Clinical Trials in Stargardt Disease Treatment

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For the patients that have allowed us the privilege to serve.

Preface

This book is a compendium of the worldwide ocular stem cell, gene therapy, pharmaceutical, and other miscellaneous studies treating Stargardt disease registered with Clinicaltrials.gov. Clinicaltrials.gov is the largest website listing of registered clinical research studies in the world.

The information presented is accurate as of November 2023. I have divided the studies into multiple categories: Completed, Active/Recruiting, Active/Not-Recruiting, Not Yet Recruiting, and Enrolling by Invitation. Regarding study location, United States locations are listed first, followed by other countries in alphabetical order. As studies have many testing sites, frequently in many countries, the sponsor location is used.

I corrected the mischaracterization of studies, only included those that truly belonged within each category, removed extraneous information, and corrected spelling and grammar, in order to produce a consistent and easy-to-read format. The Study and the Clinical Trial number are provided to make it easier for the reader to obtain further information.

I hope that by providing this reference, the field of Stargardt disease treatment will be advanced.

Parkland, FL, USA — Jeffrey N. Weiss

Contents

Chapter 1
Introduction to Stargardt Disease

Karl Stargardt (1875–1927) was a German ophthalmologist and the Chairman of the Department of Ophthalmology at the University of Marburg. In 1909, he described 7 patients with a recessively inherited macular dystrophy and progressive and severe visual loss beginning in the Tables first two decades of life. The eponymous Stargardt disease (STGD) is the most common form of inherited juvenile macular degeneration with a prevalence of 1 to 8000–10,000. There is an association with several different genes:

STGD1: the most common type (95% of cases) is autosomal recessive and caused by mutations in the ABCA4 gene, although it can also be associated with a mutation in CNGB3. Defective ABCA4 affects the ATP-binding cassette transporter protein causing the formation of toxic vitamin A biretinoids. Damaged retinal cells will form lipofuscin in the retinal pigment epithelium, the characteristic finding in this condition. There are over 1000 mutations of ABCA4 known to cause STGD1 and related retinal diseases.

STGD2 was discontinued when it was discovered to be caused by the same gene as STGD3.

STGD3: This is a rare dominant type of Stargardt disease caused by a mutation in the ELOVL4 gene.

STGD4: This type is associated with mutations in PROM1.

Efforts to address the lack of therapy for Stargardt disease have included oral therapy, intravitreal injections, stem cells, and gene therapy.

ALK-001 is a synthetic vitamin A once-a-day pill that prevents the formation of toxic vitamin A dimers in the eye. This form of vitamin A is not readily converted to lipofuscin, slowing its deposition and potentially slowing vision loss. ALK-001 and other vitamin A variants are being explored. However, oral intake of excessive vitamin A has been shown to increase lipofuscin deposition in animal models, possibly worsening the loss of vision in Stargardt disease.

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There are several surgical treatments reported:

1. Ocata therapeutics (previously Advanced Cell Technology) has completed a multicenter trial using retinal pigment epithelial cells derived from human embryonic stem cells. No ocular safety issues were encountered, though side effects from patient immunosuppression were observed. The company was subsequently acquired by Astellas Pharma and follow-up studies are continuing.
2. The Stem Cell Ophthalmology Treatment Study (SCOTS and SCOTS2) reported treating 34 eyes with Stargardt disease using autologous bone marrow-derived stem cells. With a one-year follow-up period, 21 (61.8%) improved, 8 (23.5%) remained stable, and 5 (14.7%) showed continued progression of their disease. The results were statistically significant with $p = 0.0004$. The average central vision improvement following treatment was 17.96% (95%CI, 16.39–19.53%) and ranged up to 80.5%. Of 17 patients treated, 13 (76.5%) showed visual acuity improvement in one or both eyes, 3 patients (17.6%) showed no net loss, and 1 worsened as a consequence of disease progression; 94.1% of patients had improved vision or remained stable. There were no adverse events.

