion criteria:
 1. Provide a signed informed consent form and authorization allowing the disclosure and use of protected health information.
 2. The designated primary study eye must have at least one well-demarcated area of atrophy as imaged by fundus autofluorescence with a minimum diameter of 300 microns and all lesions together must add to less than or equal to 12 mm² (equivalent to no more than 5 disc areas in a least one eye) and a BCVA of 20 ETDRS letters (20/400 Snellen equivalent) or better.
 3. Two (2) pathogenic mutations confirmed present, in the ABCA4 gene. If only one ABCA4 allele contains a pathogenic mutation, the patient shall have a typical Stargardt phenotype, namely at least one eye must have flecks at the level of the retinal pigment epithelium typical for STGD.

4. The primary study eye must have clear ocular media and adequate pupillary dilation to permit good quality FAF and sd-OCT imaging in the opinion of the investigator.
5. Be able to cooperate in performing the examinations.
6. Be willing to undergo ocular examinations once every 6 months for up to 24 months.
7. Be at least six years old.
8. Both eyes can be included if inclusion criteria are fulfilled for both eyes.

In addition, candidates of the ProgStar study that meet any of the following exclusion criteria shall not be enrolled in any of the ProgStar study neither in the index ancillary study:

1. Ocular disease, such as choroidal neovascularization, glaucoma and diabetic retinopathy, in either eye that may confound assessment of the retina morphologically and functionally.
2. Intraocular surgery in the primary study eye within 90 days prior to baseline visit.
3. Current or previous participation in an interventional study to treat STGD such as gene therapy or stem cell therapy. Current participation in a drug trial or previous participation in a drug trial within six months before enrollment. The use of oral supplements of vitamins and minerals are permitted although the current use of Vitamin A supplementation shall be documented.
4. The site Principal Investigator may declare any patient at their site ineligible to participate in the study for a sound medical reason prior to the patient's enrollment into the study.
5. Any systemic disease with a limited survival prognosis (e.g. cancer, severe/unstable cardiovascular disease).
6. Any condition that would make adherence to the examination interfere with the patient attending their regular follow-up visits schedule of once every 6 months for up to 24 months difficult or unlikely, e.g. personality disorder, use of major tranquilizers such as Haldol or Phenthiazine, chronic alcoholism, Alzheimer's Disease or drug abuse.
7. Evidence of significant uncontrolled concomitant diseases such as cardiovascular, neurological, pulmonary, renal, hepatic, endocrine or gastro-intestinal disorders.

6. Drugs/ Substances/ Devices

- a. The rationale for choosing the drug and dose or for choosing the device to be used.

Degeneration of the photoreceptors and underlying RPE in STGD typically occurs close to and within the macula center, leading to bilateral central atrophy.

MP is a valuable tool to perform a systematic and quantitative evaluation of the macular sensitivity to different intensities of light and at the same time to correlate the functional findings to anatomical changes. The Nidek MP device has a built-in eye-tracking system and permits the precise re-test of previous scanned areas [31]. In addition, this technology can provide quantitative analysis of gaze fixation, a known parameter of visual quality, which can be affected by the growth of central atrophy in patients with STGD.

The microperimeter manufactured by Nidek (MP-1, NIDEK Technologies Srl, Italy) MP-1 has been used since 2002 in research and clinical settings [28, 29] and has normative and disease data available. The device created the standards for automated fundus related perimeter and stands as the most common microperimeter found in retina services. At this time, the Nidek MP-1 is the only microperimeter that has been adapted to scotopic MP with validated protocols [41][35].

- b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. N/A
- c. Justification and safety information if non-FDA approved drugs without an IND will be administered. N/A

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7. Study Statistics

- a. Primary outcome variable.
Change in macular sensitivity measured under scotopic conditions.
- b. Secondary outcome variables. N/A
- c. Statistical plan including sample size justification and interim data analysis.

Sample Size and Power:

The ancillary study will follow the statistical standards imposed by the ProgStar Study protocol.

In the ProgStar Study, a feasibility survey was undertaken prior to establishing the study protocol. The survey consisted of a questionnaire that was sent to the participating centers to determine how many study candidates might be available at each center for this prospective study.

The primary outcome of the study is the yearly growth in the area of the atrophic lesion as measured by fundus auto-fluorescence. A recent paper by Chen et al [29] reported that in a group of 24 STGD participants with well defined atrophic lesions at baseline, the mean yearly growth of the lesion was $0.94 \text{ mm}^2 \pm 0.87$.

The reliability of measuring areas of geographic atrophy using images taken with a confocal scanning laser ophthalmoscopy has been described by Deckert et al [35]. Using 2 different readers to examine images from 34 eyes, the mean difference in area affected for the proposed quantification algorithm was 0.12 mm^2 with a 95% confidence interval (0.02, 0.22).

Using the above parameters as a reference, we calculated the power to detect yearly progression for sample sizes between 120 and 240 participants, with standard deviations between 0.9 and 1.1, and expected progression rates of 0.40 and 0.50 mm^2 per year (Figure 5). A clinically meaningful progression rate should be greater than the variability of the measurement. The power calculations were set to test for progression rates above 0.2 mm^2 which is the estimate of the upper bound of the difference that could be attributable solely to measurement error.

Figure 5: Power calculations for expected progressions rates of 0.40 and 0.50 mm^2 per year

A sample size of 170 achieves 80% power to detect a difference of 0.2 between the null hypothesis mean of 0.2 mm^2 (measurement error) and the alternative hypothesis mean progression of the lesion of 0.4 mm^2 with an estimated standard deviation of 0.9 and a significance level $\alpha = 0.05$ using a two-sided Wilcoxon test (Figure 5 (a)). Similarly, if the expected standard deviation increases to 1.0 we need 200 participants to achieve the same level of power. When the expected progression rate is $\geq 0.50 \text{ mm}^2$, a sample size of 120 participants achieves more than 80% to detect differences beyond the expected measurement error, for standard deviations ≤ 1.1 (Figure 5 (b)).

Statistical Analyses

Estimating the yearly growth in the area of the atrophic lesion as measured by fundus auto-fluorescence:

First exploratory analysis looking at the baseline, six, and twelve months overall distribution of the outcome will be performed, outliers and inconsistent measures will be identified and reviewed. Let Y_{iv} represent the area (or a transformation to achieve normality; e.g. square root) of the i th individual at visit v for $v=0, 1, 2, 3, 4$ for the baseline, 6 months, 12 months, 18 months and 24 months visits, respectively. In order to determine the average rate of progression in the population, an appropriate approach will be to allow for each individual to have his/her own intercept and slope and to average them to achieve the overall rate of decline. This is accomplished with a random coefficients regression model of the form:

$$Y_{iv} = (\mu + a_i) + (\Delta + b_i)v + \gamma Z_{iv} + e_{iv}; \text{ where } a_i \sim N(0, \sigma_1^2), b_i \sim N(0, \sigma_2^2), \text{ cov}(a_i, b_i) = \sigma_{12} \text{ and } e_{iv} \sim N(0, \sigma^2).$$

The a_i and b_i are the random departures of the line for the i th individual from the population line with intercept μ and slope Δ . The e_{iv} are the within individual departures from the line of the repeated measurements taken on the i th individual at times 0, 6, 12, 18 and 24 months. Z_{iv} represents a vector of factors that could be related to progression such as age and use of vitamin A supplementation.

The estimate of Δ and its standard error will provide the six-month progression of the lesions. In addition, to explore whether progression may be different for different initial levels, we will carry out the analysis in strata of baseline severity.

A similar approach to will be used to examine progression overtime for the secondary outcomes: retinal thinning, loss of photoreceptors, loss of retinal sensitivity, and changes of BCVA.

Scatterplots with lowess smooth average curves will be used to explore the relationship between variables. A linear mixed model will be then used to analyze and quantify the association between the different variables.

Baseline demographic characteristics are: date of birth, age, sex, and race. Randomization is not applicable.

Data Set Descriptions

Study Population: patients with STGD enrolled into the study shall have had previous genetic testing and a finding of at least 2 pathogenic mutations in the ABCA4 gene. If only one ABCA4 allele containing a pathogenic mutation is detected, a patient may be enrolled if they have a typical Stargardt phenotype, i.e. at least one eye must have flecks at the level of the retinal pigment epithelium typical of STGD.

Data Sets for Endpoint Analyses: the final data set will include all participant visits. Most of the participants will complete 5 visits. Participants lost to follow-up after the six month visit shall be included but will only partially contribute to the estimation of the progression rates.

Handling of Missing Data: the random effects methods described in section 7.2 do not require all individuals to have all the five visits. Individuals who are lost to follow up will partially contribute to the analysis and will be appropriately weighted by the maximum likelihood approach. To rule out informative censoring (i.e., fast progressors having less visits with available data) we will perform sensitivity analysis restricting to those with complete data. Were it to be necessary, we will explore multiple imputation methods to complete the trajectories shorter than two years.

Interim Analysis: an interim analysis of the study data is planned after all participants have completed their 12-month visit.

d. Early stopping rules.

This is an observational study of the natural course of STGD. All devices included in the study are used in standard of clinical care for patients affected by STGD. Therefore, no study-specific safety events are anticipated.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

This study is an observational study of the natural course of STGD that will include data from the results of both psychophysical examinations (visual acuity testing and microperimetry) and retinal imaging examinations (optical coherence tomography and fundus autofluorescence), which are an integral part of current standard of clinical Care that is routine in patients with STGD. The risk to participants will not exceed the risks associated with the current standard of clinical care examinations. The protocol for scotopic microperimetry does not use any range of the light spectrum that could cause known harm to patients with STGD or would put the patients above minimal risks.

b. Steps taken to minimize the risks. N/A

c. Plan for reporting unanticipated problems or study deviations.

Protocol Deviations:

This study shall be conducted according to this written protocol except in the case of an emergency where immediate intervention based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator) is essential for the protection, safety, and well-being of the participant. In the event of a significant deviation from the protocol as a result of an emergency, accident, or mistake, the investigator or designee must contact the Study Director, as soon as possible, by telephone. A joint decision will then be made regarding the participant's continuation in the study and

the decision documented by the investigator and the Study Director and reviewed by the monitor. In addition, the investigator must notify the IRB to the extent necessary under GCP and local requirements. The sponsor, the Foundation Fighting Blindness Clinical Research Institute shall be notified of any protocol deviations and shall forward a detailed report any serious deviations to HRPO immediately. Any non-serious deviations shall be reported to HRPO as part of the annual study progress report.

All unanticipated problems involving risk to participants or others related to participation in the study should be promptly reported to the Principal Investigator's office by phone (410-614-6908).

- d. Legal risks such as the risks that would be associated with breach of confidentiality.

Although microperimetry under scotopic condition is not a standard MP protocol used in regular clinic visits of patients with ABCA4 related retinopathies, microperimetry exam is considered a standard of care procedure. The risks that would be associated with breach of confidentiality in scotopic microperimetry would not be higher than any other standard of care procedures.

If the results of the each individual's procedures conducted during the time period of patients' participation in this study, including any clinically significant abnormal findings, if requested, will be shared with that study participants or their his/her primary care provider at any time during throughout the study since study participation is part of standard clinical care and authorized by the patient.

- e. Financial risks to the participants.

The costs associated with microperimetry examinations under scotopic conditions will be covered by the study sponsor Foundation Fighting Blindness Clinical Research Institute. Therefore, patients are not expected to be exposed to financial risks.

9. Benefits

- a. Description of the probable benefits for the participant and for society.

There would be no direct benefit to the participant from being in this study. However, the knowledge gained from this study may establish novel and reliable parameters to follow and investigate potential treatment for STGD.

10. Payment and Remuneration

- a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Compensation will not be provided to the study participants in this study.

11. Costs

- a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The microperimetry examinations under scotopic conditions will be financially supported by the Foundation Fighting Blindness Clinical Research Institute.

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CONFIDENTIAL

FOUNDATION FIGHTING BLINDNESS CLINICAL RESEARCH INSTITUTE

CONFIDENTIAL – PROPRIETARY INFORMATION

Project Title

The Natural History of the Progression of Atrophy Secondary to Stargardt Disease: A Prospective Longitudinal Observational Study

Amendment 1.0

Protocol No.:	FFBCRI-PROGSTAR-02
IND No.:	N/A
Drug Development Phase:	N/A
Issue Date:	3/11/2013

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Protocol Synopsis

Name of Sponsor:	Foundation Fighting Blindness Clinical Research Institute	Protocol #: CRI-PROGSTAR-02 IND#: N/A
Name of Product:	N/A	
Protocol Title:	The Natural History of the Progression of Atrophy Secondary to Stargardt Disease (STGD): A Prospective Longitudinal Observational Study	
Clinical Phase:	N/A – Natural History Study	
Treatment Indication:	N/A	
Objectives:	<p>The primary objective is:</p> <ul style="list-style-type: none"> • To assess the yearly rate of progression of STGD using the growth of atrophic lesions as measured by fundus autofluorescence (FAF) imaging. <p>The secondary objectives are:</p> <ul style="list-style-type: none"> • To assess the yearly rate of progression of STGD using the rate of retinal thinning and the rate of loss of photoreceptors as measured by spectral-domain optical coherence tomography (sd-OCT) • To assess the yearly rate of loss of retinal sensitivity as measured by microperimetry • To assess the yearly rate of visual acuity changes using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity protocol • To correlate the presence and progression of morphological abnormalities in FAF and sd-OCT images with visual function as measured by microperimetry and visual acuity. • To perform exploratory analysis that examines factors associated with effects on STGD progression, such as the use of vitamin A supplementation and mutations in the <i>ABCA4</i> gene 	
Study Design:	Prospective longitudinal observational study over a period of 24 months.	

Name of Sponsor:	Foundation Fighting Blindness Clinical Research Institute	Protocol #: CRI-PROGSTAR-02 IND#: N/A
Name of Product:	N/A	
Participant Population:	Up to a total of 250 (minimum of 150) patients, including males and females age 6 years and older affected by STGD that have an atrophic lesion in at least one eye with a minimum diameter of at least 300 microns, and a sum of all lesions less than or equal to 12 mm ² (five disc areas).	
Test Product, Dose, Mode of Administration:	N/A	
Outcome Variables	<ul style="list-style-type: none"> • Growth of atrophic lesions as measured by FAF imaging performed at 12 and 24 months. • Rate of retinal thinning and photoreceptor loss as measured by sd-OCT at 12 and 24 months. • Loss of retinal sensitivity as measured by microperimetry at 12 and 24 months. • Change of best-corrected visual acuity by using the ETDRS protocol at 12 and 24 months. 	
Study Duration:	Participant: 24 months involvement with data collection every 6 months. Total duration of study including patient enrollment and data analysis: 36 months.	

Table of Contents

Protocol Synopsis	6
Table of Contents	8
1 Introduction	15
1.1 Background.....	16
1.2 Treatment Strategies	19
1.3 Known and Potential Risks	20
1.3.1 Foreseeable Risks	20
1.3.2 Risk Management and Emergency Response.....	21
1.3.2.1 Minimization of Risk.....	21
1.3.2.2 Response to Risk	21
1.3.2.3 Research Injury Compensation.....	21
1.3.2.4 Precautions and Preventive Measures	21
1.3.3 Known and Potential Benefits	21
2 Study Rationale and Objectives	22
2.1 Study Rationale	22
2.2 Study Objectives.....	22
3 Study Design	23
3.1 Type/Design of Study.....	24
3.2 Study Treatments.....	24
3.3 Study Population	24
3.3.1 Recruitment Methods	24
3.3.2 Recruitment Process	24
3.3.3. Volunteer Compensation.....	25
3.3.4. Recruitment Materials	25
3.4 Eligibility Criteria.....	25
3.4.1 Informed Consent/Assent	25
3.4.2 Disclosure of DOD Sponsorship and Access to Research Records	26
3.4.3 Inclusion Criteria	27
3.4.4 Exclusion Criteria.....	28
3.5 Primary and Secondary Outcome Variables.....	29
3.6 Measures to Minimize/Avoid Bias	29
3.6.1 Blinding.....	29

3.6.2	Study Data	30
3.7	Schedule of Data Collection	31
3.7.1.1.	Screening/Baseline (Day 0).....	31
3.7.1.2.	Follow-up visits	32
3.7.2.	Safety Assessments	33
3.7.2.1.	Adverse Events	33
3.7.2.2.	Clinical Laboratory Data	33
3.7.2.3.	Evaluations	33
3.7.2.4.	Labs Performing Evaluations and Special Precautions	34
3.7.2.5.	Sharing Research Results	34
3.7.3.	Endpoints	34
3.7.3.1.	Primary Statistical Endpoint.....	34
3.7.3.2.	Secondary Statistical Endpoints	34
3.7.4.	End of Study	35
3.8.	Withdrawal Criteria, and Procedures	35
3.9.	Screen Failures	35
3.10.	Definition of Completed.....	35
3.11.	Definition of Lost to Follow-up	36
3.12.	Participant Compliance	36
3.13.	Protocol Deviations	36
3.14.	Protocol Modifications	36
4.	Study Personnel	37
4.1.	Roles and Responsibilities of Key Study Personnel.....	37
4.2.	Conflict of Interest.....	39
5.	Prohibited Medications	39
6.	Evaluation of Adverse Events.....	39
7.	Statistical Analysis	39
7.1.	Sample Size and Power	39
7.2.	Statistical Analyses.....	40
7.3.	Baseline Demographic Characteristics	41
7.4.	Data Set Descriptions	42
7.5.	Handling of Missing Data	42
7.6.	Safety Analyses	42
7.7.	Study Drug Compliance	42
7.8.	Interim Analysis	42
8.	Study Product Management	42
9.	Data Handling and Records Management.....	43

9.1.	Data Collection	43
9.1.1.	Volunteer Identification.....	44
9.1.2.	Confidentiality.....	44
9.1.3.	Access.....	45
9.1.4.	Reporting Requirements	45
9.2.	Source Documents.....	45
9.3.	File Management at the Study Site.....	46
9.4.	Records Retention at the Study Site	46
9.5.	Data Management Considerations.....	46
9.5.1.	Database Design and Creation.....	46
9.5.2.	Data Coding.....	46
9.5.3.	Data Transfer.....	46
9.5.4.	Data Validation.....	47
9.5.5.	Database Lock	47
10.	Quality Control and Quality Assurance.....	47
10.1.	Monitoring.....	47
10.2.	Auditing.....	48
11.	Ethics and Responsibility	48
11.1.	Clinical Study Report	48
12.	Confidentiality.....	49
13.	Amendment Policy.....	49
14.	References.....	50
	Appendix 1 - Agreement.....	53
	Appendix 2 – Additional Institutions and Personnel Involved With the Study	54
	Appendix 3 – Biosketches of Key Personnel	55
	Appendix 4 – Electronic Clinical Report Form (eCRF)	56

List of In-text Tables

Table 3.4.3-1	Inclusion Criteria.....	27
Table 3.4.4-1	Exclusion Criteria.....	28
Table 3.6.2	Study Data.....	29

List of Abbreviations and Definitions of Terms

Abbreviations

AE	Adverse event
AF	Autofluorescence
AHRPO	Army Human Research Protection Office
BCVA	Best Corrected Visual Acuity
CFR	Code of Federal Regulations
CO	Contract Officer
COR	Contract Officer Representative
CRF	Case Report Form
CRI	Clinical Research Institute
eCRF	Electronic Clinical Report Form
cSLO	Confocal Scanning Laser Ophthalmoscopy
DOD	Department of Defense
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FFB	Foundation Fighting Blindness
FFB CRI	Foundation Fighting Blindness Clinical Research Institute
GCP	Good Clinical Practice
HRPO	Human Research Protections Office
HSPS	Human Subjects Protection Scientist
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MedDRA [®]	Medical Dictionary for Regulatory Activities
MP	Microperimetry
mmHg	millimeters of Mercury
N/A	Not Applicable
OC	Observed cases
sd-OCT	Spectral Domain Optical Coherence Tomography
STGD	Stargardt Disease
USAMRMC	US Army Medical Research and Materiel Command

Definition of Terms

Research - A systematic investigation, including the development, testing and evaluation of an idea, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Clinical Investigation - Any experiment in which a drug or therapy is administered, dispensed, or used for treating one or more human participant. This definition applies to research involving the use of FDA-regulated products. Even if a clinical investigation does not meet the definition of research, it is participant to the same regulations as research.

Human Participant - A living individual about whom an investigator is conducting research, obtains data, through intervention or interaction with the individual, or identifiable private information.

Human Anatomical Substances - Any human organs, tissues, cells, or body fluids including but not limited to blood/sera (finger stick, ear stick, venipuncture, etc.), hair, nails, teeth, skin, sputum or cells gathered from mouth washing, nasal or oral swabs, placenta or amniotic fluid.

Individually Identifiable Private Information - *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place. This information has been provided for specific purposes by an individual and the individual can reasonably expect that private information will not be made public (for example, a medical record). *Individually identifiable* means that the identity of the participant is known or that their identity may readily be ascertained by the investigator or that their identity is associated with the information.

Protected Health Information (PHI) - Any individually identifiable health information held by a covered entity, as defined in the Health Insurance Portability and Accountability Act (HIPAA).

Covered Entity - An organization engaged in the treatment of patients, responsible for obtaining payment for such treatment, or engaged in other healthcare operations where PHI is electronically exchanged.

Authorization - Written permission from an individual allowing a Covered Entity to use or disclose specified PHI for a particular purpose (such as research).

Minimal Risk - The probability and magnitude of harm or discomfort in the research are not anticipated to be greater in and of themselves than those ordinarily encountered in daily life, or during the performance of routine physical and psychological examinations or tests.

Legally Authorized Representative (LAR) - An individual or judicial or other body authorized under applicable law to consent on behalf of a potential participant to the participant's participation in the procedure(s) involved in the research. NOTE: State law defines who may act as an LAR. The Institutional Review Board (IRB) of record should be consulted for guidance regarding who can serve as an LAR for research at the research site.

