Official Title: Phase I/IIa Dose Escalation Safety and Efficacy Study of Human Embryonic Stem Cell-Derived Retinal Pigment Epithelium Cells Transplanted Subretinally in Patients With Advanced Dry-Form Age-Related Macular Degeneration (Geographic Atrophy)

NCT Number: NCT02286089

Document Date: Protocol Amendment 14: 09-April-2019

Study Title: Phase I/IIa Dose Escalation Safety and Efficacy Study of Human Embryonic Stem Cell-Derived Retinal Pigment Epithelium Cells Transplanted Subretinally in Patients with Advanced Dry-Form Age-Related Macular Degeneration (Geographic Atrophy)

Clinical Phase:	I/IIa
Sponsor Details:	Cell Cure Neurosciences Ltd. / BioTime, Inc. Suite 500 Jerusalem BioPark Building Hadassah Ein Kerem, Jerusalem POB 12247 Jerusalem 91121 Israel And 1010 Atlantic Avenue, Suite 102 Alameda, CA 94501 USA
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Protocol Number:	CCN_CT02
Amendment number	14
Dated:	9 April 2019
Issue:	FINAL

This clinical study will be conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs), this protocol, current Good Clinical Practice (GCP), the provisions of International Conference on Harmonization (ICH) Guidelines and all local applicable laws and regulations.

CONFIDENTIAL
The information in this document is considered privileged and confidential and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Ethics Committee (EC) approval, written informed consent and the approval of local regulatory authorities as required by local law.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AMD	Age-Related Macular Degeneration
AST	Aspartate Aminotransferase
BCVA	Best Corrected Visual Acuity
BDNF	Brain-Derived Neurotrophic Factor
[redacted]	[redacted]
CA	Cancer Antigen
CEA	Carcinoembryonic Antigen
CFP	Color Fundus Photography
CMV	Cytomegalovirus
CNV	Choroidal Neovascularization
CNTF	Ciliary Neurotrophic Factor
CoA	Certificate of Analysis
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ESR	Erythrocyte Sedimentation Rate
EBs	Embryoid Bodies
EBV	Epstein–Barr Virus
ECG	Electrocardiogram
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study

Abbreviation	Definition
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence (imaging)
fCNV	Foveal Choroidal Neovascularization
FGF	Fibroblast Growth Factors
FRI	Functional Reading Independence (FRI) Index
G	Gauge (Needle wire gauge)
GA	Geographic Atrophy
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GMP	Good Manufacturing Practice
GTT	Guttae (Drops)
Gr	Gram
HBsAg	Hepatitis B Surface Antigen
HCVAb	Hepatitis C Virus Antibody
H&E	Hematoxylin and Eosin stain
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hESCs	Human Embryonic Stem Cells
HLA	Human Leukocyte Antigen(s)
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IFU	Instructions for Use
IgM	Immunoglobulin M
INR	International Normalized Ratio (of prothrombin time of blood coagulation)
IOP	Intraocular Pressure
iPSCs	Induced Pluripotent Stem Cells
IR	Infrared
IRB	Institutional Review Board
IRF	Intraretinal Fluid
LDH	Lactic Dehydrogenase

Abbreviation	Definition
[redacted]	[redacted]
MEF	Mouse Feeder Cells
MITF	Microphthalmia-associated Transcription Factor
mL	Milliliter
MM	Medical Monitor
mm	Millimeter
MTD	Maximally Tolerated Dose
NCI	National Cancer Institute
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
ng	Nanogram
[redacted]	[redacted]
OCT	Ocular Coherence Tomography
OD	Oculus Dexter (the right eye)
OKR	Optokinetic Reflex
[redacted]	[redacted]
OS	Oculus Sinister (the left eye)
OU	Oculus Utergue (both eyes)
PD	Project Director
PED	Pigment epithelial detachment
PEDF	Pigment Epithelium-Derived Factor
PMEL17	Premelanosome protein
PO	Per Os (by mouth)
POS	Photoreceptor Outer Segments
PSA	Prostate Specific Antigen
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PVR	Proliferative Vitreo-Retinopathy
QC	Quality Control
QoL	Quality of Life
qPCR	quantitative Polymerase Chain Reaction

Abbreviation	Definition
[redacted]	[redacted]
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography
SRF	Sub Retinal Fluid
SLE	Slit Lamp Examination
[redacted]	[redacted]
TGF	Transforming Growth Factor
UTCs	Umbilical Tissue-derived Cells
VEGF	Vascular Endothelial Growth Factor

Approval of Clinical Research Protocol No. CCN_CT02 – Amendment #14

Phase I/IIa Dose Escalation Safety and Efficacy Study of Human Embryonic Stem Cell-Derived Retinal Pigment Epithelium Cells Transplanted Subretinally in Patients with Advanced Dry-Form Age-Related Macular Degeneration (Geographic Atrophy)