The explanation for using stem cells to treat patients with visual acuity loss of a genetic etiology is that the stem cells may benefit damaged but repairable cells via neuroprotection mechanisms, reduce ongoing immunogenic damage, transfer cytoplasmic structures including mitochondria and lysosomes to damaged cells, and produce neuronal transformation which can fuse with Müller cells to then transdifferentiate into specialized neurons including ganglion and amacrine neurons.

The ABCA4 transporter is located primarily in the retina and is one of multiple ABCA proteins associated with lipid transport across cell membranes. It is responsible for transporting N-retinylidene-PE from the lumen to the cytoplasmic side of the disc membrane, allowing conversion of all-trans retinal to all-trans retinol, which is then transported into the RPE (Retinal Pigment Epithelial) cells. There it converts to 11-cis retinal, which is transported back into the outer segment of the photoreceptor to combine with opsin and regenerate rhodopsin or cone opsin completing the visual cycle.

With an abnormal ABCA4 transporter, removal of the N-retinylidene-PE is impaired which allows it to react with all-trans retinal to form a derivative called A2PE. Because outer segments of the photoreceptors are constantly renewed, RPE cells ingest the A2PE in phagosomes which fuse with lysosomes to degrade. However, A2PE can only be hydrolyzed to N-retinylidene-N-retinyl-ethanolamine (A2E) and cannot be further broken down. A2E accumulates progressively in the RPE cells as a component of lipofuscin. Lipofuscin is a complex combination of oxidized macromolecules which can accumulate in different tissues. With blue light exposure, lipofuscin in the RPE can form epoxides which can cause RPE apoptosis. Ultimately, RPE cell death causes photoreceptor cell death and decreased vision.

The purpose of gene replacement therapy is to attempt to decrease or stop additional retinal tissue loss by targeting photoreceptors. Though the most experience had been obtained with Adeno-associated virus vectors, the ABCA4 gene is larger

than the capacity of the current AAV vector, which makes the lentivirus the vector of choice. A lentivirus vector is being tested.

The multicenter Natural History of the Progression of Atrophy Secondary to Stargardt Disease studies describe the natural history of disease progression. The study determined that the rate of progression was mainly determined by the initial lesion size.

Further Reading

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Chapter 2
Tables

See Tables 2.1, 2.2, 2.3, and 2.4

Table 2.1 Active studies

	UNITED STATES	AUSTRALIA	SPAIN	SWITZERLAND
TOTAL NUMBER OF STUDIES	15	1	1	1
NON-PROPRIETARY	6		1	1
PROPRIETARY	8	1		
SUPPORT				
CORPORATE	8	1		
UNIVERSITY/HOSPITAL/MD			1	1
NEI	6			
NONPROFIT	1			
NO SUPPORT	1			
Phase Not Applicable	7		1	1
Phase 1				
Phase 1/2	3	1		
Phase 2	4			
Phase 2/3				
Phase 3	1			

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Table 2.2 Completed studies

	UNITED STATES	BRAZIL	CHINA	COLUMBIA	EUROPE	UNITED KINGDOM	NO LOCATION
TOTALNUMBER OF STUDIES	11	1	1	1	2	2	1
NONPROPRIETARY	5		1	1	2		
PROPRIETARY	6	1				2	1
SUPPORT							
CORPORATE	5	1				2	1
UNIVERSITY/HOSPITAL/MD	4		1	1	2		
NEI	1						
NONPROFIT	1						
NO SUPPORT							
Phase Not Applicable	4		1	1			
Phase 1	3						1
Phase 1/2	2	1				2	
Phase 2	3						
Phase 2/3							
Phase 3	1						

Table 2.3 Terminated/unknown studies

	UNITED STATES	CHINA	EUROPE	KOREA	UNITED KINGDOM
TOTAL NUMBER OF STUDIES	3	1	2	1	1
NON-PROPRIETARY	2	1	2		1
PROPRIETARY	1			1	
SUPPORT					
CORPORATE	1			1	
UNIVERSITY/HOSPITAL/MD	2	1	2		1
NEI					
NONPROFIT					
NO SUPPORT					
Phase Not Applicable	2		1		1
Phase 1			1	1	
Phase 1/2	1	1			
Phase 2					
Phase 2/3					
Phase 3					