USAMRMC Supported Research - For the purpose of this document USAMRMC supported research includes but is not limited to: (1) Research funded (through grant, contract, cooperative agreement, military interdepartmental purchase request, etc.) by the USAMRMC and (2) Research managed (technical management and/or funds management) by the USAMRMC as directed by Congress (e.g., Telemedicine and Advanced Technology Research Center (TATRC)).

Institutional Review Board (IRB) of Record - The IRB listed on an Institution's Assurance of Compliance that assumes responsibility for review and oversight of a research protocol on behalf of the institution. An IRB of record from each institution engaged in the research must review and approve the protocol; therefore, there can be more than one IRB of record for a protocol. An IRB Authorization Agreement between two IRBs of Record allows one IRB of record to defer to another.

Research Proposal - A research plan submitted to the DOD funding agency in response to a solicitation. The proposal provides an overview of all proposed work to be performed and provides the rationale explaining why the institution should be awarded funds to complete the work. A proposal may consist of multiple research projects conducted under separate protocols at one or more institutions.

Research Protocol - A comprehensive, detailed, and specific plan of action for the execution of research on human participants

Award - A financial agreement such as a grant, contract, or cooperative agreement between the Federal Government and an institution.

Scientific Review – An independent, documented review that objectively evaluates the scientific merit of a research proposal or protocol. Refer to the HRPO Policies and Procedures document on the HRPO website for additional information on scientific reviews.

Contract Officer (CO) – A federal government employee authorized to negotiate awards and commit funds on behalf of the U.S. Government.

Contract Specialist - A federal government employee assigned to assist the CO with award related issues. The contract specialist is the primary point of contract for award related issues.

Contract Officer's Representative (COR) - A federal government employee assigned by the CO to manage the technical aspects and performance of an award on behalf of the DOD program office responsible for oversight of the research. The COR may serve as the **Grant Manager or Project Manager** or may have assistance from other personnel within the DOD program office in executing COR responsibilities.

Human Subjects Protection Scientist (HSPS) - A federal government employee or contractor within the HRPO responsible for assisting investigators with the HRPO review and approval process. The HSPS is the investigator's primary point of contact for questions regarding the human research review process and other issues related to human subjects protection.

Army Human Research Protection Office (AHRPO) - The office that reports to the Assistant Surgeon General, Force Projection and is responsible for human research policy, education, and oversight for the U S Army. The AHRPO administers DOD Assurances of Compliance.

Informed Consent - Informed consent is an ongoing process that provides the participant, or legally authorized representative (LAR), with sufficient details about a study so that he/she can make a voluntary decision about participation. Often a written consent form is employed to facilitate initial discussion of a study, and includes descriptions of study procedures, potential risks and benefits, and other pertinent information. Informed consent is an ongoing, interactive process and the participant's voluntary decision about continuing to take part in the trial should be reassessed throughout the study.

Enrollment - To register, enter, screen, randomize, or otherwise formally initiate a participant's participation in a study. Informed consent precedes enrollment. The number of participant consented may differ from the number of participants enrolled in a study (e.g., a participant may give consent to participate in a study but may be determined to be ineligible upon screening; commonly called a "screen failure").

Screening - A process of actively assessing a potential participant for inclusion in a study based on compatibility with pre-determined inclusion/exclusion criteria, ability and willingness to complete the study, and other factors. Screening that does not access, collect, or record a participant's protected health information may take place before informed consent is obtained. However, informed consent must be obtained prior to screening procedures that use protected health information or involve procedures that a participant would not normally undergo.

1 Introduction

Stargardt disease (STGD1; OMIM: 248200), initially described by the German ophthalmologist Karl Stargardt in 1909, is predominantly an autosomal recessively inherited disorder, although an autosomal dominant Stargardt-like phenotype has also been described [1]. Stargardt disease is the most common form of juvenile macular degeneration with an estimated incidence of 10 – 12.5 per 100,000 and about 95% of cases are caused by mutations in the *ABCA4* gene [2, 6] that lead to an autosomal recessive inherited disorder, although an autosomal dominant Stargardt-like phenotype [3] has also been described associated with mutations in the *ELOVL4* and *PROM1* genes [4, 5].

Patients with STGD develop a progressive impairment of visual acuity, which begins most frequently within the first or second decades of life [7]. However some patients do not lose visual acuity until the fourth or even fifth decade of life. The loss of acuity is accompanied by atrophic-appearing lesions within the macula and the presence of yellow-white lesions about the retinal pigment epithelium (RPE), which are referred to as “fundus flecks”. The fundus changes apparent clinically are caused by excess accumulation of lipofuscin in the RPE (Figure 1). RPE lipofuscin is a heterogeneous material composed of a mixture of lipids, proteins, and different fluorescent compounds [8]. The natural autofluorescent properties of lipofuscin have led to the use of confocal scanning laser ophthalmoscopy (cSLO), and autofluorescence (AF) imaging, as convenient, noninvasive methods for determining the distribution of lipofuscin in human participants. [9-11].

Figure 1:

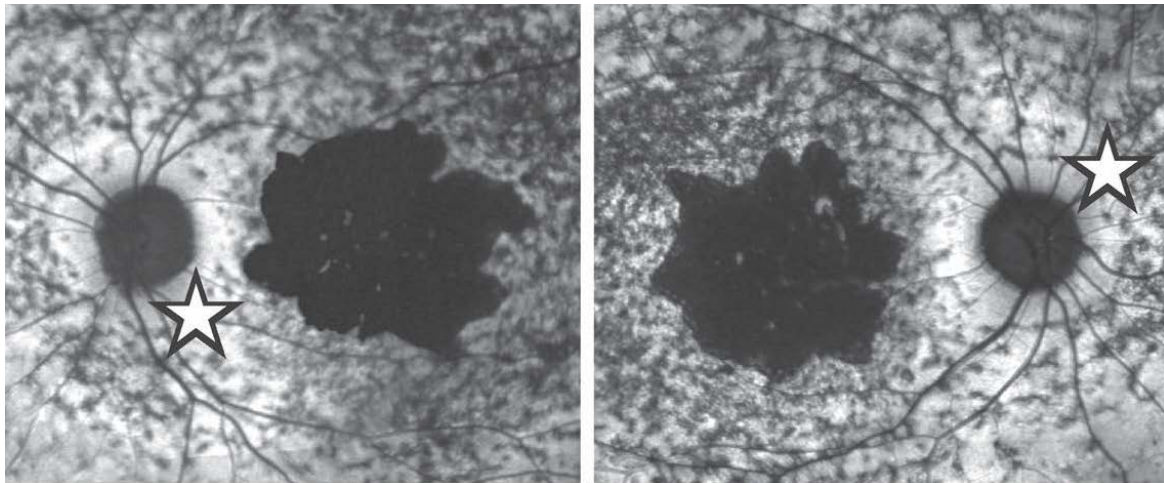


Figure 1: AF images of both eyes of a patient with bilateral central atrophy of the RPE. Stars: fixation loci determined individually in each eye. The contrast of each grayscale image is uniformly stretched for better visibility of features [12].

1.1 Background

Any new therapeutic clinical studies must be able to compare the intervention to the natural history of the disease in a longitudinal study. Therefore, the natural history of the disease in the patients to be treated must be understood. Any clinical outcome measures must be accurate, reproducible and have acceptably small intra- and inter-observer variability. For surrogate measures, the FDA states that “validated surrogate markers are those for which evidence has been established that a drug-induced effect on the surrogate predicts the desired effect on the clinical outcome of interest” [13].

Degeneration of the photoreceptors and underlying retinal pigment epithelium (RPE) in STGD, as measured by standard histology and sd-OCT imaging, typically occurs close to and within the macula [14] (Figure 2). Multiple lines of evidence indicate that lipofuscin accumulation in the RPE is responsible for RPE cell death [15-17], most probably by facilitating apoptosis and damage to lysosomal membranes [15]. Following RPE loss, photoreceptor cells degenerate rapidly [18] because of their dependence on RPE cells for the maintenance and the removal of shed photoreceptor outer segments.

Figure 2:

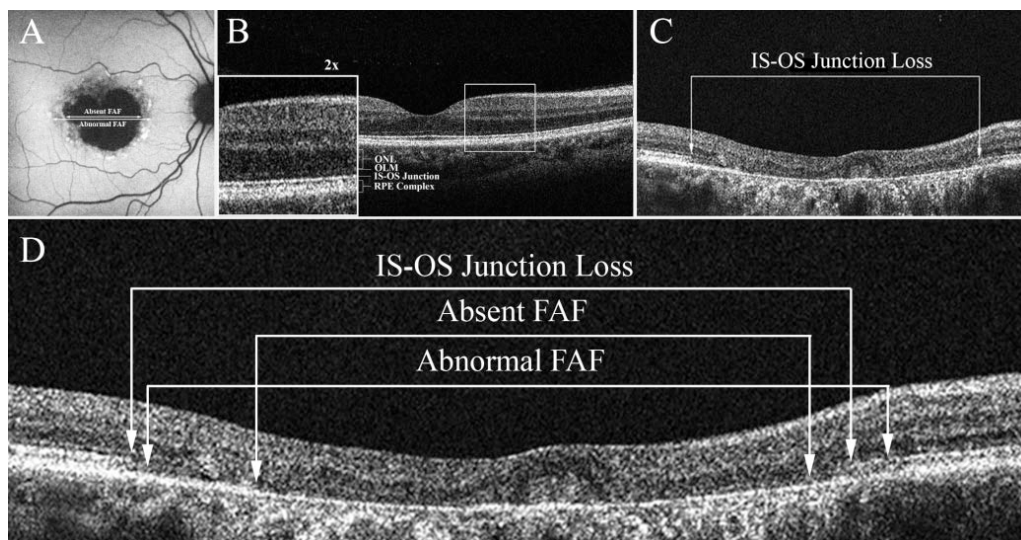


Figure 2: (A) A Fundus Autofluorescence (FAF) image of a Stargardt patient’s retina. The diameter of the central area of “absent FAF” corresponds to geographic atrophy seen clinically with a larger diameter of “abnormal FAF” visible. (B) An sd-OCT image through the fovea of a normal control eye. (C) An sd-OCT image showing the extent of the transverse loss of the inner segment-outer segment junction of the photoreceptors in the foveal region. (D) A comparison of the measurements obtained from FAF in (A) and sd-OCT in (C). [14]

During the part of the visual cycle that occurs in the discs of the outer segment of photoreceptors, opsin bound 11-cis-retinal is converted by light into all-trans retinal. This conformational change triggers a signaling cascade and is followed by the release of all-trans-

retinal, which must then be recycled back to 11-cis-retinal. Since rhodopsin is a trans-membrane protein, the all-trans retinal is released into the membrane where it can either diffuse to the cytoplasmic face of the disc membrane, where a cytoplasmic retinol dehydrogenase starts the recycling process, or it remains in the disc membrane where it can be covalently modified by membrane lipids to form N-retinylidene-phosphatidylethanolamine (NRPE), which can be trapped within the membrane or the luminal side of the disc. To be recycled, NRPE must be transported across the disc membrane to the cytoplasm for dehydrogenation.

Both *in vitro* and *in vivo* studies of the *ABCA4* knockout mouse model, support the hypothesis that the *ABCA4* protein is an outwardly directed “flippase” that transports all-trans retinal and NRPE to the cytoplasmic side of the disc membrane [19] (Figure 3). In the absence of *ABCA4* activity, the membrane trapped all-trans retinal and NRPE do not get removed for recycling [19] [20, 21]. If their concentration increases, as may occur during high levels of illumination or a failure of the flippase (Stargardt disease) to transport them away to the cytoplasm, NRPE and all-trans-retinal can react to form A2-dihydropyridine-ethanolamine (A2E-PE) [19, 22].

Photoreceptor outer segment membranes are renewed in a circadian cycle by the RPE that endocytose the distal 10% of each rod outer segment each day [17] for digestion in the RPE lysosomes. In Stargardt disease, the endocytosed outer segments contain elevated quantities of A2E-PE which are hydrolyzed within the lysosomes to generate elevated levels of A2E and related bisretinoids. These are components of lipofuscin that are to be elevated in Stargardt disease [23-27]. Studies suggest that elevated levels of these metabolites are not handled efficiently and become toxic, leading to the A2E-mediated cell death seen in Stargardt disease. This mechanism of RPE cell death is consistent with the studies of the *ABCA4* knock out mouse model that exhibit abundant lipofuscin accumulation, and elevated A2E levels that lead to eventual RPE cell death [24].

Figure 3:

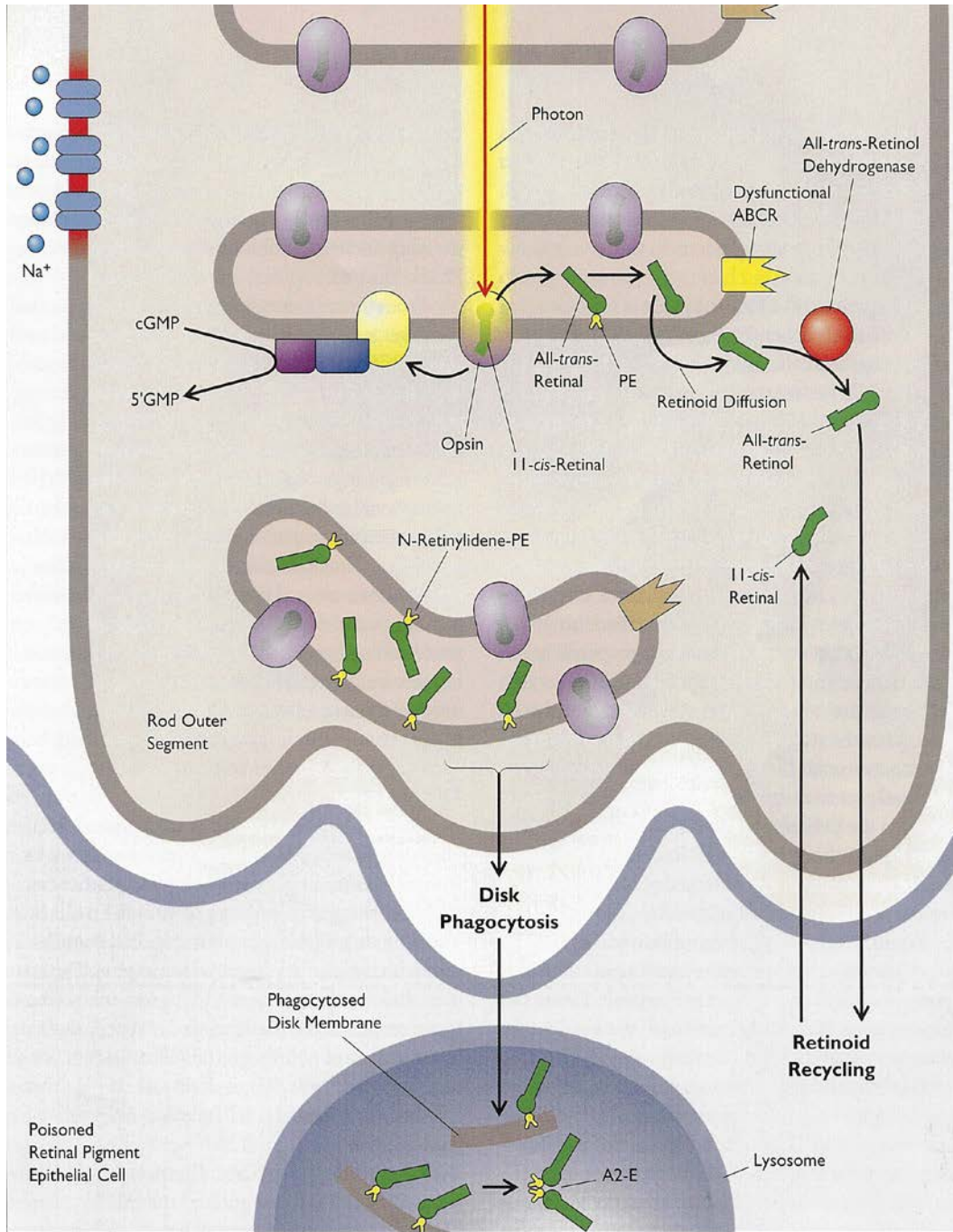


Figure 3: Scheme of visual cycle. The cell at the top of the diagram represents the distal tip of a rod outer segment. The cell at the bottom of the diagram represents part of the RPE cell that endocytoses the distal segment of the photoreceptor and degrades it inside the lysosome. Excess accumulation of A2-PE leads to excess accumulation of A2E within the RPE lysosome that leads to A2E-mediated cell death. [25]

Consistent with this mechanism, a reduction of the daily light load on the retina should reduce production of A2E, and this is observed in *ABCA4* knock-out mice reared in darkness [24].

1.2 Treatment Strategies

At present there are no FDA-approved treatments for *ABCA4*-related retinal diseases. There is a phase I gene therapy clinical trial in progress and a number of preclinical studies of compounds designed to reduce the formation of A2-PE, which may slow or prevent progression of the disease (Figure 4). What is currently unclear is whether a treatment strategy employed after significant accumulation of lipofuscin has already occurred will be able to effectively decrease the lipofuscin content and thereby save RPE and photoreceptor cells. However, none of the treatments will be able to restore visual function to areas of the retina that have already undergone RPE, choriocapillaris, and photoreceptor cell loss. While a promising intervention, gene therapy can only be effective if the target cells are still viable. Therefore the initial primary therapeutic intent is to slow or halt the progression of retinal degeneration.

Figure 4:

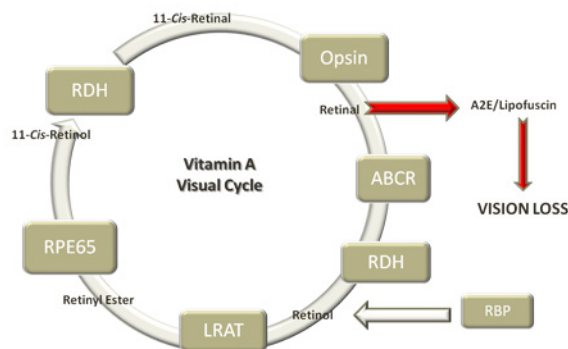


Figure 4: Scheme of Vitamin A Visual Cycle

Gene Therapy

Given that STGD is caused by the loss of function of the *ABCA4* protein, transfecting the wild type *ABCA4* gene into the nucleus of photoreceptor cells may improve the retinoid flow in the visual cycle, prevent further abnormal accumulation of lipofuscin in RPE cells, and slow the disease process in patients with STGD. This may be particularly therapeutic with early intervention before there is extensive cell loss.

There is currently one phase I/II gene therapy clinical trial for the product Stargen developed by Oxford BioMedica. The therapy consists of a single subretinal injection of a genetically engineered lentivirus (the Equine Infectious Anaemia Virus, EIAV) carrying a single copy of the wild type *ABCA4* gene. This is a dose escalation study enrolling up to 28 participants with Stargardt disease, with the primary outcome measures being the incidence of adverse events over 48 weeks and the number and percentage of patients with treatment emergent adverse events. The secondary outcome measures are a delay in retinal degeneration and changes from baseline function relative to the contralateral eye utilizing retinal analytical techniques. To date the trial has reported no significant adverse events.

Pharmacologic and Other Interventions

There are many different therapeutic approaches in the preclinical research stage for Stargardt disease. These include: stem cell therapies; dietary supplementations; molecules that slow the visual cycle thereby limiting the rate that all-trans-retinal can be generated; molecules that chelate the all-trans retinal in the membrane; derivatives of 11-cis-retinal such as deuterated forms that markedly slow the formation of A2-PE; molecules that stimulate the activity of an impaired ABCA4 protein; molecules that restrict the amount of retinal that can reach the retina; molecules that remove the lipofuscin from the RPE cells before it can have a toxic effect; molecules targeting A2E; optogenetics and visual prosthetics [26, 27].

1.3 Known and Potential Risks

This study is an observational study of the natural course of STGD that will include data from the results of both psychophysical examinations (visual acuity testing, fundus photography, and microperimetry) and retinal imaging examinations (optical coherence tomography and fundus autofluorescence), which are an integral part of current Standard or Care that is routine in patients with STGD. The risk to participants will not exceed the risks associated with the current standard of clinical care examinations.

1.3.1 Foreseeable Risks

There are no anticipated risks associated with this observational study. The risks associated with ophthalmic procedures that are part of the current standard of care for STGD patients include redness of the eye, and discomfort or allergic reaction to topical medications used to dilate the pupil prior to visual function tests. High blood pressure, cardiac dysrhythmias and closed angle glaucoma may be exacerbated by some of these medications and light sensitivity may be experienced when the pupil is dilated. These risks are not attributable to participation in this trial but to the standard of care procedures encountered at all of the patients' follow-up visits with their ophthalmologist.

The data from a full-field electroretinogram may be collected during the study from any participants that have not had this exam within the last five years. A rare side effect of this exam is corneal abrasion arising from the placement of electrodes required for testing.

All these tests and the frequency of assessments are part of the current standard of care for patients with STGD.

1.3.2 Risk Management and Emergency Response

1.3.2.1 Minimization of Risk

The participants will be informed of the information to be collected in the study by one of the delegated study staff members, in a language the participant can understand. Participants will be informed that they may withdraw from the study at any time, for any reason without jeopardizing their future treatment. Participants will be given full information regarding the procedure results involved. All procedures related to the study will be performed by trained and licensed medical and health professionals at their own ophthalmologist's facility. In the unlikely event of an adverse event associated with the study, immediate medical care will be provided. Adverse events will be reported to the IRBs and DOD as required by clinical trial regulations, to ensure the safety of participants.

The study will be compliant with the relevant parts of 45 CFR and the ICH GCP Guidelines.