Approved by:

[redacted], Clinical — Date

[redacted], MD — Date
Medical Monitor

[redacted], DVM, MS, PhD — Date
[redacted], Clinical and Medical Affairs

Confidentiality and Investigator's Agreement

Date:	09 April 2019	
Sponsor's details:	Cell Cure Neurosciences Ltd. Jerusalem BioPark Hadassah Ein Kerem POB 12247 Jerusalem 91121 Israel	BioTime, Inc. 1010 Atlantic Ave., Suite 102 Alameda, CA, USA
Protocol number:	Clinical Protocol No. CCN_CT02	
Protocol title:	Phase I/IIa Dose Escalation Safety and Efficacy Study of Human Embryonic Stem Cell-Derived Retinal Pigment Epithelium Cells Transplanted Subretinally in Patients with Advanced Dry-Form Age-Related Macular Degeneration (Geographic Atrophy)	

The information contained in this document and all information provided to you related to OpRegen® [redacted] are confidential and proprietary information to the respective companies and except as may be required by federal, state or local laws or regulations, may not be disclosed to others without prior written permission of the companies. However, the Principal Investigator (PI) may disclose such information to supervised individuals working on the study, provided the individuals agree to be bound to maintain the confidentiality of such information.

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for safely conducting the study. I will ensure that all individuals assisting me in the conduct of this study have access to the study protocol and any amendments and are aware of their obligations.

I will conduct this study in strict accordance with this protocol and according to the current GCP regulations and will attempt to complete the study within the time designated.

I will provide copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to ensure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all subject information (CRFs, shipment and drug return forms, and all other information collected during the study) in accordance with the current GCP and local regulations.

_____ _____

[*Principal Investigator*] Signature Date

_____

[*Print Principal Investigator Name and Title*]

1. STUDY SYNOPSIS

Protocol Number

CCN_CT02

Protocol Title

Phase I/IIa Dose Escalation Safety and Efficacy Study of Human Embryonic Stem Cell-Derived Retinal Pigment Epithelium Cells Transplanted Subretinally in Patients with Advanced Dry-Form Age-Related Macular Degeneration (Geographic Atrophy)

Sponsor

Cell Cure Neurosciences Ltd./BioTime, Inc.

Study Centers and Planned Geographical Distribution

Multicenter multinational trial

Clinical Phase

Phase I/IIa study

Investigational Product

OpRegen® is a cell-based product composed of retinal pigment epithelium (RPE) cells, derived from human embryonic stem cells (hESCs) through a process of directed differentiation. OpRegen® can be implanted as a single cell suspension to form a targeted suspension of $50x10^3$ to $200x10^3$ in a total volume of 50-100 µL in either an ophthalmic [redacted][1]

Study Duration

- Screening period of up to [redacted].
- Part 1: Eligible subjects will be enrolled into Part 1 of the trial for approximately 52 weeks (up to ±14 days) for a post-implantation follow up assessment.
- Part 2: Following the successful completion of Part 1 of the study, subjects will continue into Part 2 defined as the long term follow up with evaluations at [redacted], [redacted]

Study Objectives

Primary Objectives

To evaluate the safety and tolerability of human embryonic stem cell-derived retinal pigment epithelium cells (OpRegen®), transplanted subretinally to subjects with advanced dry age-related macular degeneration (AMD) with geographic atrophy (GA).

Secondary Objectives

To evaluate the preliminary efficacy of OpRegen® treatment by assessing the changes in ophthalmological parameters as measured by various methods of primary clinical relevance.

[1] Refer to Section 2.3 in the Investigator Brochure for more information about the Product Description

[redacted]

Study Endpoints

Safety and Tolerability Endpoints

Safety and tolerability of OpRegen® treatment will be assessed by:

- Incidence and frequency of treatment emergent adverse events (AEs)
- Treatment emergent changes in the following variables:
  - Vital signs
  - Hematology/ Blood Chemistry/ Urinalysis
  - Physical examination
  - Ophthalmological evaluations including:
    - ✓ Best Corrected Visual Acuity (BCVA)
    - ✓ Dilated Fundus Exam
    - ✓ Intraocular Pressure (IOP)
    - ✓ Slit Lamp Examination (SLE)
    - ✓ Spectral Domain Optical Coherence Tomography (SD-OCT)
    - ✓ Fluorescein Angiography (FA)
    - ✓ Microperimetry
    - ✓ Fundus Autofluorescence (FAF)
    - ✓ Color Fundus Photography (CFP)

[redacted]

Efficacy Endpoints of Clinical Relevance

Preliminary efficacy assessments will utilize the below listed parameters:

- Directional change in the geographic atrophy (GA) lesion area over time
- Overall change in the GA lesion area of the study eye over time using SD-OCT and FAF
- Change from baseline over time in BCVA as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) chart
- Change from initial assessment over time in retinal sensitivity (as assessed by microperimetry)
- Change from baseline over time in Reading Speed Test
- Change from baseline over time in Low Luminance BCVA
- Correlation assessment between quantitative metrics derived from FAF, SD-OCT and CFP images
- Correlation assessment between functional and structural changes
- Change over time in National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) Quality of Life (QoL) score
- Change over time in Functional Reading Independence (FRI) Index score

Study Hypothesis

Implantation of OpRegen® to subjects with advanced dry-form AMD with GA is safe, well-tolerated and provides preliminary efficacy evidence.

Study Design

Open-label, dose escalation study of approximately 24 subjects with advanced dry-AMD and GA divided into cohorts:

Cohorts 1 – 3
The first 2 cohorts, each consisting of 3 eyes of 3 legally blind subjects with best corrected visual acuity of 20/200 or less in the study eye, will receive a single subretinal implantation of OpRegen®.

The third cohort will include up to 6 eyes of 6 subjects with best corrected visual acuity of 20/200 or less in the study eye, who will receive a single subretinal implantation of OpRegen®.

Staggered intervals within and between cohorts will be applied to ensure subjects safety and welfare.

Cohort 4

The fourth cohort will include approximately 12 eyes from 12 subjects with BCVA between 20/64 and 20/250 in the study eye, who will receive a single subretinal targeted implantation of OpRegen®.

Cohort 4 will include two formulations; subjects will be treated with either OpRegen® BSS Plus or OpRegen® 'Thaw-and-Inject' (TAI) formulation, which is based on the use of CryoStor® 5, a serum-free, animal-free GMP grade cryopreservation solution. Additionally, this Cohort includes two options for subretinal delivery systems: DORC[2] or the Orbit SDS (an FDA 510K class II device cleared under K182274 on 20 November 2018). Please refer to the instructions for use (IFU) for each device for more information.

Staggered intervals will be applied between at least the first two subjects of each delivery modality to ensure subject safety and welfare.

[redacted]

[redacted]

All Cohorts

The study is being conducted in participants with confirmed bilateral GA (Study Eye and Non-Study, Fellow Eye).

Between cohorts and subjects, where applicable, the next step to proceed will be per Data Safety Monitoring Board (DSMB) recommendation, based on accumulated safety data.

Cell suspension will be delivered into the subretinal space in the macular area as described in the IFU and operating manuals for each delivery device. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Along with the relevant surgical procedure, subjects will receive systemic immunosuppression [redacted], consisting of the following:

- [redacted]
- Systemic (PO) tacrolimus 0.01 mg/kg daily [redacted] up to 6 weeks post transplantation, [redacted]
- Systemic (PO) mycophenolate mofetil, up to 2 gr/day, [redacted] for at least three months [redacted] post transplantation, [redacted]

During Part 1 of the study, subjects will be assessed at pre-scheduled intervals throughout the [redacted] following the implantation of OpRegen®. Any side effects related to the immunosuppressive treatment will be monitored and followed up (e.g. improve blood pressure control if hypertension develops). In the case of uncontrollable side effects, treatment with the immunosuppressive agents described above will be modified in consultation with the Medical Monitor.

Part 2 of the study includes long term follow-up visits that will occur at [redacted]

Study Population and Number of Subjects

The study will enroll a total of approximately 24 subjects, 50 years and older with non-neovascular (dry) age-related macular degeneration (AMD), who have funduscopic findings of geographic atrophy in the macula, BCVA of 20/200 or less (legally blind) in cohorts 1-3, and between 20/64 and 20/250 in cohort 4 in the (worse) study eye and the absence of additional concomitant ocular disorders.

Inclusion/Exclusion Criteria for Cohorts 1 – 3

Inclusion Criteria

1. Age 50 and older.
2. Diagnosis of dry- (non-neovascular) AMD in both eyes.
3. Funduscopic findings of dry-AMD with progressive geographic atrophy in the macula, [redacted]

4. Best corrected central visual acuity equal or less than 20/200 in the study eye by ETDRS vision testing.
5. Vision in the non-operated eye must be better than or equal to that in the operated eye.
6. Subjects with sufficient good health that can participate in all study-related procedures and complete the study follow-up period (based on medical records).
7. Ability to undergo a vitreoretinal surgical procedure under monitored anesthesia care.
8. Blood counts, blood chemistry, coagulation and urinalysis without abnormal significance.
9. Negative for HIV, HBC, and HCV. Negative for CMV IgM and EBV IgM.
10. Willing to defer donation of blood and tissues.
11. Able to understand study procedures and willing to sign informed consent.