Table 2.4 All studies (Except terminated and unknown)

	UNITED STATES	AUSTRALIA	CHINA	EUROPE	NO LOCATION	SOUTH AMERICA	SPAIN	SWITZERLAND
NUMBER OF STUDIES	27	1	1	4	1	2	1	1
DRUGS	15	1		1	1			
ELECTRICAL	1							
SURGERY	2			1		1		
OBSERVATION/FU	3			1				
TESTING	3			1				
NATURAL HISTORY	3						1	1
TRAINING			1					
ACUPUNCTURE						1		

Chapter 3
Recruiting Studies

Recruiting

United States

Study to Assess the Safety and Efficacy of OCU410ST for Stargardt Disease (GARDian)

ClinicalTrials.gov ID NCT05956626

Sponsor Ocugen
Information provided by Ocugen (Responsible Party)
Last Update Posted 2023-10-25

Study Overview

Brief Summary
This is a Phase 1/2 Study to Assess the Safety and Efficacy of OCU410ST for Stargardt Disease.

This is a multicenter study, which will be conducted in two phases and will enroll up to a total of 42 subjects.

Detailed Description
Name of Investigational Product: OCU410ST Name of Active Ingredient: Adeno-associated viral vector 5 human RORA (AAV5-hRORA)

Title of Study
A Phase 1/2 Study to Assess the Safety and Efficacy of OCU410ST for Stargardt Disease.

Study Center(s)
Approximately five clinical study centers in the US.

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Background
Stargardt disease is an eye disease that causes vision loss in children and young adults. It is an inherited disease caused by faulty genes that cause build up of fat deposits in the eye. Currently, there is no approved treatment available for Stargardt disease.

OCU410ST Product Information
OCU410ST is an Adeno-Associated Virus serotype 5 containing human RORA for the treatment of Stargardt disease. Dysregulation in lipid metabolism, oxidative stress, and anti-inflammatory mechanisms are critical for pathogenesis and progression of Stargardt disease. The role of hRORA in regulating these gene pathways strongly suggests that OCU410ST could restore homeostasis in the eye and thereby serve as a therapeutic candidate for Stargardt disease.

This study will be conducted in two phases enrolling up to 42 subjects.

Phase 1 is a multicenter, open-label, dose-ranging/dose escalation study with a 3+3 design enrolling up to 18 subjects

Phase 2 is a randomized, dose-expansion cohort in which 24 subjects will be randomized in a 1:1:1 ratio into either one of two treatment groups (adults and pediatric subjects) or to an untreated (adults and pediatric subjects) control group.

Official Title
A Phase 1/2 Study to Assess the Safety and Efficacy of OCU410ST for STARGARDT DISEASE

Conditions
Stargardt Disease

Intervention/Treatment
- Genetic: OCU410ST

Other Study ID Numbers
- OCU410ST-101

Study Start (Actual)
2023-08-25

Primary Completion (Estimated)
2025-10-28

Study Completion (Estimated)
2025-10-28

Enrollment (Estimated)
42

Study Type
Interventional

Phase
Phase 1 and Phase 2

Study Contact
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Principal Investigator:
Karl Csaky, MD, PhD

Eligibility Criteria
Description

Inclusion Criteria
- Are aged 18–65.
- Have clinical evidence of a macular lesion phenotypically consistent with Stargardt Disease
- The study eye should have at least one well-demarcated area of atrophy with a minimum diameter of 300 microns and total lesion size <= 18 mmE2 and a BCVA of 50 ETDRS letters or better
- Have confirmed presence of two pathogenic mutations in the ABCA4 gene
- Have detectable outer nuclear layer (ONL) in the macular region tomography (SD-OCT).
- Have BCVA of 50 letters or less (using ETDRS chart)

Key Inclusion Criteria for Pediatric Subjects
- Are aged 6–17.
- Have clinical diagnosis of Stargardt Disease
- The designated primary study eye must have at least one well-demarcated area of atrophy with a minimum diameter of 300 microns and a total lesion area <= 18 mmE2 and a BCVA of 35 ETDRS letters or better.
- Have two (2) pathogenic mutations confirmed present, in the ABCA4 gene.