1.3.2.2 Response to Risk

The study is an observational study of the natural course of STGD. Therefore, all participants in this trial will experience minimal risk not exceeding the risk of a standard of care examination of psychophysical examinations (visual acuity testing and microperimetry), retinal imaging (optical coherence tomography, fundus photography and fundus autofluorescence), and electroretinography.

1.3.2.3 Research Injury Compensation

Due to the observational design of this study and collection of data from standard of care procedures, no research injuries are expected.

1.3.2.4 Precautions and Preventive Measures

Due to the observational design of the natural course, no study specific preventive measures and precautions are needed.

1.3.3 Known and Potential Benefits

There is no direct benefit to participants in this study, although they may conceivably be good candidates for future studies of emerging STGD therapies. Participants in this study are not experimental subjects as there is neither a study intervention nor is the interaction with the participant for the primary purpose of obtaining data regarding the effect of an intervention or interaction; as such, LARS consent/child assent will be allowed in the study and children may be enrolled. Data resulting from this natural history study may influence the clinical design of

future trials designed to evaluate therapies for treating Stargardt disease. As such, this study may support work that leads to benefit for some patients in the long term.

2 Study Rationale and Objectives

2.1 Study Rationale

Although STGD is the most prevalent form of juvenile-onset macular dystrophy, with an estimated incidence of 10 – 12.5 per 100,000, it is still relatively rare and there is very limited information available about the natural course of the disease in larger numbers of STGD patients. The information currently available is predominantly based on individual reports of patient data collected from single centers [28, 29]. However, this limited data clearly points to a disease which is very heterogeneous with significant variation in the age of onset and rate of progression, and limited clear correlations between phenotype and genotype [30, 31]. These limitations highlight the urgent need for a multi-center study that documents the natural course of the disease. The information gathered from this proposed study should provide guidance and support to the identification of the most appropriate clinical outcome measures for anticipated clinical trials. It may also be used to identify and support the validation of surrogate clinical trial endpoints that are offered by recent technological advances in retinal imaging capabilities, such as fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (sd-OCT).

2.2 Study Objectives

Stargardt disease is currently an incurable and untreatable macular dystrophy that causes severe visual loss in children and young adults, thereby causing enormous morbidity with economic, psychological, emotional, and social implications. There are no FDA approved therapeutic treatments for this disease. Therefore, the objective of this study is to collect natural history data from a large population of children and adults in order to evaluate possible efficacy measures for planned clinical trials.

Primary objective:

- To assess the yearly rate of progression of STGD using the growth of atrophic lesions as measured by fundus autofluorescence (FAF) imaging.

Secondary objectives:

- To assess the yearly rate of progression of STGD using spectral-domain optical coherence tomography (sd-OCT) to measure the rates of retinal thinning and the loss of photoreceptors.
- To assess the yearly rate of loss of retinal sensitivity as measured by microperimetry.

- To assess the yearly rate of visual acuity changes as measured by best corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol [32].
- To correlate the presence and progression of morphological abnormalities in FAF and sd-OCT images with visual function as measured by microperimetry and visual acuity.
- To perform exploratory analysis of factors associated with STGD progression, such as participant's use of vitamin A supplementation and mutations in the *ABCA4* gene.

3 Study Design

The study shall utilize up to 14 clinical sites to collect prospective longitudinal observations on up to 250 participants (minimum of 150). Participants must present with atrophic lesions secondary to STGD, in at least one eye. The study shall take place over a 24 month period that includes data collection from the procedures conducted at a patients' physician visit that will be designated as the baseline visit and subsequently from the patients' following four six-month, regular follow-up visits (months six, 12, 18 and 24).

Each of the study investigators has indicated that the information that will be available at each visit will include: best-corrected visual acuity, a complete ophthalmic exam (including dilated funduscopy), autofluorescence imaging, microperimetry and spectral-domain optical coherence tomography (sd-OCT). Results will be sent by the participating centers to the Dana Center for Preventative Ophthalmology of the Wilmer Eye Institute, the Johns Hopkins University, Baltimore, for evaluation, with exception of the microperimetry, autofluorescence and optical coherence tomography, which will be sent to a central reading center at the Doheny Eye Institute, Los Angeles, California.

Primary outcome measure:

- Yearly rate of progression of STGD as reflected by the growth of atrophic lesions measured by FAF imaging.

Secondary outcome measures:

- Yearly rate of progression of STGD as reflected by the rate of retinal thinning and photoreceptor loss as measured by sd-OCT
- Yearly rate of loss of retinal sensitivity as measured by microperimetry
- Yearly changes in the best corrected visual acuity (BCVA) assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.
- Correlation of the presence and/or progression of morphological abnormalities in FAF and sd-OCT images with visual function as measured by microperimetry and BCVA.
- Exploratory analysis to examine factors associated with disease progression, such as participant's use of vitamin A supplementation and mutations in the *ABCA4* gene.

At each follow-up visit, any changes in medical and ophthalmic history as well as vitamin A

supplementation will be recorded.

3.1 Type/Design of Study

This is a prospective longitudinal observational study.

3.2 Study Treatments

This is a natural history study. There are no treatments being investigated in this trial.

3.3 Study Population

The study population shall consist of up to 250 Stargardt disease patients (minimum of 150 patients) recruited at up to 14 clinical centers across the US and Europe. Participants must be at least six years old, able to cooperate in performing the examinations and be willing to attend their regular 6 month follow-up visits for up to 24 months. There are no limitations regarding race, ethnicity or sex.

The participants must present with atrophic lesions secondary to STGD with a minimum diameter of 300 microns and all lesions together must add to less than or equal to 12 mm² (equivalent to no more than 5 disc areas) in a least one eye. Participants must have been previously genotyped to participate in the study and have at least 2 confirmed pathogenic mutations in the *ABCA4* gene. If only one *ABCA4* allele contains a pathogenic mutation, then the patient needs to show a typical phenotype, i.e. at least one eye must have flecks at the level of the retinal pigment epithelium typical for STGD. Best-corrected visual acuity (BCVA) must be 20 ETDRS letters (20/400 Snellen equivalent) or better.

3.3.1 Recruitment Methods

The investigators at each of the centers will review their own clinical patient databases and contact their patients.

3.3.2 Recruitment Process

The investigators at each of the clinical centers will identify potential study patients from their own patient populations. Potential study participants who demonstrate an interest in participating in the study will receive an explanation of the terms, and requirements of the study, in language they can understand, from an investigator in the research team. They will also receive a written copy of the Informed Consent Form to read and share with family or friends prior to their screening visit. Subsequently, an investigator or a qualified designee will answer questions and request the patient's permission to participate in the study. Participants who sign a study-specific patient informed consent form approved by the local Institutional Review Board will then be scheduled for an evaluation with their doctor to determine their eligibility.

For participants younger than 18 years of age, parental/LAR consent and patient assent will both be obtained prior to participation in this study.

3.3.3. Volunteer Compensation

This observational study collects information on the natural course of STGD and all examinations are part of the standard clinical care. Compensation will not be provided to the study participants.

3.3.4. Recruitment Materials

No centrally prepared recruitment or advertising materials are planned for this study.

3.4 Eligibility Criteria

3.4.1 Informed Consent/Assent

When individuals are identified in-person as potential study participants, the investigator will provide information about the study, and confirm contact information. The investigator or other designated study staff will obtain and document informed consent from appropriate, interested patients.

Potential study participants who demonstrate an interest in participating in the study will receive an explanation of the terms, and requirements of the study from the research team in a language they can understand. They will receive a copy of the Informed Consent Form to read and share with family or friends, if they prefer, prior to their screening visit. An investigator or designated site study staff member will answer any questions or concerns that the potential participants may raise and request the patient's permission to participate in the study. Each site will provide adequate time for the patient to make a decision whether to participate in the study. When the potential participant is a minor (less than 18 years of age), parental/LAR consent and minor participant assent will be obtained following the same procedures outlined in the previous paragraph. The minor participant will be provided with an age appropriate assent form and given a chance to freely choose whether to participate in the study.

Following the initial study consent/assent, study participants will be asked at each follow-up visit to confirm their continued consent to continue their participation in the study.

Care will be taken to ensure that the mental capacity of potential volunteers is properly assessed during each follow-up visit, as uncontrolled concomitant diseases such as neurological disorders are exclusion criteria.

Study candidates who cannot give their own consent to participate will only be enrolled into the study after consent is obtained from the individual's Legally Authorized Representative (LAR). Children shall receive an additional assent form written in age appropriate language for them to read, and will only be enrolled into the study following consent by their

individual's Legally Authorized Representative (LAR). Site investigators will consult with their local institutional review boards for guidance regarding who may serve as an LAR.

For study candidates who are illiterate or unable to understand the written consent form, the consent form will be read and explained to them in the presence of a witness. The candidate must sign or mark the form in an individually unique manner, such as with a thumbprint, to indicate their agreement to participate. The witness present during the presentation must also sign the form to attest that the content of the written consent form was conveyed accurately to the study candidate.

If a study candidate is not fluent in the primary language of the host country of the study site, all documentation including the consent form and any site information sheets approved by the local IRB shall be translated into their native language by a certified translator and the translation approved by the local HRPO. Plans shall also be made and approved to ensure a qualified translator is available during the consent process, baseline and all follow-up visits to address any concerns or ensure they provide continuing consent to study participation.

When consent is obtained in a language other than English, the foreign language version of the consent form will be an accurate translation of the English version of the consent form.

Written informed consent shall be obtained from all participants or their LAR before any study-related participation. However, investigators may discuss in general the availability of the study and the general entry criteria with a potential participant candidate without obtaining consent.

The investigator has both an ethical and legal responsibility to ensure that each participant study candidate being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on the written informed consent form approved by the same Institutional Review Board (IRB) responsible for approving this protocol.

Once the appropriate essential information has been provided to the participant and fully explained by the investigator, or a qualified designee, and the participant understands the implications of participating, the IRB-approved written informed consent/assent form(s) will be signed and dated by the participant and the person obtaining consent (investigator or designee), and by any other parties required by the site's local IRB. The participant shall be given a copy of the signed informed consent form. The original signed informed consent form shall be kept on file by the investigator; the time length will be determined by the local IRB. All of the above mentioned activities shall be completed prior to the participant's participation in the trial.

3.4.2 Disclosure of DOD Sponsorship and Access to Research Records

The informed consent form shall include a statement that discloses that the DOD is supporting the research and that representatives of the USAMRMC have the authority to review research

records of any study participant. Study candidates have a right to decline participation in research based on the source of the funding.

3.4.3 Inclusion Criteria

Study participants are required to meet the following inclusion criteria:

Table 3.4.3-1 Inclusion Criteria	
1.	Provide a signed informed consent form and authorization allowing the disclosure and use of protected health information.
2.	The designated primary study eye must have at least one well-demarcated area of atrophy as imaged by fundus autofluorescence with a minimum diameter of 300 microns and all lesions together must add to less than or equal to 12 mm ² (equivalent to no more than 5 disc areas in a least one eye) and a BCVA of 20 ETDRS letters (20/400 Snellen equivalent) or better.
3.	Two (2) pathogenic mutations confirmed present, in the <i>ABCA4</i> gene. If only one <i>ABCA4</i> allele contains a pathogenic mutation, the patient shall have a typical Stargardt phenotype, namely at least one eye must have flecks at the level of the retinal pigment epithelium typical for STGD.
4.	The primary study eye must have clear ocular media and adequate pupillary dilation to permit good quality FAF and sd-OCT imaging in the opinion of the investigator.
5.	Be able to cooperate in performing the examinations.
6.	Be willing to undergo ocular examinations once every 6 months for up to 24 months.
7.	Be at least six years old.
8.	Both eyes can be included if inclusion criteria are fulfilled for both eyes.

3.4.4 Exclusion Criteria

Study candidates shall be excluded if they meet any of the following exclusion criteria:

Table 3.4.4-1 Exclusion Criteria	
Exclusion Criteria	
1.	Ocular disease, such as choroidal neovascularization, glaucoma and diabetic retinopathy, in either eye that may confound assessment of the retina morphologically and functionally.
2.	Intraocular surgery in the primary study eye within 90 days prior to baseline visit.
3.	Current or previous participation in an interventional study to treat STGD such as gene therapy or stem cell therapy. Current participation in a drug trial or previous participation in a drug trial within six months before enrollment. The use of oral supplements of vitamins and minerals are permitted although the current use of Vitamin A supplementation shall be documented.
4.	The site Principal Investigator may declare any patient at their site ineligible to participate in the study for a sound medical reason prior to the patient's enrollment into the study.
5.	Any systemic disease with a limited survival prognosis (e.g. cancer, severe/unstable cardiovascular disease).
6.	Any condition that would interfere with the patient attending their regular follow-up visits every 6 months for up to 24 months, e.g. personality disorder, use of major tranquilizers such as Haldol or Phenothiazine, chronic alcoholism, Alzheimer's Disease or drug abuse.
7.	Evidence of significant uncontrolled concomitant diseases such as cardiovascular, neurological, pulmonary, renal, hepatic, endocrine or gastro-intestinal disorders.

3.5 Primary and Secondary Outcome Variables

The primary outcome variable for the ProgSTAR study is the yearly rate of progression of STGD as reflected by the growth of atrophic lesions measured by FAF imaging.

The secondary outcome variables are:

- Yearly rate of progression of STGD using spectral-domain optical coherence tomography (sd-OCT) to measure the rates of retinal thinning and the loss of photoreceptors.
- Yearly rate of loss of retinal sensitivity as measured by microperimetry
- Yearly change in best corrected visual acuity (BCVA) by using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.
- Correlation of the presence and/or progression of morphological abnormalities in FAF and sd-OCT images with visual function as measured by microperimetry and BCVA.
- Exploratory analysis to examine factors associated with disease progression, such as participant's use of vitamin A supplementation and mutations in the *ABCA4* gene.

3.6 Measures to Minimize/Avoid Bias

Data from all sites will be sent, using a standardized, de-identified electronic clinical report form (eCRF), to a central data management center at the Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, The Johns Hopkins University School of Medicine, except in the case of data from retinal imaging procedures and microperimetry, which will be sent to a central reading center at the Doheny Eye Institute, Keck School of Medicine, University of Southern California for further processing. Each center shall undertake standardized collection of all data. Ophthalmic outcome data from the microperimetry, sd-OCT and fundus autofluorescence assessments will be electronically submitted from the site to the appropriate reading center via secure data upload through the reading center internet website.

Once processed and analyzed by the appropriate reading center, all data will be transferred electronically from the reading center to the Dana Center system via a secure transfer process. Only coded identifiers will be used to identify participants.

3.6.1 Blinding

Not applicable.

3.6.2 Study Data

Table 3.6.2 Study Data					
ASSESSMENT/ PROCEDURE DATA COLLECTION POINTS	BASELINE Visit 1 DAY 0	VISIT 2 MONTH 6	VISIT 3 MONTH 12	VISIT 4 MONTH 18	VISIT 5 MONTH 24
Informed consent, medical history, genotype information, demographics	X				
Inclusion/Exclusion criteria assessed	X				
ETDRS BCVA Data	X	X	X	X	X
Ophthalmic fundus exam ¹ Data	X	X	X	X	X
Autofluorescence imaging Data	X	X	X	X	X
Microperimetry ² Data	X	X	X	X	X
sd-OCT Data	X	X	X	X	X
Changes in medical and ophthalmic history Data	X	X	X	X	X
Vitamin A supplementation Data	X	X	X	X	X
Full-field electroretinogram ³ Data	X				
Exit from study ⁴					X

¹: Ophthalmic examination includes slit lamp examination, cataract grading, and dilated fundus examination

²: In selected centers

³: Only if a full-field ERG was not performed within the past 5 years.

⁴: If qualified, patients may exit the study before Visit 5 to participate in an investigational treatment study for STGD

3.7 Schedule of Data Collection

Screening and baseline visits may be combined into one visit if the inclusion criteria are fulfilled and the exclusion criteria do not apply. Follow-up visits will be approximately 6, 12, 18, and 24 months after baseline visit. For these follow-up visits, a time window of \pm five (5) weeks around the calculated, expected date of the follow-up visit is acceptable for the data to be included for that time point.

3.7.1.1. Screening/Baseline (Day 0)

The Screening/Baseline visit consists of the entering of data resulting from examinations and procedures performed as part of Standard of Care during the participant's scheduled follow-up ophthalmology visit:

1. An explanation of the study and providing a copy of the consent forms (if not mailed ahead of the visit) to the study candidate
2. Signing of the informed consent for the study
3. Completion of a medical and ophthalmic history
4. Recording and documentation of demographic information
5. Recording and documentation of vitamin A supplement use
6. Recording and documentation of genetic mutations in the *ABCA4* gene
7. Measurement of refraction and best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) Testing Protocol [32]
8. Microperimetry
9. Ophthalmic examination
10. Spectral-domain optical coherence tomography
11. Fundus autofluorescence

The order of the examinations may be changed by the investigator and examinations may be performed on different days.

Description of Standard of Care examinations and procedures the investigators will utilize to obtain data that will be collected for this study include:

Refraction and best-corrected visual acuity (BCVA) according to the Early Treatment Diabetic Retinopathy Study protocol [32]:

Visual acuity is measured at a distance of one or four meters. A separate sequence of letters is used for each eye. Patients are encouraged to read each letter, and instructed to guess if unsure. The vision score is then calculated.

Fundus-Autofluorescence (FAF) and spectral-domain optical coherence tomography (sd-OCT):

Images of patient's eyes are recorded using sd-OCT, and scanning laser ophthalmoscopy (cSLO) in order to acquire fundus autofluorescence images. The computer driven cameras used in these techniques use a beam of light to take images.

Microperimetry:

Patients undergo an examination of the retinal central visual field using Microperimetry. During this procedure patients press a button when they see a little light spot on a screen of a special computer monitor. This technique uses a beam of light to take images and the test takes about 30 minutes.

Full-Field Electroretinogram (FF-ERG):

With pupils dilated, patients remain in a darkened room for at least 20 minutes. Then, electrodes are placed close to the cornea, through the use of special contact lenses, to record the electrical response of the retina to light stimuli in a manner similar to an electrocardiogram recording.

Full field ERGs are performed according to ISCEV standards [33]. A standard for four different types of response measured include:

1. Rod response in the dark adapted eye
2. Maximal/combined response in the dark adapted eye
3. Cone response
4. Response to flicker

If an acceptable ERG was performed within the last 5 years, the test result will be used for the study data evaluation by the site investigators. The ERG is not generally recommended to be repeated if a previous ERG of more than 5 years ago was documented as unrecordable (absent responses) at that time.

An ophthalmic examination to diagnose the typical clinical appearance of STGD will aid in confirming eligibility for the study.

In order to participate in the study, all patients must have documentation of two (2) pathogenic mutations confirmed in the *ABCA4* gene from previously completed genetic testing. If only one *ABCA4* allele contains a pathogenic mutation, the patient should have a typical Stargardt phenotype, namely at least one eye must have flecks at the level of the retinal pigment epithelium typical for STGD. The genetic testing will have been previously completed and outside the scope of this study.

Before any study-related data is collected, the participants will have all imaging procedures explained to them, as well as what information from their procedure will be included in the study. Study participants must sign and date all appropriate informed consent forms before any data for the study is collected.

3.7.1.2. Follow-up visits

The follow-up visits consist of the entry of data resulting from the following Standard of Care examinations and procedures obtained from the patients' regular follow-up visits:

1. Confirm that the participant wishes to continue in the study
2. Review and documentation of changes in medical and ophthalmic history
3. Documentation of vitamin A supplement use
4. Refraction and best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) Testing Protocol [32]
5. Microperimetry
6. Ophthalmic examination
7. Spectral-domain optical coherence tomography
8. Fundus autofluorescence

The data from the visits will be utilized in the study even if the order of the examinations change from visit to visit or between the practices of the different investigators, and the examinations are performed on different days (as long as the time window is respected).

3.7.2. Safety Assessments

Due to the observational design of the natural course study, no study specific safety assessments are needed.

3.7.2.1. Adverse Events

Due to the observational design of the natural course study, no adverse events are expected.

3.7.2.2. Clinical Laboratory Data

Not applicable

3.7.2.3. Evaluations

During each participant's visit to the clinic, a clinician participating in the study will record "study progress notes" to document all significant observations. At a minimum, this documentation will contain:

- The informed consent process, including any revised consents
- The date of the visit and the corresponding Visit, Day, or Week in the study schedule
- The genetic information at baseline
- Any comments made by the participant about the study, including any significant medical findings
- Any changes in Vitamin A supplement use
- A general reference to the procedures completed
- The signature (or initials) and date of all clinicians who made an entry in the progress notes
- The evaluation of refraction and best corrected visual acuity according to ETDRS
- The evaluation of full-field electroretinogram in at least one eye at baseline (or within the past five years)
- The evaluation of microperimetry test and recording of mean sensitivity

- The evaluation of spectral-domain optical coherence tomography (sd-OCT)
- The evaluation of fundus autofluorescence
- A summary of the ophthalmologic exam including status of the anterior segment of the eyes, including the cornea, anterior chamber, iris and grading cataract, and dilated fundus exam

In addition, any contact with the participant via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Information from the study progress notes and other source documents will be promptly transcribed to eCRFs for transmission to the Coordinating Center. Any changes to information in the study progress notes, other source documents, and CRFs will be properly tracked.

3.7.2.4. Labs Performing Evaluations and Special Precautions

Not applicable

3.7.2.5. Sharing Research Results

As the data collected during study participation in this observational study is collected from standard clinical care ophthalmologist visits, the results of each individual's procedures conducted during the time period of patients' participation in this study, including any clinically significant abnormal findings, will be shared with that study participant or his/her primary care provider throughout the study.