Exclusion Criteria:

1. Evidence of neovascular AMD by history, as well as by clinical exam, fluorescein angiography (FA), or ocular coherence tomography (OCT) at baseline in either eye.
2. History or presence of diabetic retinopathy, vascular occlusions, uveitis, Coat's disease, uncontrolled glaucoma, cataract or media opacity preventing posterior pole visualization or any significant ocular disease other than AMD that has compromised or could compromise vision in the study eye and confound analysis of the primary outcome.
3. History of retinal detachment repair in the study eye.
4. Axial myopia greater than -6 diopters.
5. At least 2 months following cataract removal in the study eye and Yttrium Aluminum Garnet (YAG) laser capsulotomy in the study eye in the past 4 weeks and any other ocular surgery in the study eye in the past 3 months prior to OpRegen® implantation.
6. History of cognitive impairment or dementia.
7. Contraindication for systemic immunosuppression.
8. History of any condition other than AMD associated with choroidal neovascularization in the study eye (e.g. pathologic myopia or presumed ocular histoplasmosis).
9. Any type of systemic disease or its treatment, in the opinion of the Investigator, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.
10. For female subjects; pregnancy or breastfeeding.
11. Current participation in another clinical study. Past participation (within 6 months) in any clinical study of a drug administered systemically or to the eye.
12. Currently receiving aspirin, aspirin-containing products and/or any other coagulation modifying drugs which cannot be discontinued 7 days prior to surgery
13. History of cancer (other than a non-melanoma skin cancer). For cancers in remission for more than five years, enrollment is allowed with concurred documented approval of principal investigator and oncologist prior to enrollment.[3]

Note: "Live" attenuated vaccination prohibited during active systemic immunosuppression.

[3] In the case of any suspected malignancies at screening, patient should be referred to appropriate medical specialist.

Inclusion/Exclusion Criteria for Cohort 4

Inclusion Criteria

1. Age 50 and older.
2. Diagnosis of dry- (non-neovascular) AMD in both eyes.

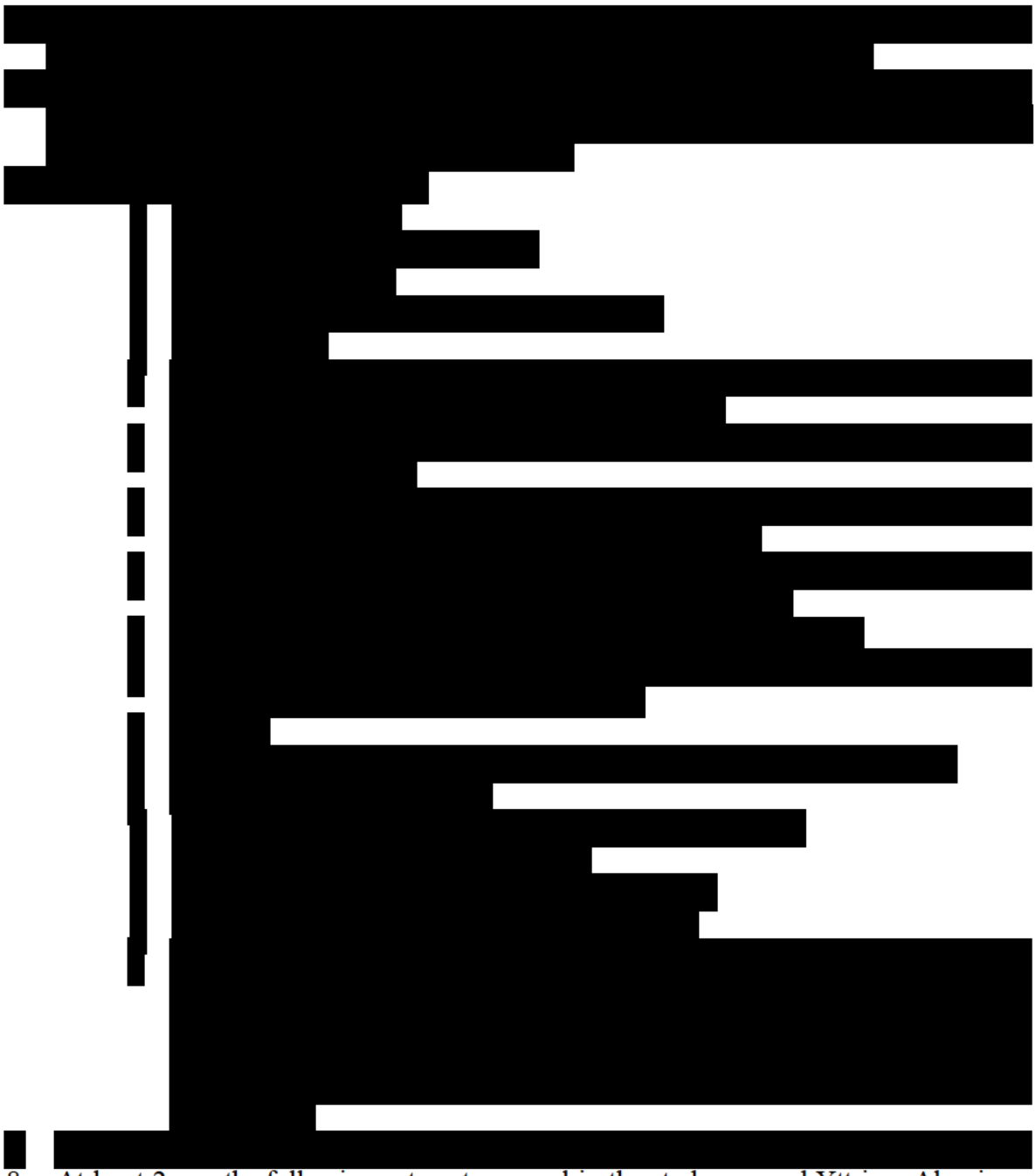
[redacted]