Key Exclusion Criteria for Adult Subjects
- Have previous treatment with a gene therapy or cell therapy product.
- Have any concurrent retroviral therapy that would inactivate the investigational product.
- Have any contradictions for subretinal injection and the use of anesthesia.
- Have genes that mimic Stargardt Disease, like ELOVL4 or PROM1.

Exclusion Criteria for Pediatric Subjects
- Have previous treatment with a gene therapy or cell therapy product.
- Have any concurrent retroviral therapy that would inactivate the investigational product.
- Have any intraocular surgery (including lens replacement surgery) within 6 months (prior to Screening) and any ophthalmic condition that may require surgery during the study period.
- Have genes that mimic Stargardt Disease, like ELOVL4 or PROM1.

Ages Eligible for Study
6–65 Years (Child, Adult, Older Adult)

Sexes Eligible for Study
All

Accepts Healthy Volunteers
No

Design Details
Primary Purpose: Treatment
Allocation: Randomized
Interventional Model: Sequential Assignment

Interventional Model Description
The study will be conducted in two phases.

Phase 1 is a multicenter, open-label, dose-ranging/dose escalation study. A 3+3 study design will be used for the sequential dose-escalation cohorts in which subjects will receive a single subretinal injection of OCU410ST.

Phase 2 is a dose-expansion phase of the study, where the subjects will be randomized in a 1:1:1 ratio to either one of two treatment groups (adult and pediatric subjects) or to an untreated (adult and pediatric subjects) control group.

Masking: Single (Outcomes Assessor)
Masking Description:
The following team members will be masked:
Bio-Statistician, Data Programmer, Imaging Reading Center Team, Head of Clinical Development, and Medical Affairs.

Arms and interventions

Participant group/arm	Intervention/treatment
Experimental: Experimental: Phase1 Dose Escalation- Low Dose (3.75 × 10E10 vg/mL): Low Dose (3.75 × 10E10 vg/mL): Subjects will receive a subretinal injection of 200 µL of OCU410ST in the low dose concentration.	Genetic: OCU410ST • Subretinal Administration of OCU410ST
Experimental: Experimental: Phase1 Dose Escalation- Medium Dose (7.5 × 10E10 vg/mL): Medium Dose (7.5 × 10E10 vg/mL): Subjects will receive a subretinal injection of OCU410ST in the Medium dose concentration.	Genetic: OCU410ST • Subretinal Administration of OCU410ST
Experimental: Experimental: Phase1 Dose Escalation- High Dose (2.25 × 10E11 vg/mL): High Dose (2.25 × 10E11 vg/mL): Subjects will receive a subretinal injection of OCU410ST in the high-dose concentration.	Genetic: OCU410ST • Subretinal Administration of OCU410ST
Experimental: Experimental: Phase 2 Dose Expansion: Dose 1 from Phase 1-Randomized Adult Arm Subjects will receive a subretinal injection of OCU410ST with Maximum tolerated dose (MTD) from Phase 1.	Genetic: OCU410ST • Subretinal Administration of OCU410ST
Experimental: Experimental: Phase 2 Dose Expansion: Dose 1 from Phase 1-Randomized Pediatric Arm Subjects will receive a subretinal injection of OCU410ST with Maximum tolerated dose (MTD) from Phase 1.	Genetic: OCU410ST • Subretinal Administration of OCU410ST
Experimental: Experimental: Phase 2 Dose Expansion: Dose 2 from Phase 1-Randomized Adult Arm Subjects will receive a subretinal injection of OCU410ST with Lower Dose than Maximum tolerated dose (MTD) from Phase 1	Genetic: OCU410ST • Subretinal Administration of OCU410ST
Experimental: Experimental: Phase 2 Dose Expansion: Dose 2 from Phase 1-Randomized Pediatric Arm Subjects will receive a subretinal injection of OCU410ST with Lower Dose than Maximum tolerated dose (MTD) from Phase 1	Genetic: OCU410ST • Subretinal Administration of OCU410ST
No Intervention: No Intervention- Randomized Control Adult Arm No Intervention Control Arm: Subject will not receive any active study intervention	
No Intervention: No Intervention- Randomized Control Pediatric Arm No Intervention Control Arm: Subject will not receive any active study intervention	