3.7.3. Endpoints

3.7.3.1. Primary Statistical Endpoint

The primary endpoint is the rate of growth of atrophic lesions as measured by FAF imaging, calculated at 12 and 24 months.

3.7.3.2. Secondary Statistical Endpoints

The secondary endpoints are:

- Rate of retinal thinning and photoreceptor loss as measured by sd-OCT calculated at 12 and 24 months.
- Loss of retinal sensitivity as measured by microperimetry calculated at 12 and 24 months.
- Change of best-corrected visual acuity by using the ETDRS protocol calculated at 12 and 24 months.

3.7.4. End of Study

The End-of-Study date for each participant is defined as the last date of contact with the participant, or the last date an attempt was made to contact the participant, recorded on the follow-up CRF page. Typically, the End-of-Study date will be the date of the 24 month follow up visit.

3.8. Withdrawal Criteria, and Procedures

All participants have the right to withdraw from the study at any time, for any reason, without prejudice. The investigator may discontinue any participant's participation when in the investigator's judgment it is necessary for any reason. This can include the failure of a participant to comply with the protocol or when the investigator considers withdrawal is in the best interest of the participant.

When a participant is withdrawn from participation in the study, or if the study is terminated prematurely, the investigator will collect all data from previous study visits at the last scheduled visit, or will request that the participant return for a follow-up visit. All measurements will be recorded in the source documents and on the electronic clinical report form.

When a participant decides to withdraw study consent, an investigator at the site will attempt to contact the participant and determine the reason that led the participant to the decision. When known, the reasons for withdrawal shall be fully evaluated and recorded appropriately in source documents and the eCRF.

If the study sponsor, the Foundation Fighting Blindness Clinical Research Institute (FFB CRI), discontinues the study for any reason, such reasons will be thoroughly documented in the source documents and eCRFs, and all local study site IRB's and HRPO will be notified immediately.

3.9. Screen Failures

A screen failure participant candidate is a study candidate who has provided written informed consent for participation but who is not entered into the study.

3.10. Definition of Completed

The study period is defined as the time period during which participants are evaluated for the primary and secondary objectives of the study. Participants who complete all follow-up studies and are evaluated at the last scheduled visit of their study period will be defined as having completed the study.

3.11. Definition of Lost to Follow-up

Study participants who miss a follow-up study visit and cannot be contacted after multiple contacts at different times of day during a period of 10 days, and who do not have a known reason for discontinuation (e.g., withdrew consent) will be classified as “lost to follow-up”.

3.12. Participant Compliance

Not applicable.

3.13. Protocol Deviations

This study shall be conducted according to this written protocol except in the case of an emergency where immediate intervention based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator) is essential for the protection, safety, and well-being of the participant. In the event of a significant deviation from the protocol as a result of an emergency, accident, or mistake, the investigator or designee must contact the Study Director, as soon as possible, by telephone. A joint decision will then be made regarding the participant’s continuation in the study and the decision documented by the investigator and the Study Director and reviewed by the monitor. In addition, the investigator must notify the IRB to the extent necessary under GCP and local requirements. The sponsor, the Foundation Fighting Blindness Clinical Research Institute shall be notified of any protocol deviations and shall forward a detailed report any serious deviations to HRPO immediately. Any non-serious deviations shall be reported to HRPO as part of the annual study progress report.

3.14. Protocol Modifications

No changes shall be made to this protocol by site principal investigators or any other site staff without prior written consent and approval from the Study Director, the Sponsor [the Foundation Fighting Blindness Clinical Research Institute (FFB CRI)], their respective IRBs, and HRPO. Amendments shall be submitted to the IRBs for review and approval prior to implementation. Any permanent change to the protocol, whether an overall change or a study center specific change(s), must be treated as a protocol amendment. Any amendment to the protocol that is deemed necessary as the study progresses will be fully discussed by the investigator(s). Except for administrative amendments, investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined as amendments that do not affect the safety of the research participants, the scope of the investigation, or the quality of the trial. However, if a protocol amendment is required to eliminate an apparent and immediate hazard to participants, the amendment should be implemented immediately, and the IRB notified within 5 days.

Any deviation to the protocol that may have an effect on the safety or rights of the participant or the integrity of the study must be reported to the local IRBs and to the USAMRMC ORP

HRPO as soon as the deviation is identified. Any corrective actions taken to avoid future deviations shall be included in the report.

All unanticipated problems involving risk to participants or others related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

When, in the judgment of the chair of the local IRB and the investigators, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the participant, the current approved written informed consent form shall be revised and if applicable, the participants shall be asked to sign a new written informed consent.

Major modifications to the research protocol and any modifications that could potentially increase risk to participants will be submitted by the Sponsor to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted by the Sponsor with the continuing review report to the USAMRMC ORP HRPO for acceptance.

4. Study Personnel

4.1. Roles and Responsibilities of Key Study Personnel

Hendrik P.N. Scholl, M.D., M.A, is the Study Director and the Principal Investigator at the Wilmer Eye Institute site. His responsibilities include: the overall study design; coordination and execution of the study; analysis of the data; review of any protocol deviations; and dissemination of the study findings. Dr. Scholl will also submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; performing scheduled ophthalmic study visits; documenting the clinical visits; resolving any data concerns; and overall oversight of the protocol at the Wilmer Eye Institute site.

Janet Sunness, M.D. is the site Principal Investigator at the Greater Baltimore Medical Center site. She will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; performing scheduled ophthalmic study visits; documenting the clinical visits; resolving any data concerns; and overall oversight of the protocol at Greater Baltimore Medical Center.

Artur Cideciyan, Ph.D. is the site Principal Investigator at the Hospital University of Pennsylvania, Scheie Eye Institute. He will submit the study protocol to the local IRB, obtain informed and be responsible for: obtaining the medical history of participants; performing

Protocol No. FFBCRI-PROGSTAR-02

scheduled ophthalmic study visits; documenting the clinical visits; resolving any data concerns; and overall oversight of the protocol at Scheie Eye Institute.

Elias Traboulsi, M.D. is the site Principal Investigator at Cleveland Clinic's Cole Eye Institute. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; performing scheduled ophthalmic study visits; documenting the clinical visits; resolving any data concerns; and overall oversight of the protocol at Cleveland Clinic's Cole Eye Institute.

José-Alain Sahel, M.D. is the site Principal Investigator at the Centre de Recherche Institut de la Vision Paris. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; performing scheduled ophthalmic study visits; documenting the clinical visits; resolving any data concerns; and overall oversight of the protocol at the Centre de Recherche Institut de la Vision, Paris.

Eberhart Zrenner, M.D. is the site Principal Investigator at the University Eye Hospital Tübingen. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; performing scheduled ophthalmic study visits; documenting the clinical visits; resolving any data concerns; and overall oversight of the protocol at University Eye Hospital Tübingen.

Michel Michaelides, M.D., F.R.C.Ophth. is the site Principal Investigator at the Moorfields Eye Hospital NHS Foundation Trust. He or designated members of the research team will: submit the study protocol to the local IRB and obtain informed consent; be responsible for obtaining the medical history of participants, performing scheduled ophthalmic study visits, documenting the clinical visits and resolving any data concerns. He will have overall oversight of the protocol at Moorfields Eye Hospital NHS Foundation Trust.

Paul S. Bernstein, MD, PhD is the site Principal Investigator at the University of Utah, School of Medicine, Moran Eye Center. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; performing scheduled ophthalmic study visits; documenting the clinical visits; resolving any data concerns; and overall oversight of the protocol at the University of Utah.

David G. Birch, PhD is the site Principal Investigator at the Retina Foundation of the Southwest. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; performing scheduled ophthalmic study visits; documenting the clinical visits; resolving any data concerns; and overall oversight of the protocol at the Retina Foundation of the Southwest.

Sheila West, Ph.D., is Director of the Dana Center for Preventive Ophthalmology at the

Wilmer Eye Institute. She will lead the data management coordinating center activities associated with this study and be responsible for study site monitoring, data collection and management, and statistical analysis of the study data.

Srinivas R. Sadda, M.D. is Associate Professor of Ophthalmology and Director of the Doheny Image Reading Center at the Keck School of Medicine, University of Southern California. He will lead the image collection and reading, and imaging analysis of the study data arising from retinal imaging and microperimetry.

4.2. Conflict of Interest

As this protocol does not support the development of a drug, device, or other intellectual property, there is no immediate concern about conflict of interest. If any concerns arise, conflict of interest statements will be obtained on a case-by-case basis.

5. Prohibited Medications

Study participants may use any systemic medications that are necessary. However, study participants shall not participate in, or take concomitant therapy, to treat Stargardt disease. Study candidates who have previously participated in an interventional study for Stargardt disease are also excluded – see study exclusion criteria.

6. Evaluation of Adverse Events

Not applicable.

7. Statistical Analysis

7.1. Sample Size and Power

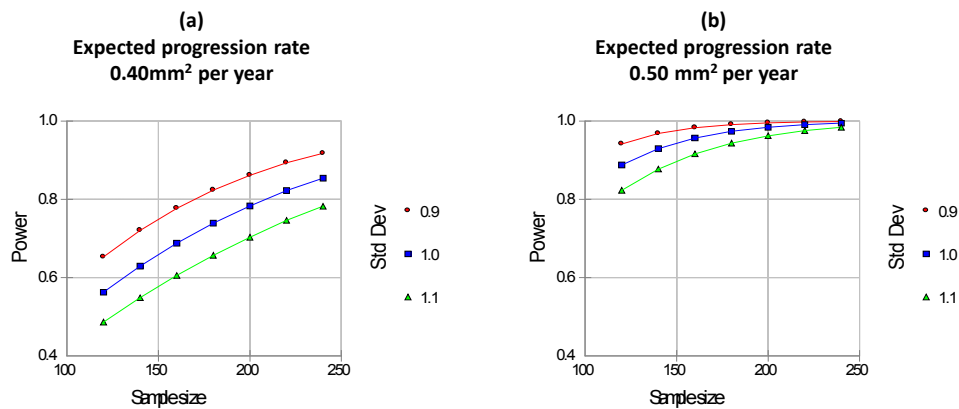
Prior to establishing this study protocol, a feasibility survey was undertaken. The survey consisted of a questionnaire that was sent to the participating centers to determine how many study candidates might be available at each center for this prospective study.

The primary outcome of the study is **the yearly growth in the area of the atrophic lesion** as measured by fundus auto-fluorescence. A recent paper by Chen et al [34] reported that in a group of 24 STGD participants with well defined atrophic lesions at baseline, the mean yearly growth of the lesion was $0.94 \text{ mm}^2 \pm 0.87$.

The reliability of measuring areas of geographic atrophy using images taken with a confocal scanning laser ophthalmoscopy has been described by Deckert et al [35]. Using 2 different readers to examine images from 34 eyes, the mean difference in area affected for the proposed quantification algorithm was 0.12 mm^2 with a 95% confidence interval (0.02, 0.22).

Using the above parameters as a reference, we calculated the power to detect yearly progression for sample sizes between 120 and 240 participants, with standard deviations between 0.9 and 1.1, and expected progression rates of 0.40 and 0.50 mm² per year (Figure 5). A clinically meaningful progression rate should be greater than the variability of the measurement. The power calculations were set to test for progression rates above 0.2 mm² which is the estimate of the upper bound of the difference that could be attributable solely to measurement error.

Power to detect progression rates for a range of sample sizes and standard deviations with a two-sided significance level $\alpha=0.05$ *



*Assuming that test retest differences could be as high as 0.2

Figure 5: Power calculations for expected progressions rates of 0.40 and 0.50 mm² per year

A sample size of 170 achieves 80% power to detect a difference of 0.2 between the null hypothesis mean of 0.2 mm² (measurement error) and the alternative hypothesis mean progression of the lesion of 0.4 mm² with an estimated standard deviation of 0.9 and a significance level $\alpha= 0.05$ using a two-sided Wilcoxon test (Figure 5 (a)). Similarly, if the expected standard deviation increases to 1.0 we need 200 participants to achieve the same level of power. When the expected progression rate is ≥ 0.50 mm², a sample size of 120 participants achieves more than 80% to detect differences beyond the expected measurement error, for standard deviations ≤ 1.1 (Figure 5 (b)).

7.2. Statistical Analyses

Estimating **the yearly growth in the area of the atrophic lesion** as measured by fundus auto-fluorescence:

First exploratory analysis looking at the baseline, six, and twelve months overall distribution of the outcome will be performed, outliers and inconsistent measures will be identified and reviewed. Let Y_{iv} represent the area (or a transformation to achieve normality; e.g. square

root) of the i^{th} individual at visit v for $v=0, 1, 2, 3, 4$ for the baseline, 6 months, 12 months, 18 months and 24 months visits, respectively. In order to determine the average rate of progression in the population, an appropriate approach will be to allow for each individual to have his/her own intercept and slope and to average them to achieve the overall rate of decline. This is accomplished with a random coefficients regression model of the form:

$$Y_{iv} = (\mu + a_i) + (\Delta + b_i)v + \gamma Z_{iv} + e_{iv}; \text{ where } a_i \sim N(0, \sigma_1^2), b_i \sim N(0, \sigma_2^2), \text{ cov}(a_i, b_i) = \sigma_{12} \text{ and } e_{iv} \sim N(0, \sigma^2).$$

The a_i and b_i are the random departures of the line for the i^{th} individual from the population line with intercept μ and slope Δ . The e_{iv} are the within individual departures from the line of the repeated measurements taken on the i^{th} individual at times 0, 6, 12, 18 and 24 months. Z_{iv} represents a vector of factors that could to be related to progression such as age and use of vitamin A supplementation.

The estimate of Δ and its standard error will provide the six month progression of the lesions. In addition, to explore whether progression may be different for different initial levels, we will carry out the analysis in strata of baseline severity.

A similar approach to will be used to examine progression overtime for the secondary outcomes: retinal thinning, loss of photoreceptors, loss of retinal sensitivity, and changes of BCVA.

7.3. Baseline Demographic Characteristics

Baseline demographic characteristics are: date of birth, age, sex, and race. Randomization is not applicable.

7.4. Data Set Descriptions

Study Population

Patients with STGD enrolled into the study shall have had previous genetic testing and a finding of at least 2 pathogenic mutations in the *ABCA4* gene. If only one *ABCA4* allele containing a pathogenic mutation is detected, a patient may be enrolled if they have a typical Stargardt phenotype, i.e. at least one eye must have flecks at the level of the retinal pigment epithelium typical of STGD.

Data Sets for Endpoint Analyses

The final data set will include all participant visits. Most of the participants will complete 5 visits. Participants lost to follow-up after the six month visit shall be included but will only partially contribute to the estimation of the progression rates.

7.5. Handling of Missing Data

The random effects methods described in section 7.2 do not require all individuals to have all the five visits. Individuals who are lost to follow up will partially contribute to the analysis and will be appropriately weighted by the maximum likelihood approach. To rule out informative censoring (i.e., fast progressors having less visits with available data) we will perform sensitivity analysis restricting to those with complete data. Were it to be necessary, we will explore multiple imputation methods to complete the trajectories shorter than two years.

7.6. Safety Analyses

This is an observational study of the natural course of STGD. All investigations included are part of standard of clinical care for patients affected by STGD. Therefore, no study-specific safety events are anticipated.

7.7. Study Drug Compliance

Not applicable

7.8. Interim Analysis

An interim analysis of the study data is planned after all participants have completed their 12 month visit.

8. Study Product Management

Not applicable

9. Data Handling and Records Management

Any questions about the protocol or eCRFs will be referred to the sponsor or its representatives, by the Dana Center.

9.1. Data Collection

Study Forms

Most patient data are collected on paper and kept at each individual clinic center. Therefore, in this study, paper copies of the study forms shall be created from an electronic clinical report form (eCRF) that was developed specifically for the study using REDCap software (Appendix 4, Data Collection forms). Once the paper study forms have been completed with patient data, the clinical investigator shall review the data for accuracy and sign their signature to approve the forms.

Once the data are approved by the investigator, the clinic coordinator will log into REDCap using a unique user id and password. When entering a new study participant, the coordinator must first fill out the eligibility form that assigns a unique ID to the participant. If the clinic coordinator is entering data for a participant already enrolled in the study, the coordinator must first enter the participant's ID, and then select the appropriate form. Data are subsequently entered into the forms using 100% double data entry.

The programs developed in REDCap contain a series of data checks within each form to check that:

- a) All entries are within the allowed range.
- b) There is internal consistency (i.e., skip patterns) within each form.
- c) Duplicate entries do not occur.
- d) All required fields are entered; if not, the record is flagged as incomplete.
- e) Double data entry is completed after the first entry to ensure the integrity of the data.
- f) Any reports created indicate any missing or incomplete records.
- g) Reports are issued to help the Clinic Coordinator manage upcoming appointments, and follow-up with missed appointments.
- h) All data entries and changes are logged in an electronic audit trail that tracks who made the change, on what date and time the change was made, and the field name(s) and value(s) of the change. The system also logs any changes made to the structure of the forms by the DCPO DCC.

There are two methods planned in order to transfer imaging data to the Central Reading Center. This is described in detail in a separate standard operating procedure. Generally, imaging data are not compressed.

Option 1: The Reading Center has its own secure servers where images are to be downloaded directly from the clinic centers

Option 2: Create a CD-DVD to be mailed to the reading center

During each participant's visit to the clinic, a study clinician will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents
- The date of the visit and the corresponding Visit, Day, or Week in the study schedule
- Any comments made by the participant about the study, including any significant medical findings
- A general reference to the procedures completed
- A dated signature, or initials, of all clinicians who made an entry in the progress notes.

In addition, any contact with the participant via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Information from the study progress notes and other source documents will be promptly and legibly transcribed to eCRFs for transmission to the data management center.

Any changes to information in the study progress notes, other source documents, and CRFs will be initialed and dated on the day the change is made by a site study staff member authorized to make the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data (e.g., ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change shall be written in the source documentation by the clinician. Correction fluid shall not be used at any time.

9.1.1. Volunteer Identification

Each center shall de-identify patient data. Patient data shall be encoded by a five-digit code number: the first two numbers shall indicate the number of the study center and the last three numbers shall label the patients in an ascending ordinal scale (for example, following patient's enrollment on the study). Data shall be collected using electronic clinical report form (e-CRF) and shall be centrally managed at the Dana Center for Preventive Ophthalmology.

9.1.2. Confidentiality

The data collected during the study are part of standard clinical care. Charts shall be secured to protect privacy of patients and maintain confidentiality. Clinical data shall be entered on electronic Case Report Forms (eCRFs) for transmission to the coordinating center in accordance with the procedures specified in the current Manual of Standard Operating Procedures (SOPs) for this trial. Data on eCRFs transmitted to the coordinating center shall correspond to, and be supported by, source documentation maintained at the site. All study forms and records transmitted to the coordinating center shall carry only coded identifiers such that personal identifying information is not transmitted to the coordinating center.

The Johns Hopkins Biostatistics Center (JHBC) servers that host the data are protected by both a hardware firewall and a web application firewall. In addition, they have multi-level intrusion detection, network security audits, and secondary hardware on standby for immediate replacement. JHBC administrators connect to the REDCap servers for system administration using a VPN connection and a two-factor authentication method. All data transmitted between the client browser and REDCap web servers are encrypted using an SSL connection. JHBC system administrators regularly monitor server logs and services to ensure that the servers are secured. They also ensure that server updates are applied in a timely manner and that the data are regularly backed up and stored securely off-site.

Ophthalmic outcome data from the microperimetry, sd-OCT and fundus autofluorescence assessments will be submitted electronically from the site to the Reading Center via secure data upload.

Once processed and analyzed by the Reading Center, the data will be transferred electronically from the Reading Center to the Dana Center system via a secure transfer process. Only coded identifiers will be used to identify participants.

9.1.3. Access

At each site, the site investigator and the personnel designated by him shall have access to source documents. De-identified data shall be collected at the Data Coordinating Center at Johns Hopkins. All site investigators, their designated personnel, study staff at Johns Hopkins University and study staff at the reading center shall have access to the database of de-identified data.

Representatives of the USAMRMC and FFB CRI have the authority to review research records.

9.1.4. Reporting Requirements

The investigators of each site shall take care to meet the requirements for reporting sensitive information to state or local authorities. For example the investigators might seek guidance from their institutional review boards when considering how to report information such as positive human immunodeficiency virus (HIV) status, hepatitis or tuberculosis test results, illegal residency, child or spouse abuse, or participation in other illegal activities.

9.2. Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents shall include, but are not limited to, progress notes, electronic data, screening logs, study worksheets, and data recorded from automated instruments. All source documents pertaining to this study shall be maintained by the investigators and made available for inspection by authorized persons.

9.3. File Management at the Study Site

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the ICH GCP Guideline.

9.4. Records Retention at the Study Site

The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study, including any data quality queries received from the data management center. Such documentation is participant to inspection by FFB CRI and relevant agencies, such as USAMRMC. If the investigator withdraws from the study, all study related records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given to FFB CRI in writing.

The investigator shall not dispose of any records relevant to this without written permission from FFB CRI and providing FFB CRI the opportunity to collect such records. Generally, records are kept for a minimum of ten years

9.5. Data Management Considerations

Data will be stored in the REDCap system (section 9.1).

Every effort shall be made to ensure that data management practices adhere to international standardization of the following data management procedures.

9.5.1. Database Design and Creation

An appropriate database shall be designed and created within a validated Clinical Data Management System (CDMS). This database shall be designed to store the data recorded on the CRFs and shall ensure a one-to-one mapping between the CRF and the electronic copy stored in the system (section 9.1).

9.5.2. Data Coding

Upon completion of CRF data entry, a secondary, in-house clinical review shall be conducted. Adverse event coding shall be undertaken using the current version of the MedDRA dictionary (version 12.1). The version of this dictionary will remain the same throughout the study.