11. BCVA letter score of ≥ 29 letters and ≤ 64 letters (Snellen equivalent of 20/64 – 20/250) in treated eye using ETDRS charts at starting distance of 4m.
12. Visual acuity as measured by ETDRS in the non-operated eye must be better than or equal to that in the operated eye.
13. Subjects with sufficient good health that can participate in all study-related procedures and complete the study follow-up period (based on medical records).
14. Ability to undergo a vitreoretinal surgical procedure under monitored anesthesia care.
15. Blood counts, blood chemistry, coagulation and urinalysis without abnormal significance.
16. Negative for TB, HIV, HBC, and HCV. Negative for acute or reactivated CMV IgM and EBV IgM or asymptomatic in the opinion of the investigator.
17. Willing to defer donation of blood and tissues.
18. Able to understand study procedures and willing to sign informed consent.

Exclusion Criteria:

1. Evidence of neovascular AMD by history, as well as by clinical exam, fluorescein angiography (FA) at ocular coherence tomography (OCT) at baseline in either eye.

[redacted]



8. At least 2 months following cataract removal in the study eye and Yttrium Aluminum Garnet (YAG) laser capsulotomy for both eyes. Any other ocular surgery in either eye in the past 3 months prior to OpRegen® implantation.
9. Current participation in another clinical study of an active drug (placebo and sham will be allowed). Past participation (within 6 months) in any clinical study of a drug administered systemically (except for vitamins and minerals) or to the eye.
10. History of cognitive impairment or dementia
11. Contraindication for systemic immunosuppression
12. Any type of systemic disease or its treatment, in the opinion of the Investigator, including any medical condition (controlled or uncontrolled) that could be expected to

progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.

13. For female subjects; pregnancy or breastfeeding
14. Currently receiving aspirin, aspirin-containing products and/or any other coagulation modifying drugs which cannot be discontinued 7 days prior to surgery
15. History of cancer (other than a non-melanoma skin cancer). For cancers in remission for more than five years, enrollment is allowed with concurred documented approval of principal investigator and oncologist prior to enrollment.[4]
16. Known allergy to any of the study medications or formulations
17. Inability to comply with study or follow-up procedures
18. Inability to obtain CFP, FAF, OCT/OCTA and microperimetry of sufficient quality to be analyzed and graded by the Central Reading Center

Note: "Live" attenuated vaccination prohibited during active systemic immunosuppression.

Final decision for subject eligibility upon confirmation of Central Reading Center and the Sponsor.

Statistical Considerations

As this is an open label, phase I/IIa dose escalation, safety, tolerability and preliminary efficacy study, neither power assessment, nor formal hypotheses testing are currently planned for study outcome measures.

The planned sample size of approximately 24 treated eyes, [redacted], with targeted doses of $50x10^3$ and up to $200x10^3$ cells, is considered clinically appropriate for further characterization of the safety, tolerability and preliminary efficacy of OpRegen in the treatment of subjects with advanced dry-form AMD with GA.

Comprehensive interim reports of accumulated safety, tolerability and preliminary available efficacy data will be presented to the independent Data Safety Monitoring Board (DSMB) prior to escalation to the next to come study dose and to enrolment of the next to come study cohort. Between cohorts, and subjects if applicable, the next step to proceed will occur per DSMB recommendation, based on accumulated safety data.

All measured variables and derived parameters will be listed individually and if appropriate, presented in summary tables by dose regimen group and overall, providing sample size, absolute and relative frequency for categorical variables, or sample size, arithmetic mean, standard deviation, median, minimum and maximum for continuous variables. Confidence intervals will be presented for the efficacy endpoints for exploratory purposes only. Complete analyses to be prospectively performed will be outlined in a separate statistical analysis plan (SAP).