Primary outcome measures

Outcome measure	Measure description	Time frame
Safety (Participants With Ocular and Non-ocular AEs (Adverse Events) and SAEs (Serious Adverse Events))	The primary endpoint is safety, determined by the number of ocular and non-ocular Study Drug-related adverse events (SDAE), treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs).	12 months (Screening to 12 months post-OCU410ST administration)
Ophthalmic Safety: Change From Baseline in BCVA (Best-Corrected Visual Acuity)	Visual function of the study eye was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best-Corrected Visual Acuity (BCVA) letter score. A higher score represents better vision.	12 months (Screening to 12 months post-OCU410ST administration)
Ophthalmic Safety: Ophthalmoscope Measurements	We will use Slit-lamp Biomicroscopy to visualize the anatomy of ocular structures before and after subretinal injections and follow-up visits.	12 months (Screening to 12 months post OCU410ST administration)
Ophthalmic Safety: Change in the Intraocular Pressure (mmHg)	Measured by applanation or rebound tonometry with confirmation with Goldmann tonometer if IOP is outside normal range (8–21mmHg).	12 months (Screening to 12 months post-OCU410ST administration)
Change Using Qualitative and quantitative assessments of autofluorescence pattern (FAF)	Changes in the intensity of FAF will be evaluated from the baseline measurements, to assess the loss of retinal layers.	12 months (Screening to 12 months post-OCU410ST administration)
Ophthalmic Safety: Changes in Full Field ERG	The International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines will be followed for conducting ff-ERG (Full-field Electroretinography)	12 months (Screening to 12 months post-OCU410ST administration)

Secondary outcome measures

Outcome measure	Measure description	Time frame
Humoral and cellular immune response	Blood samples will be collected for the assessment. The secondary safety endpoints include change from baseline in Humoral and cellular immune response in response to OCU410ST administration	12 months (Screening to 12 months post-OCU410ST administration)
Shedding of Viral Vector	Blood samples will be collected for the assessment to determine AAV vector shedding in systemic circulation after OCU410ST administration	12 months (Screening to 12 months post-OCU410ST administration)

Outcome measure	Measure description	Time frame
Change in laboratory parameters for Hematology	Blood samples will be collected to determine any significant change in hematology parameters including hematocrit, hemoglobin, red and white blood cell count, and any other parameters deemed necessary by study investigator from baseline after OCU410ST administration.	12 months (Screening to 12 months post-OCU410ST administration)
Change in laboratory parameters for Serum Chemistry	Blood samples will be collected to determine any significant change in serum chemistry parameters including electrolytes, renal functions, liver functions, comprehensive metabolic panel, and any other parameters deemed necessary by study investigator from baseline after OCU410ST administration.	12 months (Screening to 12 months post-OCU410ST administration)

Other outcome measures

Outcome measure	Measure description	Time frame
Changes in macular thickness on Spectra Domain Optical Coherence Tomography (SD-OCT)	The change in the macular thickness will be measured by spectral domain optical coherence tomography (SD-OCT)	12 months (Screening to 12 months post-OCU410ST administration)
Change in Quality-of-life measure using NEI VFQ-25 (Adult subjects only)	The National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ25) questionnaires will be administered to assess the impact of vision on quality of subject's life.	12 months (Screening to 12 months post-OCU410ST administration)

Sponsor
Ocugen

Collaborators
No information provided

Investigators
- Study Director: Huma Qamar, MD, MPH, CMI, Ocugen., Inc.

General Publications
No publications available