9.5.3. Data Transfer

Data shall be transferred to the Dana Center of Preventive Ophthalmology, Wilmer Eye Institute of the Johns Hopkins University, Baltimore, Maryland. The transfer shall be

electronic and shall happen on a defined schedule, in a data format mutually agreed upon by the Dana Center of Preventive Ophthalmology (study central data management center).

9.5.4. Data Validation

After the data have been entered and verified, various edit checks shall be performed to ensure the accuracy, integrity and validation of the database against the CRFs. Inconsistencies that arise from these edit checks shall be resolved with the investigator or designee.

9.5.5. Database Lock

Upon completion of the trial and completion of data entry, verification and validation, the database shall be locked and write access removed.

10. Quality Control and Quality Assurance

10.1. Monitoring

The Data Coordinating Center shall undertake on-site monitoring of study data for the duration of the study. These clinical site monitoring visits shall be conducted regularly during the two-year study conduct phase. The anticipated monitoring visit schedule for each site will be based on the time of the enrollment of the first study participant at the site and includes: one evaluation/initiation visit prior to the start of study procedures, one visit 3 months following enrollment of the first participant at the site or when at least 5 participants have been enrolled, and a second visit at 14 months or when the first five participants have completed their first annual follow-up visit. Other clinical site monitoring visits shall be conducted on an as-needed basis. It is anticipated that remote data monitoring of randomly determined data points will be completed by the Data Coordinating Center.

The Data Coordinating Center may also conduct study site visits, on the sponsor's behalf. The study shall be monitored in compliance with the relevant parts of 45 CFR and according to the ICH GCP Guidelines. Site visits shall include, but are not limited to, verifying the presence of required documents, verifying the informed consent process, and comparing case report forms with source documents. Each investigator agrees to participate in site visits conducted at a reasonable time in a reasonable manner. Regulatory authorities may also audit the investigator during or after the study. If a regulatory authority announces an audit, the investigator should contact the sponsor immediately, and must fully cooperate with these audits within a reasonable time in a reasonable manner.

The knowledge of any pending compliance inspection or visit by the DHHS-OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the

regulations or requirements shall be reported immediately to the Study Director, FFB CRI, and USAMRMC ORP HRPO.

FFB CRI has ethical, legal, and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research and GCP principles. As part of a concerted effort to fulfill these obligations, FFB CRI's or its designee's monitors shall visit the center during the study in addition to maintaining frequent telephone and written communications.

10.2. Auditing

FFB CRI may conduct audits at the study site(s). Audits shall include, but are not limited to, verifying the presence of required documents, verifying the informed consent process, and comparing the case report forms with source documents. The investigator agrees to participate with such audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. If a regulatory authority announces an audit, the investigator should contact FFB CRI immediately, and must fully cooperate with the audits within a reasonable time in a reasonable manner.

11. Ethics and Responsibility

This study shall be conducted in compliance with this study protocol, the ICH GCP Guidelines, the applicable regulatory requirements, and the current Declaration of Helsinki.

11.1. Clinical Study Report

A yearly continuing review report shall be submitted to the local IRB(s) by each of the clinical sites, if required by the host country. A copy of this report and IRB approval notification shall be submitted to the HRPO and WIRB by the Sponsor as soon as these documents become available. In host countries that do not require an annual IRB report, the site will prepare and submit an annual report summary to the Sponsor to submit to WIRB and HRPO, per HRPO guidelines. A copy of the approved final study report and the central IRB approval notification shall also be submitted to the HRPO by the Sponsor as soon as available.

The report shall include a discussion of the study objectives, methodology, clinical observations and conclusions in relation to the study objectives.

12. Confidentiality

All information generated in this study shall be considered highly confidential and shall not be disclosed to any persons not directly concerned with the study without written prior permission from FFB CRI. However, authorized HRPO representatives, regulatory officials, and FFB CRI personnel (or their representatives) shall be allowed full access to inspect and copy the records. All participants' materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by FFB CRI. Participants shall be identified only by their unique participant numbers in CRFs. However, their full names may be made known to a regulatory agency or other authorized officials, if necessary.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of participant information.

13. Amendment Policy

The investigator shall not make any changes to this protocol without prior written consent from FFB CRI and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), shall be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses shall be fully discussed between the investigator(s), the study director and FFB CRI. If agreement is reached regarding the need for an amendment, it shall be written by FFB CRI. The written amendment shall be submitted to the study central IRB identified with this responsibility (WIRB); upon approval by WIRB, each of the clinical sites will submit the amendment to their local IRB for review and approval. Except for 'administrative amendments', investigators shall await IRB approval of protocol amendments before implementing any change(s). Administrative amendments are defined as amendments that have no effect on the safety of the research participants, the scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to participants should be implemented immediately, and the IRB notified within 5 days. FFB CRI shall submit protocol amendments to the HRPO or other regulatory agencies, as required.

When, in the judgment of the chairman of the local IRB, the investigators, the study director and/or FFB CRI, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the participant, the currently approved written informed consent form shall require similar modification. In such cases, a new informed consent shall be obtained from participants enrolled in the study before expecting continued participation.

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Protocol No. FFBCRI-PROGSTAR-02

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Appendix 1 - Agreement

Agreement Signatures

I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I shall personally conduct the study as described herein and in FFB CRI's Clinical Research Agreement.

I shall provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who participate in the study. I shall discuss the protocol with them to assure myself that they are sufficiently informed about the endpoint parameters and the conduct of the study in general to perform the study correctly. I am aware that this protocol must be approved by the local IRB responsible for my Clinical Study Facility and that IRB approval is required prior to commencement of this study. I agree to adhere strictly to the attached protocol unless it is amended in the manner set forth in Paragraph 1 of FFB CRI's Clinical Research Agreement. In that case, I agree to adhere strictly to the amended protocol. I agree that clinical data entered on case report forms by me and my staff shall be used by FFB CRI in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow monitors and auditors, or their designees, full access to all medical records at the research facility for participants screened or enrolled in the study.

I agree to provide all participants with informed consent forms, as required by government and ICH regulations. I agree to report to FFB CRI any adverse experiences in accordance with the terms of FFB CRI, or designee's, Clinical Research Agreement and FDA regulations, 45 CFR 312.64. I further agree to provide all required information regarding financial certification or disclosure to FFB CRI for all investigators and sub-investigators in accordance with the terms of FDA regulation 45 CFR 54. I understand that participation in the protocol involves a commitment to publish the data from this study in a cooperative publication prior to publication of efficacy and safety results on an individual basis.

_____ Signature Site Principal Investigator	_____ Date	_____ Signature Hendrik P.N. Scholl, M.D., M.A. Study Director	_____ Date
_____ Signature Sheila West, Ph.D. Study Biostatistician	_____ Date	_____ Signature Patricia Zilliox, Ph.D., Pharm.D. Sponsor Representative	_____ Date

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Appendix 3 – Biosketches of Key Personnel

The biosketches of Key Personnel are attached.

Protocol No. FFBCRI-PROGSTAR-02

Appendix 4 – Electronic Clinical Report Form (eCRF)

Print version of the electronic clinical report forms are attached

FOUNDATION FIGHTING BLINDNESS CLINICAL RESEARCH INSTITUTE

CONFIDENTIAL – PROPRIETARY INFORMATION

Project Title

**The Natural History of the Progression of Atrophy Secondary to Stargardt Disease:
A Retrospective Longitudinal Observational Study**

Protocol No.:	FFBCRI-PROGSTAR-01
IND No.:	N/A
Drug Development Phase:	N/A
Issue Date:	03/21/2013

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Protocol Synopsis

Name of Sponsor:	Foundation Fighting Blindness Clinical Research Institute	Protocol #: FFBCRI-PROGSTAR-01
Name of Product:	N/A	IND#: N/A
Protocol Title:	The Natural History of the Progression of Atrophy Secondary to Stargardt Disease (STGD): A Retrospective Longitudinal Observational Study	
Clinical Phase:	N/A – Natural History Study	
Treatment Indication:	N/A	
Objectives:	<p>The primary objective is:</p> <ul style="list-style-type: none"> • To assess the yearly rate of progression of STGD using the growth or the development of atrophic lesions as measured by fundus autofluorescence (FAF) imaging. <p>The secondary objectives are:</p> <ul style="list-style-type: none"> • To assess the yearly rate of progression of STGD using the rate of retinal thinning and the rate of loss of photoreceptors as measured by spectral-domain optical coherence tomography (sd-OCT). • To assess the yearly rate of loss of retinal sensitivity as measured by microperimetry. • To assess the yearly rate of best-corrected visual acuity changes. • To correlate the presence and progression of morphological abnormalities in FAF and sd-OCT images with visual function as measured by microperimetry and visual acuity. • To perform exploratory analysis that examines factors associated with effects on STGD progression, such as the use of vitamin A supplementation and mutations in the <i>ABCA4</i> gene. 	
Study Design:	Retrospective longitudinal observational study over a period of at least 24 months, and up to 60 months.	

Name of Sponsor:	Foundation Fighting Blindness Clinical Research Institute	Protocol #: FFBCRI-PROGSTAR-01
Name of Product:	N/A	IND#: N/A
Participant Population:	Up to a total of 250 (minimum of 150) patients, including males and females age 6 years and older affected by STGD that have an atrophic lesion in at least one eye with a minimum diameter of at least 300 microns, and a sum of all lesions areas less than or equal to 12 mm ² (five disc areas) at the most recent visit. Participants must have been previously genotyped to participate in the study and have at least 2 confirmed pathogenic mutations in the <i>ABCA4</i> gene. If only one <i>ABCA4</i> allele contains a pathogenic mutation, then the patient needs to show a typical phenotype, i.e. at least one eye must have flecks at the level of the retinal pigment epithelium typical for STGD.	
Test Product, Dose, Mode of Administration:	N/A	
Outcome variables:	<ul style="list-style-type: none"> • Growth or development of atrophic lesions as measured by FAF imaging over a period of at least 24 months, and up to 60 months. • Rate of retinal thinning and photoreceptor loss as measured by sd-OCT over a period of at least 24 months, and up to 60 months. • Loss of retinal sensitivity as measured by microperimetry over a period of at least 24 months, and up to 60 months. • Change of best-corrected visual acuity over a period of at least 24 months, and up to 60 months. 	
Study Duration:	Total duration of study including patient enrollment and data analysis: 12 months.	

Table of Contents

Protocol Synopsis	5
Table of Contents	7
1 Introduction	14
1.1 Background.....	15
1.2 Treatment Strategies	18
1.3 Known and Potential Risks	19
1.3.1 Foreseeable Risks	19
1.3.2 Risk Management and Emergency Response.....	19
1.3.2.1 Minimization of Risk.....	19
1.3.2.2 Response to Risk	20
1.3.2.3 Research Injury Compensation.....	20
1.3.2.4 Precautions and Preventive Measures	20
1.3.3 Known and Potential Benefits.....	20
2 Study Rationale and Objectives	20
2.1 Study Rationale	20
2.2 Study Objectives.....	21
3 Study Design.....	21
3.1 Type/Design of Study.....	23
3.2 Study Treatments.....	24
3.3 Study Population	24
3.3.1 Recruitment Methods	24
3.3.2 Recruitment Process	24
3.3.3. Volunteer Compensation.....	25
3.3.4. Recruitment Materials	25
3.4 Eligibility Criteria.....	25
3.4.1 Informed Consent/Assent	25
3.4.2 Disclosure of DOD Sponsorship and Access to Research Records	26
3.4.3 Inclusion Criteria	26
3.4.4 Exclusion Criteria.....	28
3.5 Primary and Secondary Outcome Variables.....	29
3.6 Measures to Minimize/Avoid Bias	29
3.6.1 Blinding.....	29
3.6.2 Study Data	30
3.7 Data collection.....	31
3.7.1. Safety Assessments	32
3.7.1.1. Adverse Events.....	32

3.7.1.2.	Clinical Laboratory Data	32
3.7.1.3.	Evaluations	32
3.7.1.4.	Labs Performing Evaluations and Special Precautions	32
3.7.1.5.	Sharing Research Results	33
3.7.2.	Endpoints	33
3.7.2.1.	Primary Statistical Endpoint.....	33
3.7.2.2.	Secondary Statistical Endpoints	33
3.8.	Withdrawal Criteria, and Procedures	33
3.9.	Definition of Completed.....	33
3.10.	Participant Compliance	34
3.11.	Protocol Deviations	34
3.12.	Protocol Modifications	34
4.	Study Personnel	35
4.1.	Roles and Responsibilities of Key Study Personnel.....	35
4.2.	Conflict of Interest.....	37
5.	Prohibited Medications	37
6.	Evaluation of Adverse Events.....	37
7.	Statistical Analysis.....	37
7.1.	Sample Size and Power	37
7.2.	Statistical Analyses.....	38
7.3.	Demographic Characteristics.....	39
7.4.	Data Set Descriptions	39
7.5.	Handling of Missing Data	39
7.6.	Safety Analyses	39
7.7.	Study Drug Compliance	39
7.8.	Interim Analysis	39
8.	Study Product Management.....	40
9.	Data Handling and Records Management.....	40
9.1.	Data Collection.....	40
9.1.1.	Volunteer Identification.....	41
9.1.2.	Confidentiality.....	41
9.1.3.	Access.....	42
9.1.4.	Reporting Requirements.....	42
9.2.	Source Documents.....	42
9.3.	File Management at the Study Site.....	43
9.4.	Records Retention at the Study Site	43
9.5.	Data Management Considerations.....	43
9.5.1.	Database Design and Creation.....	43
9.5.2.	Data Coding.....	43

9.5.3.	Data Transfer	44
9.5.4.	Data Validation.....	44
9.5.5.	Database Lock	44
10.	Quality Control and Quality Assurance.....	44
10.1.	Monitoring.....	44
10.2.	Auditing.....	45
11.	Ethics and Responsibility.....	45
11.1.	Clinical Study Report	45
12.	Confidentiality	45
13.	Amendment Policy.....	46
14.	References.....	47
	Appendix 1 - Agreement	50
	Appendix 2– Additional Institutions and Personnel Involved With the Study	51
	Appendix 3 – Biosketches of Key Personnel	52
	Appendix 4 – Electronic Clinical Report Form (eCRF)	53

List of In-text Tables

Table 3.4.3-1	Inclusion Criteria	27
Table 3.4.4-1	Exclusion Criteria	28
Table 3.6.2	Study Procedures.....	30

List of Abbreviations and Definitions of Terms

Abbreviations

AE	Adverse event
AF	Autofluorescence
AHRPO	Army Human Research Protection Office
BCVA	Best Corrected Visual Acuity
CFR	Code of Federal Regulations
CO	Contract Officer
COR	Contract Officer Representative
CRF	Case Report Form
CRI	Clinical Research Institute
eCRF	Electronic Clinical Report Form
cSLO	Confocal Scanning Laser Ophthalmoscopy
DOD	Department of Defense
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FFB	Foundation Fighting Blindness
FFB CRI	Foundation Fighting Blindness Clinical Research Institute
GCP	Good Clinical Practice
HRPO	Human Research Protections Office
HSPS	Human Subjects Protection Scientist
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
IS-OS	Inner Segment – Outer Segment junction of photoreceptor cells
LOCF	Last Observation Carried Forward
MedDRA [®]	Medical Dictionary for Regulatory Activities
MP	Microperimetry
mmHg	Millimeters of Mercury
N/A	Not Applicable
OC	Observed cases
sd-OCT	Spectral Domain Optical Coherence Tomography
STGD	Stargardt Disease
USAMRMC	US Army Medical Research and Materiel Command

WOCBP Women of Child Bearing Potential

Definition of Terms

Research - A systematic investigation, including the development, testing and evaluation of an idea, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Clinical Investigation - Any experiment in which a drug or therapy is administered, dispensed, or used for treating one or more human participant. This definition applies to research involving the use of FDA-regulated products. Even if a clinical investigation does not meet the definition of research, it is participant to the same regulations as research.

Human Participant - A living individual about whom an investigator is conducting research, obtains data through intervention or interaction with the individual, or identifiable private information.

Human Anatomical Substances - Any human organs, tissues, cells, or body fluids including but not limited to blood/sera (finger stick, ear stick, venipuncture, etc.), hair, nails, teeth, skin, sputum or cells gathered from mouth washing, nasal or oral swabs, placenta or amniotic fluid.

Individually Identifiable Private Information - *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place. This information has been provided for specific purposes by an individual and the individual can reasonably expect that private information will not be made public (for example, a medical record). *Individually identifiable* means that the identity of the participant is known or that their identity may readily be ascertained by the investigator or that their identity is associated with the information.

Protected Health Information (PHI) - Any individually identifiable health information held by a covered entity, as defined in the Health Insurance Portability and Accountability Act (HIPAA).

Covered Entity - An organization engaged in the treatment of patients, responsible for obtaining payment for such treatment, or engaged in other healthcare operations where PHI is electronically exchanged.

Authorization - Written permission from an individual allowing a Covered Entity to use or disclose specified PHI for a particular purpose (such as research).

Minimal Risk - The probability and magnitude of harm or discomfort in the research are not anticipated to be greater in and of themselves than those ordinarily encountered in daily life, or during the performance of routine physical and psychological examinations or tests.

Legally Authorized Representative (LAR) - An individual or judicial or other body authorized under applicable law to consent on behalf of a potential participant to the participant's participation in the procedure(s) involved in the research. NOTE: State law defines who may act as an LAR. The Institutional Review Board (IRB) of record should be consulted for guidance regarding who can serve as an LAR for research at the research site.

USAMRMC Supported Research - For the purpose of this document USAMRMC supported research includes but is not limited to: (1) Research funded (through grant, contract, cooperative agreement, military interdepartmental purchase request, etc.) by the USAMRMC and (2) Research managed (technical management and/or funds management) by the USAMRMC as directed by Congress (e.g., Telemedicine and Advanced Technology Research Center (TATRC)).

Institutional Review Board (IRB) of Record - The IRB listed on an Institution's Assurance of Compliance that assumes responsibility for review and oversight of a research protocol on behalf of the institution. An IRB of record from each institution engaged in the research must review and approve the protocol; therefore, there can be more than one IRB of record for a protocol. An IRB Authorization Agreement between two IRBs of Record allows one IRB of record to defer to another.

Research Proposal - A research plan submitted to the DOD funding agency in response to a solicitation. The proposal provides an overview of all proposed work to be performed and provides the rationale explaining why the institution should be awarded funds to complete the work. A proposal may consist of multiple research projects conducted under separate protocols at one or more institutions.

Research Protocol - A comprehensive, detailed, and specific plan of action for the execution of research on human participants.

Award - A financial agreement such as a grant, contract, or cooperative agreement between the Federal Government and an institution.

Scientific Review – An independent, documented review that objectively evaluates the scientific merit of a research proposal or protocol. Refer to the HRPO Policies and Procedures document on the HRPO website for additional information on scientific reviews.

Contract Officer (CO) – A federal government employee authorized to negotiate awards and commit funds on behalf of the U.S. Government.

Contract Specialist - A federal government employee assigned to assist the CO with award related issues. The contract specialist is the primary point of contract for award related issues.

Contract Officer’s Representative (COR) - A federal government employee assigned by the CO to manage the technical aspects and performance of an award on behalf of the DOD program office responsible for oversight of the research. The COR may serve as the **Grant Manager or Project Manager** or may have assistance from other personnel within the DOD program office in executing COR responsibilities.

Human Subjects Protection Scientist (HSPS) - A federal government employee or contractor within the HRPO responsible for assisting investigators with the HRPO review and approval process. The HSPS is the investigator’s primary point of contact for questions regarding the human research review process and other issues related to human subjects protection.

Army Human Research Protection Office (AHRPO) - The office that reports to the Assistant Surgeon General, Force Projection and is responsible for human research policy, education, and oversight for the U S Army. The AHRPO administers DOD Assurances of Compliance.

Informed Consent - Informed consent is an ongoing process that provides the participant, or legally authorized representative (LAR), with sufficient details about a study so that he/she can make a voluntary decision about participation. Often a written consent form is employed to facilitate initial discussion of a study, and includes descriptions of study procedures, potential risks and benefits, and other pertinent information. Informed consent is an ongoing, interactive process and the participant’s voluntary decision about continuing to take part in the trial should be reassessed throughout the study.

Enrollment - To register, enter, screen, randomize, or otherwise formally initiate a participant’s participation in a study. Informed consent precedes enrollment. The number of participant consented may differ from the number of participants enrolled in a study (e.g., a participant may give consent to participate in a study but may be determined to be ineligible upon screening; commonly called a “screen failure”).

Screening - A process of actively assessing a potential participant for inclusion in a study based on compatibility with pre-determined inclusion/exclusion criteria, ability and willingness to complete the study, and other factors. Screening that does not access, collect, or record a participant’s protected health information may take place before informed consent is obtained. However, informed consent must be obtained prior to screening procedures that use protected health information or involve procedures that a participant would not normally undergo.

1 Introduction

Stargardt disease (STGD1; OMIM: 248200), initially described by the German ophthalmologist Karl Stargardt in 1909, is an autosomal recessive inherited disorder, although an autosomal dominant Stargardt-like phenotype has also been described [1]. Stargardt disease is the most common form of juvenile macular degeneration with an estimated incidence of 10 – 12.5 per 100,000 and is caused by mutations in the *ABCA4* gene [2]. An autosomal dominant Stargardt-like phenotype [3] has also been described associated with mutations in the *ELOVL4*, *PROM1* and *PRPH2* genes [4, 5].

Patients with STGD develop a progressive impairment of visual acuity, which begins most frequently within the first or second decades of life [6]. However some patients do not lose visual acuity until the fourth or even fifth decade of life. The loss of acuity is accompanied by atrophic-appearing lesions within the macula and the presence of yellow-white lesions at the level of the retinal pigment epithelium (RPE), which are referred to as “fundus flecks”. The fundus changes apparent clinically are caused by excess accumulation of lipofuscin in the RPE (Figure 1). RPE lipofuscin is a heterogeneous material composed of a mixture of lipids, proteins, and different fluorescent compounds [7]. The natural autofluorescent properties of lipofuscin have led to the use of confocal scanning laser ophthalmoscopy (cSLO), and autofluorescence (AF) imaging, as convenient, noninvasive methods for determining the distribution of lipofuscin in human participants. [8-10].