[4] In the case of any suspected malignancies at screening, patient should be referred to appropriate medical specialist.

2. STUDY SCHEME

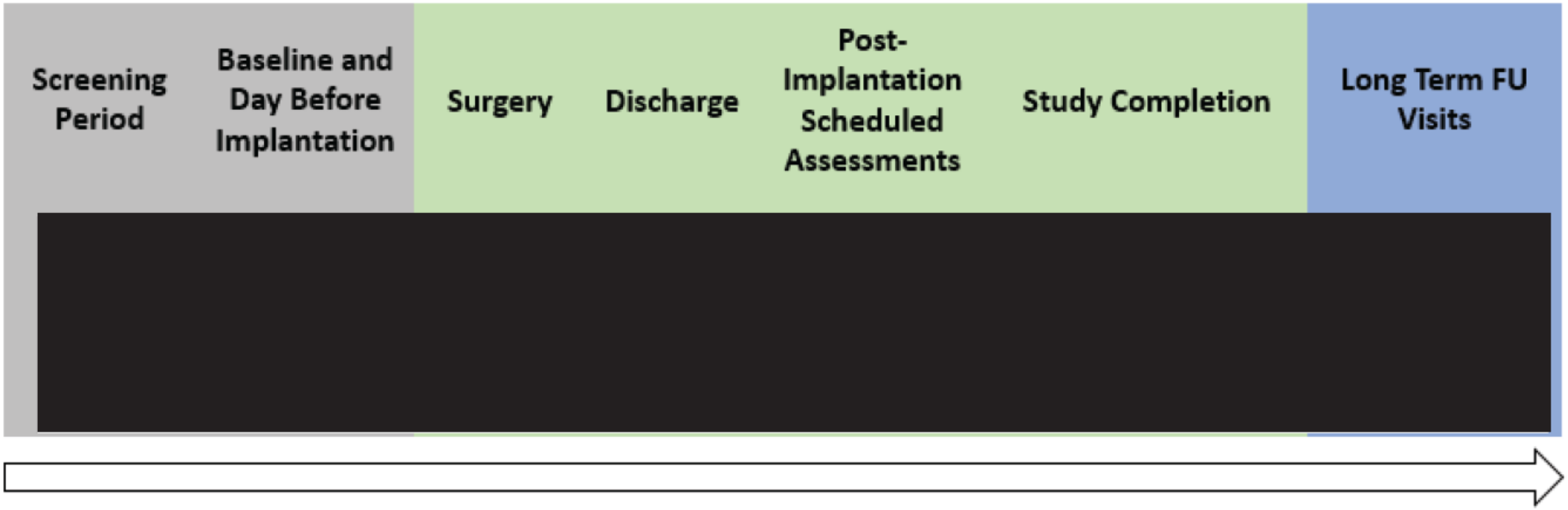


Figure 1: CLINICAL STUDY SCHEME

3. SCIENTIFIC BACKGROUND

3.1 OVERVIEW

OpRegen consists of retinal pigment epithelium (RPE) cells that were produced by directed differentiation of a human embryonic stem cell (hESC) line and are suspended in injection solution to be implanted subretinally.

The Sponsor intends to carry out a Phase I/IIa study of OpRegen in subjects with GA, the advanced form of dry-AMD, to address the safety of this therapeutic cell formulation product and to obtain initial indications of any potentially clinically significant efficacy.

This clinical trial will be conducted in accordance with the standards of Good Clinical Practice (GCP) and International Conference on Harmonization guidelines, applicable government regulations and the institutional research policies and procedures. This protocol along with the Investigators' Brochure, Informed Consent and other supporting documentation will be submitted to the Institutional Review Board (IRB) and regulatory authorities, for review and formal approval prior to subject enrollment.

4. BACKGROUND

4.1 PROPOSED INDICATION

AMD is a progressive chronic disease of the central retina and a leading cause of vision loss worldwide. Most visual loss occurs in the late stages of the disease due to one of two processes: neovascular ("wet") AMD and geographic atrophy (GA, "dry"). In GA, progressive atrophy of the retinal pigment epithelium, choriocapillaris, and photoreceptors occurs (Lim, et al. 2012). The dry form of AMD is more common (85-90% of all cases), but may progress to the "wet" form, which, if left untreated, leads to rapid and severe vision loss (Nowak 2006).

The pathogenesis of the disease involves abnormalities in four functionally interrelated tissues, RPE, Bruch's membrane, choriocapillaris and photoreceptors. However, impairment of RPE cell function is an early and crucial event in the molecular pathways leading to clinically relevant AMD changes (Nowak 2006). Refer to the Investigator's Brochure, Section 1.1.1 for more information.

4.2 THE RETINAL PIGMENT EPITHELIUM AND ITS CHARACTERISTICS

Description and characteristics of RPE cells are presented in the Investigator's Brochure in Section 1.1.2.

4.3 TREATMENT APPROACHES

There is currently no effective or approved treatment for dry-AMD. Prophylactic measures include vitamin/mineral supplements. These reduce the risk of developing wet AMD but do not affect the development of progression of GA.

There are currently no FDA approved treatments for GA secondary to AMD. GA is a chronic, progressive condition that leads to central blind spots and often, permanent loss of vision.

The development of several investigational agents has been halted because of disappointing results, however intensive AMD research continues, raising hopes for improved treatments. Though multifactorial, the underlying mechanism of non-neovascular AMD (dry-AMD) is the death of RPE cells. The RPE comprise a single layer of cells, which perform many functions necessary for healthy photo transduction (Strauss O 2005) and any dysfunction in these activities may lead to vision loss. Cell transplantation of healthy RPE to replace dystrophic or lost RPE has been considered a potential therapy to preserve or even restore vision loss.

The Sponsor uses a GMP-compliant hESC line, ethically approved for inclusion in the NIH Human Embryonic Stem Cell Registry, for derivation of the RPE cells, using the directed differentiation approach, described in the subsequent section.

4.3.1 Background on hESC Derived RPE Cells

Two general approaches have been used to obtain RPE cells from hESCs, spontaneous differentiation and directed differentiation. More information regarding hESC derived RPE cells can be found in section 1.1.3 of the Investigator's Brochure.

4.3.2 Derivation of OpRegen

As described in the IB (Section 1.1.3), the transplantation of RPE cells has long been considered as a possible therapy for attenuating disease progression and improving vision in AMD (Binder S, Stanzel BV, et al. 2007, da Cruz L, et al. 2007, Lund RD, et al. 2006). hESCs can serve as a potential unlimited source of RPE cells that may overcome the restrictions of limited supply. An overview of the Sponsor's directed differentiation protocol can be found in Section 2.4 of the IB.

6. RATIONALE FOR CLINICAL STUDY DESIGN AND DOSAGES

This is a first-in-man study to evaluate safety and efficacy of OpRegen, transplanted subretinally in subjects with advanced form of dry-AMD. The study is designed as a single-arm, dose escalation, multiple-cohort trial.

The rationale for key study design components is provided in the following sections.

6.1 STUDY POPULATION

The rationale for the study population is based on the Sponsor's goal of testing of the safety and exploration of the efficacy of OpRegen in subjects with dry-AMD. For the sake of safety and for ethical reasons, the first three cohorts include legally blind subjects with BCVA of 20/200 or less. The fourth study cohort includes subjects with BCVA between 20/64 and 20/250, where measures of GA progression and changes in visual acuity and other functional outcomes may be more efficiently applied and interpreted.

6.2 COHORT SIZE

The proposed cohort size is comparable with the expected amount of risk and should be sufficient to demonstrate safety and tolerability of OpRegen in the chosen population. Exploration of the efficacy measures will be performed in the fourth cohort of approximately 12 subjects (12 eyes) and may be used in designing the future clinical studies of OpRegen.

6.3 STUDY ENDPOINTS

The measures chosen to evaluate the safety and tolerability of OpRegen and the surgical procedure during and after implantation take into account the cellular characteristics of OpRegen and the implantation procedure. Clinical endpoints include rate of GA progression, retinal sensitivity to light and changes in visual acuity. These measures are acceptable in the ophthalmology field for assessment of retinal and macular function in dry-AMD with GA (O'hEineachain R).

6.4 DOSAGE

The clinical targeted dosages of up to $200x10^3$ are considered feasible based on the results of the pre-clinical studies. [redacted]

6.5 STAGGERED ENROLLMENT

The targeted doses of $50x10^3$ and up to $200x10^3$ cells will be implanted sequentially, with staggered intervals as follows:

- In the first cohort there will be a staggered interval of six weeks between the first and second subjects, and four weeks between the second and third subjects.

[redacted] After the meeting, the DSMB will provide their recommendation for cohorts 1-3 to pursue one of the following alternatives: proceed to the next higher dose; stop dose escalation; investigate a lower dose; or repeat a dose level.

Based on the previous pre-clinical experience and common clinical practice with dry-AMD subjects and cell-therapy treatments, proposed staggered intervals should allow monitoring and investigation of adverse events, prior to exposure of additional subjects to the product. The staggered interval between cohorts and subjects allows sufficient safety assessment prior to exposing subjects to the next higher dose of OpRegen and before initiation of treating subjects with better visual function.