Figure 1:

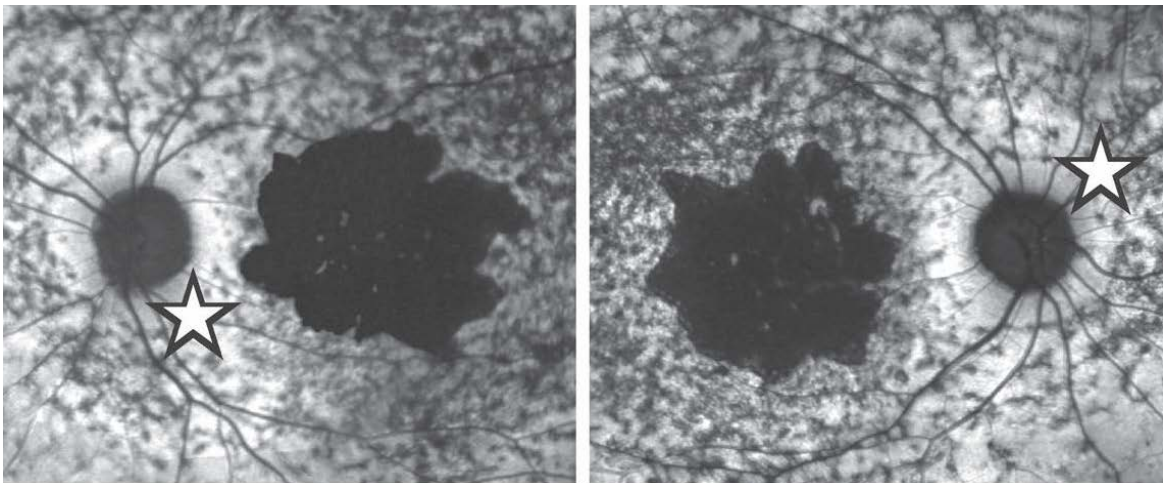


Figure 1: AF images of both eyes of a patient with bilateral central atrophy of the RPE. Stars: fixation loci determined individually in each eye. The contrast of each grayscale image is uniformly stretched for better visibility of features [11].

1.1 Background

Any new therapeutic clinical studies must be able to compare the intervention to the natural history of the disease in a longitudinal study. Therefore, the natural history of the disease in the patients to be treated must be understood. Any clinical outcome measures must be accurate, reproducible and have acceptable intra- and inter-observer variability. For surrogate measures, the FDA states that “validated surrogate markers are those for which evidence has been established that a drug-induced effect on the surrogate predicts the desired effect on the clinical outcome of interest” [12].

Degeneration of the photoreceptors and underlying retinal pigment epithelium (RPE) in STGD, as measured by standard histology and sd-OCT imaging, typically occurs close to or within the macula [13] (Figure 2). Photoreceptors degenerate either primarily due to accumulation of toxic retinoids within outer segments [14, 15] or secondarily following RPE loss because of their dependence on RPE cells for the maintenance and the removal of shed photoreceptor outer segments [16]. Multiple lines of evidence indicate that lipofuscin accumulation in the RPE is associated with RPE cell death [17-19], most probably by facilitating apoptosis and damage to lysosomal membranes [17].

Figure 2:

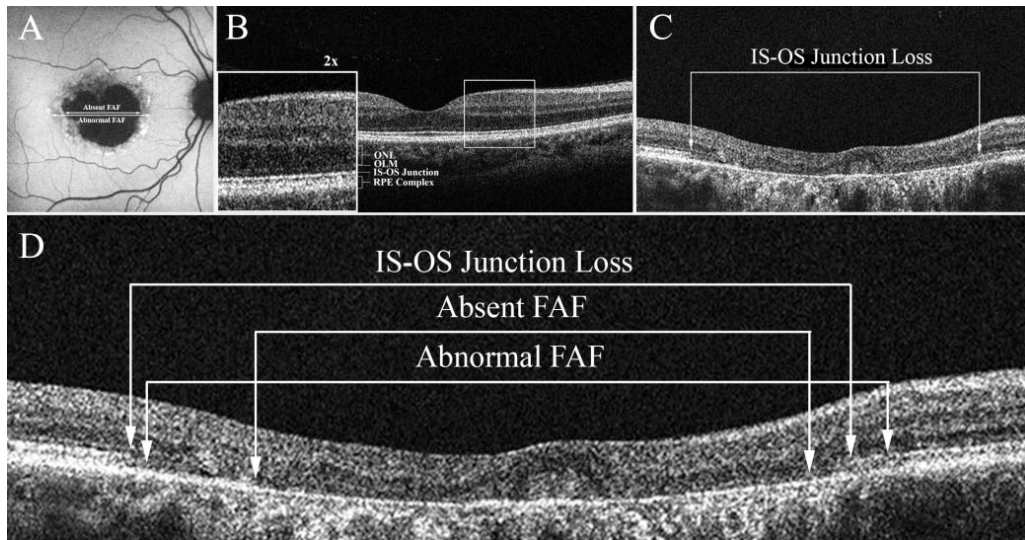


Figure 2: The complementary nature of FAF and sd-OCT imaging. (A) A Fundus Autofluorescence (FAF) image of a Stargardt patient’s retina. The diameter of the central area of “absent FAF” corresponds to geographic atrophy seen clinically with a larger diameter of “abnormal FAF” visible. (B) An sd-OCT image through the fovea of a normal control eye. (C) An sd-OCT image showing the extent of the transverse loss of the inner segment-outer segment junction of the photoreceptors in the foveal region. (D) A comparison of the measurements obtained from FAF in (A) and sd-OCT in (C). [13]

During the part of the visual cycle that occurs in the discs of the outer segment of photoreceptors, opsin bound 11-*cis*-retinal is converted by light into all-*trans*-retinal. This

conformational change triggers a signaling cascade. The all-*trans*-retinal is then released from opsin and, must be recycled back to 11-*cis*-retinal to maintain light responsiveness. Since rhodopsin is a trans-membrane protein, the all-*trans*-retinal is released into the membrane where it can either diffuse to the cytoplasmic face of the disc membrane, where a cytoplasmic retinol dehydrogenase starts the recycling process, or it remains in the disc membrane where it can be covalently modified by membrane lipids to form N-retinylidene-phosphatidylethanolamine (NRPE), which can be trapped within the membrane or the luminal side of the disc. To be recycled, trapped NRPE must be transported across the disc membrane to the cytoplasm for dehydrogenation.

Both *in vitro* and *in vivo* studies of the *ABCA4* knockout mouse model support the hypothesis that the *ABCA4* protein is an outwardly directed “flippase” that transports all-*trans*-retinal and NRPE to the cytoplasmic side of the disc membrane [20, 21] (Figure 3). In the absence of *ABCA4* activity, the membrane trapped all-*trans*-retinal and NRPE do not get removed for recycling [22] [23, 24]. If their concentration increases, as may occur during high levels of illumination or a lack of flippase activity (Stargardt disease), NRPE and all-*trans*-retinal can react to form A2-dihydropyridine-ethanolamine (A2E-PE) [22, 25]. Accumulation of bisretinoids within the outer segments is believed to be toxic to photoreceptors [14, 15].

Photoreceptor outer segment membranes are renewed in a circadian cycle by the RPE cells that endocytose the distal 10% of each rod outer segment each day [16] and digest them in lysosomes. In Stargardt disease, the endocytosed outer segments contain elevated quantities of A2E-PE which are hydrolyzed within the lysosomes to generate elevated levels of A2E and related bisretinoids. These are components of lipofuscin that are known to be elevated in Stargardt disease [26]. Studies suggest that elevated levels of these metabolites are not handled efficiently and become toxic, leading to the A2E-mediated cell death seen in Stargardt disease. This mechanism of RPE cell death is consistent with the studies of the *ABCA4* knockout mouse model that exhibits abundant lipofuscin accumulation, and elevated A2E levels that lead to eventual RPE cell death and subsequent photoreceptor loss [27].

Figure 3:

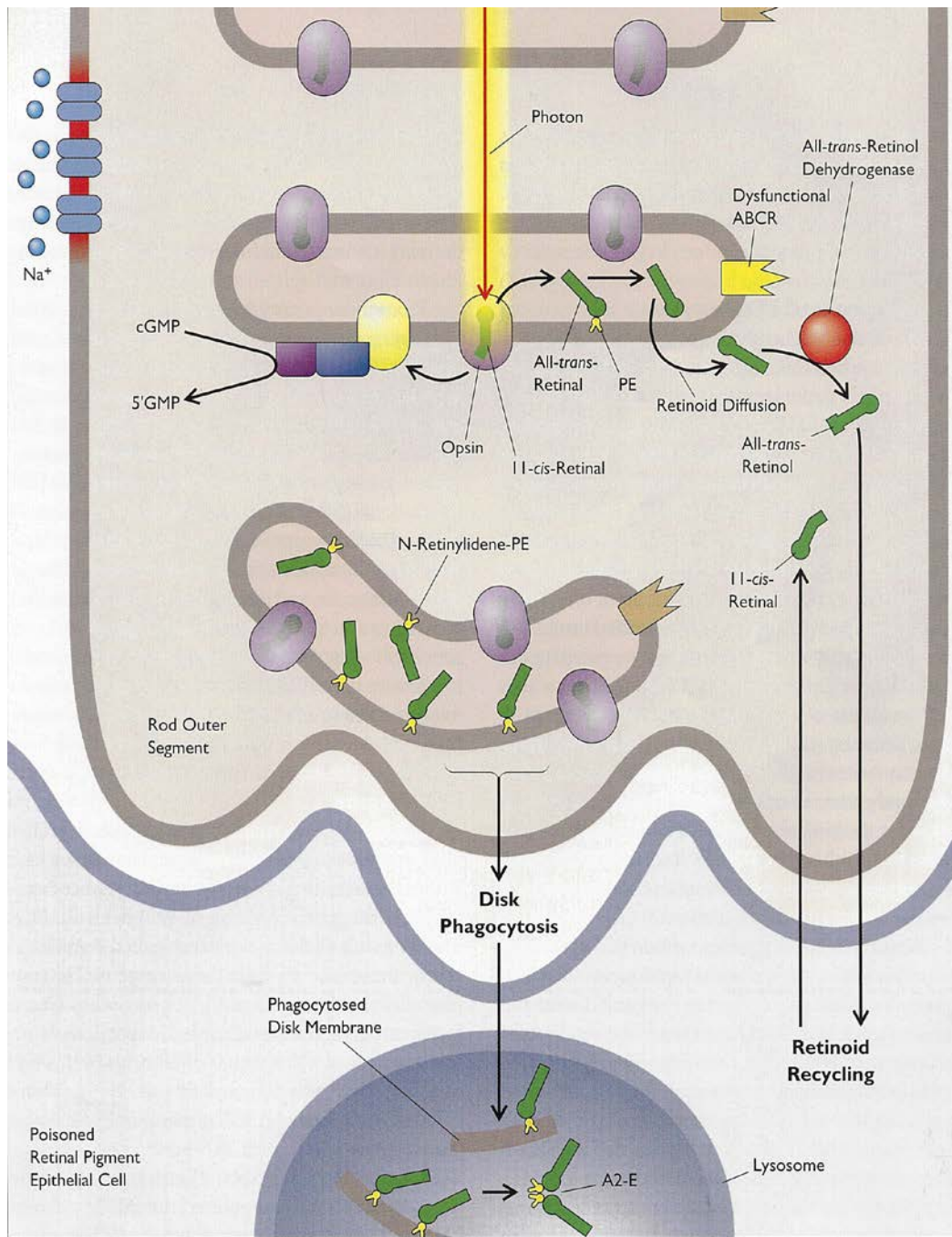


Figure 3: Scheme of the visual cycle. The cell at the top of the diagram represents the distal tip of a rod outer segment. The cell at the bottom of the diagram represents part of the RPE cell that endocytoses the distal segment of the photoreceptor and degrades it inside the lysosome. Excess accumulation of A2-PE leads to excess accumulation of A2E within the RPE lysosome that leads to A2E-mediated cell death. [20]

Consistent with this mechanism, a reduction of the daily light load on the retina would be predicted to reduce production of A2E, and this is observed in *ABCA4* knockout mice reared in darkness [27]. However more recent results have shown continued accumulation of A2E in the dark [28] suggesting a role in 11-*cis*-retinal in A2E generation.

1.2 Treatment Strategies

At present there are no FDA-approved treatments for *ABCA4*-related retinal diseases. There is a phase I/IIa gene therapy clinical trial in progress. There are also a number of preclinical studies of compounds designed to reduce the formation of A2-PE or A2E-related toxicity, which may slow or prevent progression of the disease (Figure 4). What is currently unclear is whether a treatment strategy employed after significant accumulation of lipofuscin has already occurred will be able to effectively decrease the lipofuscin content and thereby save RPE and photoreceptor cells. However, none of these treatments will be able to restore visual function to areas of the retina that have already undergone RPE, choriocapillaris, and photoreceptor cell loss. Stem cell therapy may be able to address this concern, but the technology is still several years from the clinic. While a promising intervention, gene therapy can only be effective if the target cells are still viable. Therefore the initial primary therapeutic intent is to slow or halt the progression of retinal degeneration.

Figure 4:

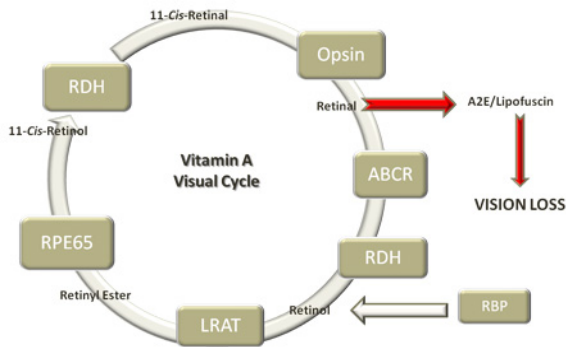


Figure 4: Scheme of Vitamin A Visual Cycle

Gene Therapy

Given that STGD is caused by the loss of function of the *ABCA4* protein, transfecting the wild type *ABCA4* gene into the nucleus of photoreceptor cells may improve the retinoid flow in the visual cycle, prevent further abnormal accumulation of lipofuscin in RPE cells, and slow the disease process in patients with STGD. This may be particularly therapeutic with early intervention before there is extensive cell loss.

There is currently one phase I/IIa gene therapy clinical trial for the product Stargen developed by Oxford BioMedica. The therapy consists of a single subretinal injection of a genetically engineered lentivirus (the Equine Infectious Anaemia Virus, EIAV) carrying a single copy of the wild type *ABCA4* gene. This is a dose escalation study enrolling up to 28 participants with Stargardt disease, with the primary outcome measures being the incidence of adverse events over 48 weeks and the number and percentage of patients with treatment emergent adverse events. The secondary outcome measures are a delay in retinal degeneration and changes from baseline function relative to the contralateral eye utilizing retinal analytical techniques. To date the trial has reported no significant adverse events.

Pharmacologic and Other Interventions

There are many different therapeutic approaches in the preclinical research stage for Stargardt disease. These include: stem cell therapies; dietary supplementations; molecules that slow the visual cycle thereby limiting the rate that all-*trans*-retinal can be generated; molecules that chelate the all-*trans*-retinal in the membrane; derivatives of 11-*cis*-retinal such as deuterated forms that markedly slow the formation of A2-PE; molecules that stimulate the activity of an impaired ABCA4 protein; molecules that restrict the amount of retinal that can reach the retina; molecules that remove the lipofuscin from the RPE cells before it can have a toxic effect; molecules targeting A2E; optogenetics and visual prosthetics [29, 30].

1.3 Known and Potential Risks

This study is a retrospective observational study of the natural course of STGD and therefore no risks are involved.

1.3.1 Foreseeable Risks

Due to the retrospective design of the study, there are no foreseeable risks to the participants.

1.3.2 Risk Management and Emergency Response

1.3.2.1 Minimization of Risk

The participants will be informed of the risks and consequences of the study by one of the delegated study staff members, in a language the participant can understand. Participants will be informed that they may withdraw from the study at any time, for any reason without jeopardizing their future treatment. Participants will be given full information regarding the study protocol.

The study will be compliant with the relevant parts of 45 CFR and the ICH GCP Guidelines.

1.3.2.2 Response to Risk

N/A

1.3.2.3 Research Injury Compensation

N/A

1.3.2.4 Precautions and Preventive Measures

N/A

1.3.3 Known and Potential Benefits

There is no direct benefit to participants in this study, although they may conceivably be good candidates for future studies of emerging STGD therapies. Participants in this study are not experimental subjects as there is neither a study intervention nor is the interaction with the participant for the primary purpose of obtaining data regarding the effect of an intervention or interaction; as such, LARS consent/child assent will be allowed in the study and children may be enrolled. Data resulting from this natural history study may influence the clinical design of future trials designed to evaluate therapies for treating Stargardt disease. As such, this study may support work that leads to benefit for some patients in the long term.

2 Study Rationale and Objectives

2.1 Study Rationale

Although STGD is the most prevalent form of juvenile-onset macular dystrophy, with an estimated incidence of 10 – 12.5 per 100,000, it is still relatively rare and there is very limited information available about the natural course of the disease in larger numbers of STGD patients. In one study, initiation and longitudinal progression of dysfunction in the peripheral retinal regions was used to provide quantitative severity scale for specific *ABCA4* mutations [31]. There is less information currently available about the progression of macular disease and it is predominantly based on individual reports of patient data collected from single centers [32, 33]. However, this limited data clearly points to a disease which is very heterogeneous with significant variation in the age of onset and rate of progression, and limited clear correlations between phenotype and genotype [34, 35]. These limitations highlight the urgent need for a multi-center study that documents the natural course of the macular disease. The information gathered from this proposed study should provide guidance and support to the identification of the most appropriate clinical outcome measures for anticipated clinical trials. It may also be used to identify and support the validation of surrogate clinical trial endpoints that are offered by recent technological advances in retinal imaging capabilities, such as fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (sd-OCT).

2.2 Study Objectives

Stargardt disease is currently an incurable and untreatable macular dystrophy that causes severe visual loss in children and young adults, thereby causing enormous morbidity with economic, psychological, emotional, and social implications. There are no FDA approved therapeutic treatments for this disease. Therefore, the objective of this study is to collect natural history data from a large population of children and adults in order to evaluate possible efficacy measures for planned clinical trials.

Primary objective:

- To assess the yearly rate of progression of STGD using the growth or the development of atrophic lesions as measured by fundus autofluorescence (FAF) imaging.

Secondary objectives:

- To assess the yearly rate of progression of STGD using spectral-domain optical coherence tomography (sd-OCT) to measure the rates of retinal thinning and the loss of photoreceptors.
- To assess the yearly rate of loss of retinal sensitivity as measured by microperimetry.
- To assess the yearly rate of best-corrected visual acuity changes.
- To correlate the presence and progression of morphological abnormalities in FAF and sd-OCT images with visual function as measured by microperimetry and visual acuity.
- To perform exploratory analysis of factors associated with STGD progression, such as participant's use of vitamin A supplementation and mutations in the *ABCA4* gene.

3 Study Design

The study shall utilize data from up to 14 clinical sites to collect retrospective longitudinal observations on up to 250 participants (minimum of 150). Participants must present with atrophic lesions secondary to STGD, in at least one eye at the most recent visit. The study shall take place over a 12 months period including patient enrollment and data analysis.

Each of the study investigators has indicated that the information that will be available at each visit will include: data of at least two, up to three previous visits over a period of at least 24 months, up to 60 months, including visual acuity, complete ophthalmic exam recordings (including dilated funduscopy), autofluorescence imaging, microperimetry and spectral-domain optical coherence tomography (sd-OCT). The screening visit of the prospective FFBCRI-PROGSTAR-02 study can serve as one visit. The study visits with

study procedures are summarized in Table 3.6.2 and graphically shown in Figure 5. In brief, if a patient is being screened for the prospective FFBCRI-PROGSTAR-02 study that visit can serve as the baseline visit for this retrospective (FFBCRI-PROGSTAR-01) study. If the patient participates in the prospective FFBCRI-PROGSTAR-02 study, the screening visit serves as “visit 1” of the prospective FFBCRI-PROGSTAR-02 study and simultaneously as the “visit -1” of the retrospective FFBCRI-PROGSTAR-01 study described herein if they have also been seen previously for at least 24 months, up to 60 months.

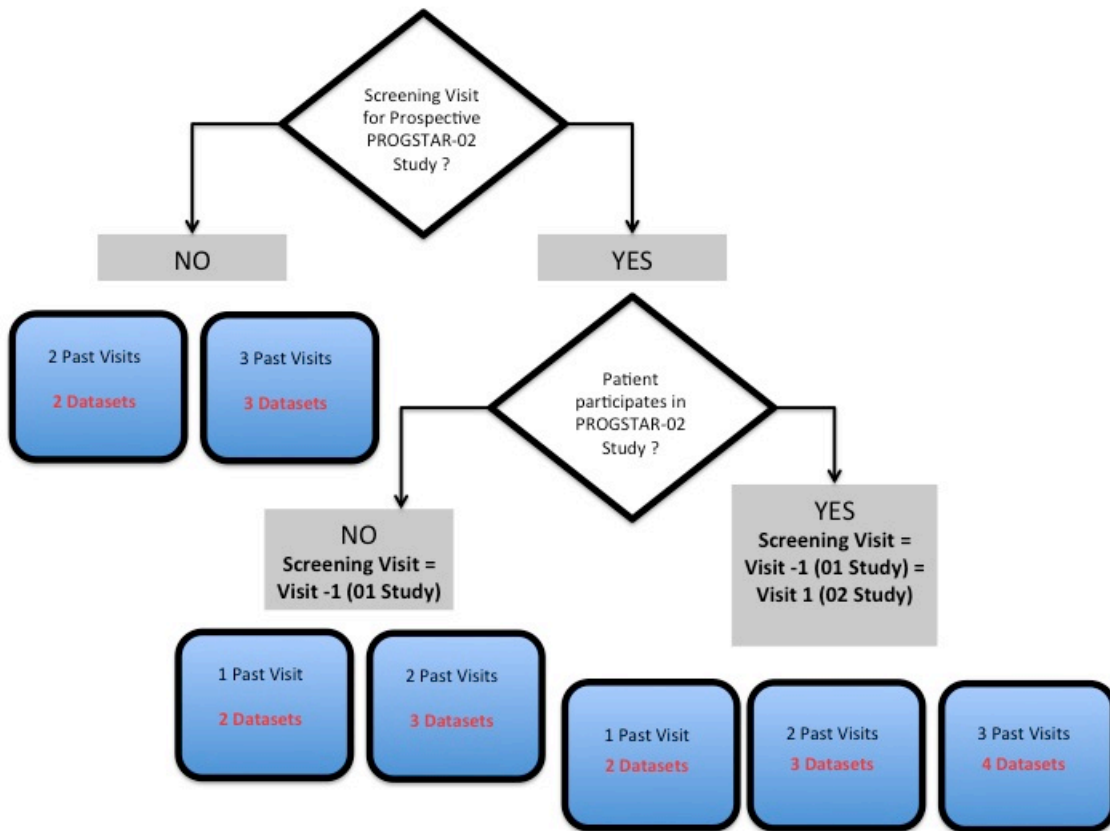


Figure 5: Overview to show the difference in possible datasets in the retrospective FFBCRI-PROGSTAR-01 Study, depending on number of available visits. 01 Study: the retrospective study. 02 Study: the prospective FFBCRI-PROGSTAR-02 Study.

Results will be sent by the participating centers to the Dana Center for Preventative Ophthalmology of the Wilmer Eye Institute, the Johns Hopkins University, Baltimore, for evaluation, with the exception of the microperimetry, autofluorescence and optical coherence tomography, which will be sent to a central reading center at the Doheny Eye

Institute, Los Angeles, California.

Primary outcome measure:

- Yearly rate of progression of STGD as reflected by the growth or the development of atrophic lesions measured by FAF imaging. Because patients have to have an atrophic lesion at the most recent visit, it is possible that they had no detectable lesion at earlier visits. Therefore, there are distinct scenarios as illustrated in Figure 6:

	Visit -3	Visit -2	Visit -1	Comment
Scenario 1	Atrophic Lesion: YES	Atrophic Lesion: YES	Atrophic Lesion: YES	2 Measurements of growth rate
Scenario 2	Atrophic Lesion: NO	Atrophic Lesion: YES	Atrophic Lesion: YES	1 Measurements of growth rate and secondary variables to study development of lesion
Scenario 3	Atrophic Lesion: NO	Atrophic Lesion: NO	Atrophic Lesion: YES	No Measurements of growth rate, but secondary variables to study development of lesion

Figure 6: Possible scenarios regarding the presence or the development of atrophic lesions as the primary outcome measure.

Secondary outcome measures:

- Yearly rate of progression of STGD as reflected by the rate of retinal thinning and photoreceptor loss as measured by sd-OCT.
- Yearly rate of loss of retinal sensitivity as measured by microperimetry.
- Yearly changes in best-corrected visual acuity.
- Correlation of the presence and/or progression of morphological abnormalities in FAF and sd-OCT images with visual function as measured by microperimetry and best-corrected visual acuity.
- Exploratory analysis to examine factors associated with disease progression, such as participant's use of vitamin A supplementation and mutations in the *ABCA4* gene.

3.1 Type/Design of Study

This is a retrospective, longitudinal, observational, study.

3.2 Study Treatments

This is a natural history study. There are no treatments being investigated in this trial.

3.3 Study Population

The study population shall consist of up to 250 Stargardt disease patients, with a minimum of 150 patients, recruited at up to 14 clinical centers across the US and Europe. Participants must be at least six years old at study enrollment. There are no limitations regarding race, ethnicity, or sex.

The participants must present with atrophic lesions secondary to STGD with a minimum diameter of 300 microns and the area of all lesions together must add to less than or equal to 12 mm² and must represent no more than 5 disc areas in a least one eye at the most recent visit (which can coincide with the screening visit of the PROGSTAR 02 study). Participants must have been genotyped to participate in the study and have at least 2 confirmed pathogenic mutations in the *ABCA4* gene. If only one *ABCA4* allele contains a pathogenic mutation, then for inclusion in this study the patient must show a typical phenotype, i.e. at least one eye must have flecks at the level of the retinal pigment epithelium typical for STGD.

3.3.1 Recruitment Methods

The investigators at each of the centers will review their own clinical patient databases and contact their patients.

3.3.2 Recruitment Process

The investigators at each of the clinical centers will identify potential study patients from their own patient populations. Potential study participants who demonstrate an interest in participating in the study will receive an explanation of the terms, and requirements of the study, in language they can understand, from an investigator in the research team. They will also receive a written copy of the Informed Consent Form to read and share with family or friends prior to their screening visit. Subsequently, an investigator or a qualified designee will answer questions and request the patient's permission to participate in the study. Participants will sign a study-specific patient informed consent form approved by the local Institutional Review Board.

For participants younger than 18 years of age, parental/LAR consent and patient assent will both be obtained prior to participation in this study.

3.3.3. Volunteer Compensation

This observational study collects existing information on the natural course of STGD and all examinations were part of the standard clinical care. Compensation will not be provided to the study participants.

3.3.4. Recruitment Materials

No centrally prepared recruitment or advertising materials are planned for this study. Recruitment materials such as telephone scripts or written letters may be prepared by individual sites.

3.4 Eligibility Criteria

3.4.1 Informed Consent/Assent

When individuals are identified in-person as potential study participants, the investigator will provide information about the study, and confirm contact. The investigator or other designated study staff will obtain and document informed consent from appropriate, interested patients.

Potential study participants who demonstrate an interest in participating in the study will receive an explanation of the terms and requirements of the study from the research team in a language they can understand. They will receive a copy of the Informed Consent Form to read and share with family or friends. An investigator or designated site study staff member will answer any questions or concerns that the potential participants may raise and request the patient's permission to participate in the study. Each site will provide adequate time for the patient to make a decision whether to participate in the study. When the potential participant is a minor (less than 18 years of age), parental consent/LAR and minor participant assent will be obtained following the same procedures outlined in the previous paragraph. The minor participant will be provided with an age appropriate assent form and given a chance to freely choose whether to participate in the study.

Study candidates who cannot give their own consent to participate will only be enrolled into the study after consent is obtained from the individual's Legally Authorized Representative (LAR). Children shall receive an additional assent form written in age appropriate language for them to read, and will only be enrolled into the study following consent by their individual's Legally Authorized Representative (LAR). Site investigators will consult with their local institutional review boards for guidance regarding who may serve as an LAR.

For study candidates who are illiterate or unable to understand the written consent form, the consent form will be read and explained to them in the presence of a witness. The candidate must sign or mark the form in an individually unique manner, such as with a thumbprint, to indicate their agreement to participate. A witness may also sign the form to

attest that the content of the written consent form was conveyed accurately to the study candidate.

If a study candidate is not fluent in the primary language of the host country of the study site, all documentation including the consent form and any site information sheets approved by the local IRB shall be translated into their native language by a certified translator and the translation approved by the local IRB and HRPO. Plans shall also be made and approved to ensure a qualified translator is available during the consent process, baseline and all follow-up visits to address any concerns or ensure they provide continuing consent to study participation.

When consent is obtained in a language other than English, the foreign language version of the consent form will be a certified accurate translation of the English version of the consent form.

Written informed consent shall be obtained from all participants or their LAR before any data will be collected for study use. However, investigators may discuss in general the availability of the study and the general entry criteria with a potential participant candidate without obtaining consent.

The investigator has both an ethical and legal responsibility to ensure that each participant study candidate being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on the written informed consent form approved by the same Institutional Review Board (IRB) responsible for approving this protocol.

Once the appropriate essential information has been provided to the participant and fully explained by the investigator, or a qualified designee, and the participant understands the implications of participating, the IRB-approved written informed consent/assent form(s) will be signed and dated by the participant and the person obtaining consent (investigator or designee), and by any other parties required by the site's local IRB. The participant shall be given a copy of the signed informed consent form. The original signed informed consent form shall be kept on file by the investigator; the time length will be determined by the local IRB. All of the above mentioned activities shall be completed prior to the participant's participation in the trial.

3.4.2 Disclosure of DOD Sponsorship and Access to Research Records

The informed consent form shall include a statement that discloses that the DOD is supporting the research and that representatives of the USAMRMC have the authority to review research records of any study participant. Study candidates have a right to decline participation in research based on the source of the funding.

3.4.3 Inclusion Criteria

Study participants are required to meet the following inclusion criteria:

Table 3.4.3-1 Inclusion Criteria	
1.	Provide a signed informed consent/assent form and authorization allowing the disclosure and use of protected health information.
2.	The study eye must have at least one well-demarcated area of atrophy as imaged by fundus autofluorescence with a minimum diameter of 300 microns and the area of all lesions together must add to less than or equal to 12 mm ² (equivalent to no more than 5 disc areas in a least one eye) at the most recent visit.
3.	Two (2) or more pathogenic mutations confirmed present, in the <i>ABCA4</i> gene. If only one <i>ABCA4</i> allele contains pathogenic mutation(s), the patient shall have a typical Stargardt phenotype, namely at least one eye must have flecks at the level of the retinal pigment epithelium typical for STGD.
4.	Sufficient quality of imaging and psychophysical procedures in the opinion of the investigator.
5.	Patients have been followed for at least two (2) visits over a period of at least 24 months, up to 60 months, and had at least two examinations (same at all visits out of: Fundus Autofluorescence obtained with a Heidelberg Engineering instrument (e.g. HRA2, Spectralis); sd-OCT obtained with the Heidelberg Spectralis; Microperimetry obtained with the Nidek MP-1).
6.	Be at least six years old at the most recent visit (“visit -1”).
7.	Both eyes can be included if inclusion criteria are fulfilled for both eyes.

3.4.4 Exclusion Criteria

Study candidates shall be excluded if they meet any of the following exclusion criteria:

Table 3.4.4-1 Exclusion Criteria	
Exclusion Criteria	
1.	Ocular disease, such as choroidal neovascularization, glaucoma and diabetic retinopathy, in either eye that may confound assessment of the retina morphologically and functionally.
2.	Intraocular surgery in the primary study eye within 90 days prior to baseline visit.
3.	Current or previous participation in an interventional study to treat STGD such as gene therapy or stem cell therapy. Current participation in a drug trial or previous participation in a drug trial within six months before enrollment. The use of oral supplements of vitamins and minerals are permitted although the use of Vitamin A supplementation shall be documented if available.
4.	The site Principal Investigator may declare any patient at their site ineligible to participate in the study for a sound medical reason prior to the patient's enrollment into the study.

3.5 Primary and Secondary Outcome Variables

The primary outcome variable for the ProgSTAR study is the yearly rate of progression of STGD as reflected by the growth or the development of atrophic lesions measured by FAF imaging.

The secondary outcome variables are:

- Yearly rate of progression of STGD using spectral-domain optical coherence tomography (sd-OCT) to measure the rates of retinal thinning and the loss of photoreceptors.
- Yearly rate of loss of retinal sensitivity as measured by microperimetry.
- Yearly change in best corrected visual acuity (VA).
- Correlation of the presence and/or progression of morphological abnormalities in FAF and sd-OCT images with visual function as measured by microperimetry and BCVA.
- Exploratory analysis to examine factors associated with disease progression, such as participant's use of vitamin A supplementation and mutations in the *ABCA4* gene.

3.6 Measures to Minimize/Avoid Bias

Data from all sites will be sent, using a standardized, de-identified electronic clinical report form (eCRF), to a central data management center at the Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, The Johns Hopkins University School of Medicine, except in the case of data from retinal imaging procedures and microperimetry, which will be sent to a central reading center at the Doheny Eye Institute, Keck School of Medicine, University of Southern California for further processing. Each center shall have undertaken standardized collection of all data. Ophthalmic outcome data from the microperimetry, sd-OCT and fundus autofluorescence assessments will be electronically submitted from the site to the appropriate reading center via secure data upload through the reading center internet website.

Once processed and analyzed by the appropriate reading center, all data will be transferred electronically from the reading center to the Dana Center system via a secure transfer process. Only coded identifiers will be used to identify participants.

3.6.1 Blinding

Not applicable.

3.6.2 Study Data

Table 3.6.2 Study Data				
ASSESSMENT/DATA COLLECTION POINTS	VISIT -4 (if applicable)	VISIT -3 (if applicable)	VISIT -2	Visit -1 (if Patient has Screening Visit of FFBCRI-PROGSTAR 02)
(Best-corrected) visual acuity data	X	X	X	X
Ophthalmic fundus exam data	X	X	X	X
Autofluorescence imaging data and/or	X	X	X	X
Microperimetry data and/or	X	X	X	X
sd-OCT data	X	X	X	X
Vitamin A supplementation data recorded if available	X	X	X	X

See also Fig. 5 where it is explained that there will be two to four datasets (“visits”) per patient.

3.7 Data collection

The Screening consists of review of existing data obtained through the following procedures:

Medical and ophthalmic history:

1. Recording and documentation of demographic information
2. Recording and documentation of vitamin A supplement use
3. Recording and documentation of genetic mutations in the *ABCA4* gene

Description of Standard of Care examinations and procedures the investigators had utilized to obtain data that had been collected for this study include:

Best-corrected Visual acuity (VA):

Visual acuity was measured at a distance of one or four meters using an ETDRS chart. Patients were encouraged to read each letter, and instructed to guess if unsure.

Fundus-Autofluorescence (FAF) and spectral-domain optical coherence tomography (sd-OCT):

Images of patient's eyes were recorded using sd-OCT, and scanning laser ophthalmoscopy (cSLO) in order to acquire fundus autofluorescence images. The computer driven cameras used in these techniques used a beam of light to take images.

Microperimetry:

Patients had undergone an examination of the retinal central visual field using microperimetry. During this procedure patients had to press a button when they saw a little light spot on a screen of a special computer monitor.

An ophthalmic examination will be used to determine if the participant exhibits the typical clinical appearance of STGD in assessing eligibility for the study.

In order to participate in the study, all patients must have documentation of two (2) pathogenic mutations confirmed in the *ABCA4* gene from previously completed genetic testing. If only one *ABCA4* allele contains a pathogenic mutation(s), the patient should have a typical Stargardt phenotype, namely at least one eye must have flecks at the level of the retinal pigment epithelium typical for STGD. The genetic testing will have been previously completed and outside the scope of this study.

The data from the visits will be utilized in the study even if the order of the examinations change from visit to visit or between the practices of the different investigators, and the examinations are performed on different days as long as all measurements were completed within a time window of \pm five (5) weeks of each other.

3.7.1. Safety Assessments

Due to the observational design of the natural course study, no study specific safety assessments are needed.

3.7.1.1. Adverse Events

Due to the observational design of the natural course study, no adverse events are expected.

3.7.1.2. Clinical Laboratory Data

Not applicable

3.7.1.3. Evaluations

A member of the study group participating in the study will document all significant observations. At a minimum, this documentation will contain:

- The informed consent process, including any revised consents
- The date of the visit and evidence that the required measurements were performed within 5 weeks of each other
- The genetic information at time of enrollment
- Whether the patient with one affected allele presents with typical Stargardt disease the basis for that conclusion
- Any comments made by the participant about the study, including any significant medical findings
- Any Vitamin A supplement use if available
- A general reference to the provided procedures
- The signature (or initials) and date of all clinicians who made an entry in the progress notes
- The evaluation of (best-corrected) visual acuity
- The evaluation of microperimetry test and recording of mean sensitivity and/or
- The evaluation of spectral-domain optical coherence tomography (sd-OCT) and/or
- The evaluation of fundus autofluorescence
- A summary of the ophthalmologic exam including status of the anterior segment of the eyes, including the cornea, anterior chamber, iris and grading cataract, and dilated fundus exam

In addition, any contact with the participant via telephone or other means that provides significant clinical information will also be documented as described above. Information from the study progress notes and other source documents will be promptly transcribed to eCRFs for transmission to the Coordinating Center. Any changes to information in the study progress notes, other source documents, and CRFs will be properly tracked.

3.7.1.4. Labs Performing Evaluations and Special Precautions

Not applicable

3.7.1.5. Sharing Research Results

As the data collected in this observational study is collected from standard clinical care ophthalmologist visits, the results of each individual's procedures conducted, including any clinically significant abnormal findings, will be shared with that study participant or his/her primary care provider.

3.7.2. Endpoints

3.7.2.1. Primary Statistical Endpoint

The primary endpoint is the rate of the growth or the development of atrophic lesions as measured by FAF imaging calculated over a period of at least 24 months, up to 60 months.

3.7.2.2. Secondary Statistical Endpoints

The secondary endpoints are:

- Rate of retinal thinning and photoreceptor loss as measured by sd-OCT calculated over a period of at least 24 months, up to 60 months.
- Loss of retinal sensitivity as measured by microperimetry calculated over a period of at least 24 months, up to 60 months.
- Change of best-corrected visual acuity by using the ETDRS protocol calculated over a period of at least 24 months, up to 60 months.

3.8. Withdrawal Criteria, and Procedures

All participants have the right to withdraw from the study at any time, for any reason, without prejudice. When known, the reasons for withdrawal shall be fully evaluated and recorded appropriately in source documents and the eCRF.

If the study sponsor, the Foundation Fighting Blindness Clinical Research Institute (FFB CRI), discontinues the study for any reason, such reasons will be thoroughly documented in the source documents and eCRFs, and all local study site IRB's and HRPO will be notified immediately.

3.9. Definition of Completed

The study period is defined as the time period during which participants are evaluated for the primary and secondary objectives of the study. Participants who have been followed for at least two (2) visits and were followed over a period of at least 24 months, up to 60 months and had at least two examinations (same data at all visits: Fundus Autofluorescence obtained with a Heidelberg Engineering instrument; SD-OCT obtained with the Heidelberg Spectralis; microperimetry obtained with the Nidek MP-1) shall be defined as having completed the study.

3.10. Participant Compliance

Not applicable.

3.11. Protocol Deviations

This study shall be conducted according to this written protocol. In the event of a significant deviation from the protocol as a result of an emergency, accident, or mistake, the investigator or designee must contact the Study Director, as soon as possible, by telephone. A joint decision will then be made regarding the participant's continuation in the study and the decision documented by the investigator and the Study Director and reviewed by the monitor. In addition, the investigator must notify the IRB to the extent necessary under GCP and local requirements. The sponsor, the Foundation Fighting Blindness Clinical Research Institute shall be notified of any protocol deviations and shall forward a detailed report any serious deviations to HRPO immediately. Any non-serious deviations shall be reported to HRPO as part of the annual study progress report.

3.12. Protocol Modifications

No changes shall be made to this protocol by site principal investigators or any other site staff without prior written consent and approval from the Study Director, the Sponsor [the Foundation Fighting Blindness Clinical Research Institute (FFB CRI)], their respective IRBs, and HRPO. Amendments shall be submitted to the IRBs for review and approval prior to implementation. Any permanent change to the protocol, whether an overall change or a study center specific change(s), must be treated as a protocol amendment. Any amendment to the protocol that is deemed necessary as the study progresses will be fully discussed by the investigator(s). Except for administrative amendments, investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined as amendments that do not affect the safety of the research participants, the scope of the investigation, or the quality of the trial. However, if a protocol amendment is required to eliminate an apparent and immediate hazard to participants, the amendment should be implemented immediately, and the IRB notified within 5 days.

Any deviation to the protocol that may have an effect on the safety or rights of the participant or the integrity of the study must be reported to the local IRBs and to the USAMRMC ORP HRPO as soon as the deviation is identified. Any corrective actions taken to avoid future deviations shall be included in the report.

All unanticipated problems involving risk to participants or others related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will be provided to HRPO following the initial notification. In addition to the methods above, the

complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

When, in the judgment of the chair of the local IRB and the investigators, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the participant, the current approved written informed consent form shall be revised and if applicable, the participants shall be asked to sign a new written informed consent.

Major modifications to the research protocol and any modifications that could potentially increase risk to participants will be submitted by the Sponsor to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted by the Sponsor with the continuing review report to the USAMRMC ORP HRPO for acceptance.

4. Study Personnel

4.1. Roles and Responsibilities of Key Study Personnel

Hendrik P.N. Scholl, M.D., M.A, is the Study Director and the Principal Investigator at the Wilmer Eye Institute site. His responsibilities include: the overall study design; coordination and execution of the study; analysis of the data; review of any protocol deviations; and dissemination of the study findings. Dr. Scholl will also submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; documenting findings obtained at previous clinical visits from patient charts; resolving any data concerns; and overall oversight of the protocol at the Wilmer Eye Institute site.

Janet Sunness, M.D. is the site Principal Investigator at the Greater Baltimore Medical Center site. She will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; documenting findings obtained at previous clinical visits from patient charts; resolving any data concerns; and overall oversight of the protocol at Greater Baltimore Medical Center.

Artur Cideciyan, Ph.D. is the site Principal Investigator at the University of Pennsylvania, Scheie Eye Institute. He will submit the study protocol to the local IRB, obtain informed and be responsible for: obtaining the medical history of participants; documenting findings obtained at previous clinical visits from patient charts; resolving any data concerns; and overall oversight of the protocol at Scheie Eye Institute.

Elias Traboulsi, M.D. is the site Principal Investigator at Cleveland Clinic's Cole Eye Institute. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; documenting findings obtained at previous clinical visits from patient charts; resolving any data concerns; and overall oversight of the protocol at Cleveland Clinic's Cole Eye Institute.

José-Alain Sahel, M.D. is the site Principal Investigator at the Centre de Recherche Institut de la Vision(Center for Rare Diseases, Hôpital Quinze-Vingts) Paris. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; documenting findings obtained at previous clinical visits from patient charts; resolving any data concerns; and overall oversight of the protocol at the Centre de Recherche Institut de la Vision, Paris.

Eberhart Zrenner, M.D. is the site Principal Investigator at the University Eye Hospital Tübingen. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; documenting findings obtained at previous clinical visits from patient charts; resolving any data concerns; and overall oversight of the protocol at University Eye Hospital Tübingen.

Michel Michaelides, M.D., F.R.C.Ophth. is the site Principal Investigator at the Moorfields Eye Hospital NHS Foundation Trust. He or designated members of the research team will: submit the study protocol to the local IRB and obtain informed consent; be responsible for obtaining the medical history of participants, documenting findings obtained at previous clinical visits from patient charts. He will have overall oversight of the protocol at Moorfields Eye Hospital NHS Foundation Trust.

Paul S. Bernstein, MD, PhD is the site Principal Investigator at the University of Utah, School of Medicine, Moran Eye Center. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; documenting findings obtained at previous clinical visits from patient charts; resolving any data concerns; and overall oversight of the protocol at the University of Utah.

David G. Birch, PhD is the site Principal Investigator at the Retina Foundation of the Southwest. He will submit the study protocol to the local IRB, obtain informed consent and be responsible for: obtaining the medical history of participants; documenting findings obtained at previous clinical visits from patient charts; resolving any data concerns; and overall oversight of the protocol at the Retina Foundation of the Southwest.

Sheila West, Ph.D., is Director of the Dana Center for Preventive Ophthalmology at the Wilmer Eye Institute. She will lead the data management coordinating center activities associated with this study and be responsible for study site monitoring, data collection and management, and the statistical analysis of the study data.

Srinivas R. Sadda, M.D. is Associate Professor of Ophthalmology and Director of the Doheny Image Reading Center at the Keck School of Medicine, University of Southern California. He will lead the image collection, reading, and imaging analysis of the study data arising from retinal imaging and microperimetry.

4.2. Conflict of Interest

As this protocol does not support the development of a drug, device, or other intellectual property, there is no immediate concern about conflict of interest. If any concerns arise, conflict of interest statements will be obtained on a case-by-case basis.

5. Prohibited Medications

Study participants may use any systemic medications that are necessary. However, study participants should not participate or have participated in, or taken concomitant therapy, to treat Stargardt disease within six months before the observation period. Study candidates who have participated in an interventional study for Stargardt disease before the end of the retrospective observation period are also excluded – see study exclusion criteria.

6. Evaluation of Adverse Events

Not applicable.

7. Statistical Analysis

7.1. Sample Size and Power

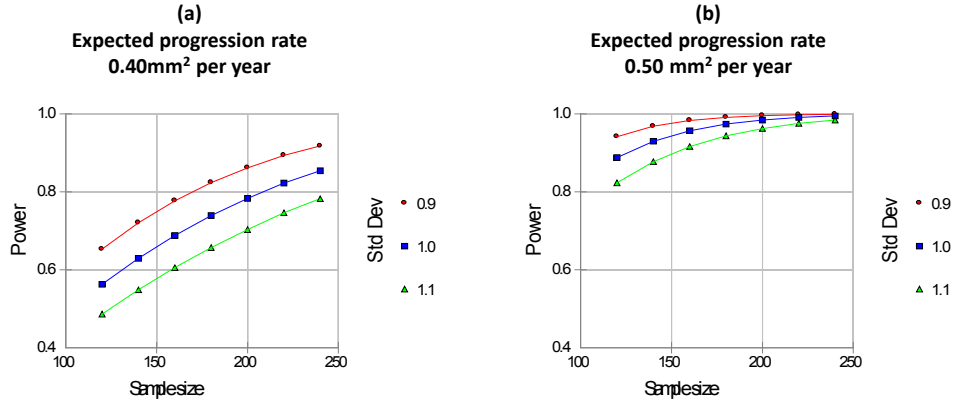
Prior to establishing this study protocol, a feasibility survey was undertaken. The survey consisted of a questionnaire that was sent to the participating centers to determine how many study candidates might be available at each center for this prospective study.

The primary outcome of the study is **the yearly growth in the area of the atrophic lesion** as measured by fundus auto-fluorescence. A recent paper by Chen et al [36] reported that in a group of 24 STGD participants with well defined atrophic lesions at baseline, the mean yearly growth of the lesion was $0.94 \text{ mm}^2 \pm 0.87$.

The reliability of measuring areas of geographic atrophy using images taken with a confocal scanning laser ophthalmoscopy has been described by Deckert et al [37]. Using 2 different readers to examine images from 34 eyes, the mean difference in area affected for the proposed quantification algorithm was 0.12 mm^2 with a 95% confidence interval (0.02, 0.22).

Using the above parameters as a reference, we calculated the power to detect yearly progression for sample sizes between 120 and 240 participants, with standard deviations between 0.9 and 1.1, and expected lesion progression rates of 0.40 and 0.50 mm^2 per year (Figure 7). A clinically meaningful progression rate should be greater than the variability of the measurement. The power calculations were set to test for lesion progression rates above 0.2 mm^2 which is the estimate of the upper bound of the difference that could be attributable solely to measurement error.

Power to detect progression rates for a range of sample sizes and standard deviations with a two-sided significance level $\alpha=0.05$ *



*Assuming that test retest differences could be as high as 0.2

Figure 7: Power calculations for expected lesion progression rates of 0.40 and 0.50 mm² per year

A sample size of 170 achieves 80% power to detect a difference of 0.2 between the null hypothesis mean of 0.2 mm² (measurement error) and the alternative hypothesis mean progression of the lesion of 0.4 mm² with an estimated standard deviation of 0.9 and a significance level $\alpha= 0.05$ using a two-sided Wilcoxon test (Figure 5 (a)). Similarly, if the expected standard deviation increases to 1.0 we need 200 participants to achieve the same level of power. When the expected progression rate is ≥ 0.50 mm², a sample size of 120 participants achieves more than 80% to detect differences beyond the expected measurement error, for standard deviations ≤ 1.1 (Figure 5 (b)).

7.2. Statistical Analyses

Estimating **the yearly growth in the area of the atrophic lesion** as measured by fundus auto-fluorescence:

First exploratory analysis looking at the overall distribution of the outcome at all visits will be carried out, outliers and inconsistent measures will be identified and reviewed. By design, the interval between visits will be variable. For each individual, a slope will be estimated using the available data points by fitting a regression line to the data points. For example, if the i^{th} subject contributes with 3 visits the times $t_{i0}, t_{i,-1}, t_{i,-2}$ with outcome observations $y_{i0}, y_{i,-1}, y_{i,-2}$ will be used to estimate the slope b_i , which will be obtained from the regression $y_{ik}=a+b_i t_{ik}$. ($k=0,-1,-2$). Once the data from each individual has been used to estimate the slope (b), the second stage of the analysis will be to explore which exposures/risk factors determine the heterogeneity of the slopes. Using the slope as the outcome, multivariate regression models will be constructed to identify factors correlating

with progression. Specifically, the correlation to progression of age, severity at first visit, and use of vitamin A supplementation will be examined.

A similar approach to will be used to examine progression over time for the secondary outcomes: retinal thinning, loss of photoreceptors, loss of retinal sensitivity, and changes of BCVA.

7.3. Demographic Characteristics

Demographic characteristics are: date of birth, age, sex, and race. Randomization is not applicable.

7.4. Data Set Descriptions

Study Population

Patients with STGD enrolled into the study shall have had previous genetic testing and a finding of at least 2 pathogenic mutations in the *ABCA4* gene. However, if only one *ABCA4* allele containing a pathogenic mutation is detected, a patient may be enrolled if they have a typical Stargardt phenotype, i.e. at least one eye must have flecks at the level of the retinal pigment epithelium typical of STGD.

Data Sets for Endpoint Analyses

The possible final data sets are illustrated in Figure 5.

7.5. Handling of Missing Data

A requirement for inclusion to the study is that the subject has information on the main outcome for all the eligible visits. We do not expect missing data for the main outcomes because of the study design.

7.6. Safety Analyses

This is an observational study of the natural course of STGD. All investigations included were part of standard of clinical care for patients affected by STGD. Therefore, no study-specific safety events are anticipated.

7.7. Study Drug Compliance

Not applicable

7.8. Interim Analysis

An interim analysis of the study data is not planned.

8. Study Product Management

Not applicable

9. Data Handling and Records Management

Any questions about the protocol or eCRFs will be referred to the sponsor or its representatives, by the Dana Center.

9.1. Data Collection

Study Forms

Most patient data are collected on paper and kept at each individual clinic center. Therefore, in this study, paper copies of the study forms shall be created from an electronic clinical report form (eCRF) that was developed specifically for the study using REDCap software (Appendix 4, Data Collection forms). Once the paper study forms have been completed with patient data, the clinical investigator shall review the data for accuracy and sign their signature to approve the forms.

Once the data are approved by the investigator, the clinic coordinator will log into REDCap using a unique user id and password. When entering a new study participant, the coordinator must first fill out the eligibility form that assigns a unique ID to the participant. If the clinic coordinator is entering data for a participant already enrolled in the study, the coordinator must first enter the participant's ID, and then select the appropriate form. Data are subsequently entered into the forms using 100% double data entry.

The programs developed in REDCap contain a series of data checks within each form to check that:

- a) All entries are within the allowed range.
- b) There is internal consistency (i.e., skip patterns) within each form.
- c) Duplicate entries do not occur.
- d) All required fields are entered; if not, the record is flagged as incomplete.
- e) Double data entry is completed after the first entry to ensure the integrity of the data.
- f) Any reports created indicate any missing or incomplete records.
- g) Reports are issued to help the Clinic Coordinator manage upcoming appointments, and follow-up with missed appointments.
- h) All data entries and changes are logged in an electronic audit trail that tracks who made the change, on what date and time the change was made, and the field name(s) and value(s) of the change. The system also logs any changes made to the structure of the forms by the DCPO DCC.

There are two methods planned in order to transfer imaging data to the Central Reading Center. This is described in detail in a separate standard operating procedure. Generally, imaging data are not compressed.

Option 1: The Reading Center has its own secure servers, where images are to be directly uploaded by the clinic centers

Option 2: Create a CD-DVD to be mailed to the reading center

A member of the study group will document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents
- The date of the visit and the corresponding Visit, Day, or Week in the study schedule
- A general reference to the procedures completed
- A dated signature, or initials, of all clinicians who made an entry in the progress notes.

In addition, any contact with the participant via telephone or other means that provides significant clinical information will also be documented.

Information from the study progress notes and other source documents will be promptly and legibly transcribed to eCRFs for transmission to the data management center.

Any changes to information in the study progress notes, other source documents, and CRFs will be initialed and dated on the day the change is made by a site study staff member authorized to make the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data (e.g., ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change shall be written in the source documentation by the clinician. Correction fluid shall not be used at any time.

9.1.1. Volunteer Identification

Each center shall de-identify patient data. Patient data shall be encoded by a five-digit code number: the first two numbers shall indicate the number of the study center and the last three numbers shall label the patients in an ascending ordinal scale (for example, following patient's enrollment on the study). Data shall be collected using electronic clinical report form (e-CRF) and shall be centrally managed at the Dana Center for Preventive Ophthalmology.

9.1.2. Confidentiality

The data collected during the study had been obtained at the study sites as part of standard clinical care. Charts shall be secured to protect privacy of patients and maintain confidentiality. Clinical data shall be entered on electronic Case Report Forms (eCRFs) for transmission to the coordinating center in accordance with the procedures specified in the current Manual of Standard Operating Procedures (SOPs) for this trial. Data on eCRFs transmitted to the coordinating center shall correspond to, and be supported by, source documentation maintained at the site. All study forms and records transmitted to the

coordinating center shall carry only coded identifiers such that personal identifying information is not transmitted to the coordinating center.

The Johns Hopkins Biostatistics Center (JHBC) servers that host the data are protected by both a hardware firewall and a web application firewall. In addition, they have multi-level intrusion detection, network security audits, and secondary hardware on standby for immediate replacement. JHBC administrators connect to the REDCap servers for system administration using a VPN connection and a two-factor authentication method. All data transmitted between the client browser and REDCap web servers are encrypted using an SSL connection. JHBC system administrators regularly monitor server logs and services to ensure that the servers are secured. They also ensure that server updates are applied in a timely manner and that the data are regularly backed up and stored securely off-site.

Ophthalmic outcome data from the microperimetry, sd-OCT and fundus autofluorescence assessments will be submitted electronically from the site to the Reading Center via secure data upload.

Once processed and analyzed by the Reading Center, the data will be transferred electronically from the Reading Center to the Dana Center system via a secure transfer process. Only coded identifiers will be used to identify participants.

9.1.3. Access

At each site, the site investigator and the personnel designated by him shall have access to source documents. De-identified data shall be collected at the Data Coordinating Center at Johns Hopkins. All site investigators, their designated personnel, study staff at Johns Hopkins University and study staff at the reading center shall have access to the database of de-identified data.

Representatives of the USAMRMC and FFB CRI have the authority to review research records.

9.1.4. Reporting Requirements

The investigators of each site shall take care to meet the requirements for reporting sensitive information to state or local authorities. For example the investigators might seek guidance from their institutional review boards when considering how to report information such as positive human immunodeficiency virus (HIV) status, hepatitis or tuberculosis test results, illegal residency, child or spouse abuse, or participation in other illegal activities.

9.2. Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents shall include, but are not limited to, progress notes, electronic data, screening logs, study worksheets, and data recorded from automated

instruments. All source documents pertaining to this study shall be maintained by the investigators and made available for inspection by authorized persons.

9.3. File Management at the Study Site

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the ICH GCP Guideline.

9.4. Records Retention at the Study Site

The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study, including any data quality queries received from the data management center. Such documentation is subject to inspection by FFB MRI and relevant agencies, such as USAMRMC. If the investigator withdraws from the study, all study related records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given to FFB MRI in writing.

The investigator shall not dispose of any records relevant to this study without written permission from FFB MRI and without providing FFB MRI the opportunity to collect such records. Generally, records are kept for a minimum of ten years

9.5. Data Management Considerations

Data will be stored in the REDCap system (section 9.1).

Every effort shall be made to ensure that data management practices adhere to international standardization of the following data management procedures.

9.5.1. Database Design and Creation

An appropriate database shall be designed and created within a validated Clinical Data Management System (CDMS). This database shall be designed to store the data recorded on the CRFs and shall ensure a one-to-one mapping between the CRF and the electronic copy stored in the system (section 9.1).

9.5.2. Data Coding

Upon completion of CRF data entry, a secondary, in-house clinical review shall be conducted. Adverse event coding shall be undertaken using the current version of the MedDRA dictionary (version 12.1). The version of this dictionary will remain the same throughout the study.

9.5.3. Data Transfer

Data shall be transferred to the Dana Center of Preventive Ophthalmology, Wilmer Eye Institute of the Johns Hopkins University, Baltimore, Maryland. The transfer shall be electronic and shall happen on a defined schedule, in a data format mutually agreed upon by the Dana Center of Preventive Ophthalmology (study central data management center).

9.5.4. Data Validation

After the data have been entered and verified, various edit checks shall be performed to ensure the accuracy, integrity and validation of the database against the CRFs. Inconsistencies that arise from these edit checks shall be resolved with the investigator or designee.

9.5.5. Database Lock

Upon completion of the trial and completion of data entry, verification and validation, the database shall be locked and write access removed.

10. Quality Control and Quality Assurance

10.1. Monitoring

The Data Coordinating Center shall undertake on-site monitoring of study data for the duration of the study. These clinical site monitoring visits shall be conducted during the 6-months study conduct phase. Other clinical site monitoring visits shall be conducted on an as-needed basis. It is anticipated that remote data monitoring of randomly determined data points will be completed by the Data Coordinating Center.

The Data Coordinating Center may also conduct study site visits, on the sponsor's behalf. The study shall be monitored in compliance with the relevant parts of 45 CFR and according to the ICH GCP Guidelines. Site visits shall include, but are not limited to, verifying the presence of required documents, verifying the informed consent process, and comparing case report forms with source documents. Each investigator agrees to participate in site visits conducted at a reasonable time in a reasonable manner. Regulatory authorities may also audit the investigator during or after the study. If a regulatory authority announces an audit, the investigator should contact the sponsor immediately, and must fully cooperate with these audits within a reasonable time in a reasonable manner.

The knowledge of any pending compliance inspection or visit by the DHHS-OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the

regulations or requirements shall be reported immediately to the Study Director, FFBCRI, and USAMRMC ORP HRPO.

FFB CRI has ethical, legal, and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research and GCP principles. As part of a concerted effort to fulfill these obligations FFB CRI study monitors or its designee shall visit the center during the study in addition to maintaining frequent telephone and written communications.

10.2. Auditing

FFB CRI may conduct audits at the study site(s). Audits shall include, but are not limited to, verifying the presence of required documents, verifying the informed consent process, and comparing the case report forms with source documents. The investigator agrees to participate with such audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. If a regulatory authority announces an audit, the investigator should contact FFB CRI immediately, and must fully cooperate with the audits within a reasonable time in a reasonable manner.

11. Ethics and Responsibility

This study shall be conducted in compliance with this study protocol, the ICH GCP Guidelines, the applicable regulatory requirements, and the current Declaration of Helsinki.

11.1. Clinical Study Report

A review report shall be submitted to the local IRB(s) by each of the clinical sites, if required by the host country. A copy of this report and IRB approval notification shall be submitted to the HRPO by the sites as soon as these documents become available. In host countries that do not require an annual IRB report, the site will prepare and submit an annual report summary to HRPO, per HRPO guidelines. A copy of the approved final study report and the central IRB approval notification shall also be submitted to the HRPO by the Sponsor as soon as available.

The report shall include a discussion of the study objectives, methodology, clinical observations and conclusions in relation to the study objectives.

12. Confidentiality

All information generated in this study shall be considered highly confidential and shall not be disclosed to any persons not directly concerned with the study without written prior

permission from FFB MRI. However, authorized HRPO representatives, regulatory officials, and FFB MRI personnel (or their representatives) shall be allowed full access to inspect and copy the records. All participants' materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by FFB MRI. Participants shall be identified only by their unique participant numbers in CRFs. However, their full names may be made known to a regulatory agency or other authorized officials, if necessary.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of participant information.

13. Amendment Policy

The investigator shall not make any changes to this protocol without prior written consent from FFB MRI and subsequent approval by the IRB and HRPO. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), shall be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses shall be fully discussed between the investigator(s), the study director and FFB MRI. If agreement is reached regarding the need for an amendment, it shall be written by FFB MRI. The written amendment shall be submitted to the study central IRB identified with this responsibility (WIRB); upon approval by WIRB, to HRPO and then to each of the clinical sites will submit the amendment to their local IRB for review and approval. Except for 'administrative amendments', investigators shall await IRB approval of protocol amendments before implementing any change(s). Administrative amendments are defined as amendments that have no effect on the safety of the research participants, the scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to participants should be implemented immediately, and the IRB notified within 5 days. FFB MRI shall submit protocol amendments to the HRPO, or other regulatory agencies, as required.

When, in the judgment of the chairman of the local IRB, HRPO, the investigators, the study director and/or FFB MRI, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the participant, the currently approved written informed consent form shall require similar modification. In such cases, a new informed consent shall be obtained from participants enrolled in the study before expecting continued participation.

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Appendix 1 - Agreement

Agreement Signatures

I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I shall personally conduct the study as described herein and in FFB CRI's Clinical Research Agreement.

I shall provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who participate in the study. I shall discuss the protocol with them to assure myself that they are sufficiently informed about the endpoint parameters and the conduct of the study in general to perform the study correctly. I am aware that this protocol must be approved by the local IRB responsible for my Clinical Study Facility and that IRB approval is required prior to commencement of this study. I agree to adhere strictly to the attached protocol unless it is amended in the manner set forth in Paragraph 1 of FFB CRI's Clinical Research Agreement. In that case, I agree to adhere strictly to the amended protocol. I agree that clinical data entered on case report forms by me and my staff shall be used by FFB CRI in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow monitors and auditors, or their designees, full access to all medical records at the research facility for participants screened or enrolled in the study.

I agree to provide all participants with informed consent forms, as required by government and ICH regulations. I agree to report to FFB CRI any adverse experiences in accordance with the terms of FFB CRI, or designee's, Clinical Research Agreement and FDA regulations, 45 CFR 312.64. I further agree to provide all required information regarding financial certification or disclosure to FFB CRI for all investigators and sub-investigators in accordance with the terms of FDA regulation 45 CFR 54. I understand that participation in the protocol involves a commitment to publish the data from this study in a cooperative publication prior to publication of efficacy and safety results on an individual basis.

_____ Signature Site Principal Investigator	_____ Date	_____ Signature Hendrik P.N. Scholl, M.D., M.A. Study Director	_____ Date
_____ Signature Sheila West, Ph.D. Study Biostatistician	_____ Date	_____ Signature Patricia Zilliox, Ph.D. Sponsor Representative	_____ Date

Appendix 2– Additional Institutions and Personnel Involved With the Study

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Appendix 3 – Biosketches of Key Personnel

The biosketches of Key Personnel are attached.

Appendix 4 – Electronic Clinical Report Form (eCRF)

Print version of the electronic clinical report forms are attached