6.6 SUBRETINAL ROUTES OF ADMINISTRATION

6.6.1 Vitrectomy and Retinotomy

The subretinal implantation of cells is customarily accomplished with a conventional partial vitrectomy followed by retinotomy. Pars plana vitrectomy (PPV) has become an important tool in vitreoretinal surgery and in the treatment of retinal disease. The traditional 3-port procedure is well-known to retina specialists and is performed with microsurgical equipment resulting in incisions that are usually self-sealing. The vitreous is gently removed with a vitreous cutter and the cell suspension of OpRegen is implanted subretinally through a small retinotomy. The wound is self-healing. The procedure can be visualized through the dilated pupil with a special wide-field lens. Although vitrectomy is useful to diagnose and treat many retinal diseases, it is not without challenge, most notably clouding of the lens as a result of perturbations to the vitreous and potential egress of implanted cells through the retinotomy site until healed.

[redacted]

[redacted]

7. STUDY OBJECTIVES, HYPOTHESIS AND STUDY ENDPOINTS

7.1 HYPOTHESIS

Implantation of OpRegen to subjects with advanced dry-form AMD with GA is safe, well-tolerated and provides preliminary efficacy evidence.

7.2 STUDY OBJECTIVES

7.2.1 Primary Objectives

To evaluate the safety and tolerability of human embryonic stem cell-derived retinal pigment epithelium cells (OpRegen), transplanted subretinally to subjects with advanced dry age-related macular degeneration (AMD) with geographic atrophy (GA).

7.2.2 Secondary Objectives

To evaluate the preliminary efficacy of OpRegen treatment by assessing the changes in ophthalmological parameters as measured by various methods of primary clinical relevance.

[redacted]

7.3 STUDY ENDPOINTS

7.3.1 Safety and Tolerability Endpoints

Safety and tolerability of OpRegen treatment will be assessed by:

- Incidence and frequency of treatment emergent AEs
- Treatment emergent changes in the following variables:
  - Vital signs
  - Hematology/ Blood Chemistry/Urinalysis
  - Physical examination

- Ophthalmological evaluations including:
  - ✓ BCVA
  - ✓ Dilated Fundus Exam
  - ✓ IOP
  - ✓ SLE
  - ✓ SD-OCT
  - ✓ FA
  - ✓ Microperimetry
  - ✓ FAF
  - ✓ CFP

[redacted]

7.3.4 Efficacy Endpoints of Clinical Relevance

Preliminary efficacy assessments will utilize the below listed parameters:

- Directional change in the GA lesion area over time
- Overall change in the GA lesion area of the study eye over time using SD-OCT and FAF
- Change from baseline over time in BCVA as measured by ETDRS chart
- Change from initial assessment over time in retinal sensitivity (as assessed by microperimetry)
- Change from baseline over time in Reading Speed Test
- Change from baseline over time in Low Luminance BCVA

- Correlation assessment between quantitative metrics derived from FAF, SD-OCT and CFP images
- Correlation assessment between functional and structural changes
- Change over time in NEI VFQ-25 Quality of Life score
- Change over time in Functional Reading Independence (FRI) Index score

8. STUDY POPULATION

8.1 SUBJECTS CHARACTERISTICS

The subjects who will be enrolled for this clinical trial are males and females, 50 years of age and older, who were diagnosed with dry (non-neovascular) AMD in both eyes. The subjects will be enrolled in four cohorts. The first three cohorts will include subjects with visual acuity equal or less than 20/200 in the study eye. A fourth cohort will include subjects with visual acuity between 20/64 and 20/250 in the study eye.

8.1.1 Number of Subjects

Approximately 24 subjects will be enrolled in four cohorts, with three subjects enrolled in each of the first two cohorts, up to 6 subjects in the third cohort, and approximately 12 subjects enrolled in the fourth cohort.

8.1.2 Special Populations

There is no specific goal for gender inclusion/exclusion in this clinical trial, therefore no individual will be excluded from participation based on gender. In case women of childbearing age are participating in this study, they must have two negative pregnancy tests within one month prior to study agent implantation and must agree to use effective contraception for one year following implantation of OpRegen.

No clinically significant sex/gender differences in the intervention effect are expected. There is no intent to exclude from participation based on race and/or ethnicity.

8.2 ELIGIBILITY CRITERIA FOR COHORTS 1-3

8.2.1 Inclusion Criteria

1. Age 50 and older.
2. Diagnosis of dry (non-neovascular) age related macular degeneration in both eyes.
3. Funduscopic findings of dry AMD with progressive geographic atrophy in the macula, [redacted]
4. Best corrected central visual acuity equal or less than 20/200 in the study eye by ETDRS vision testing.
5. Vision in the non-operated eye must be better than or equal to that in the operated eye.

6. Subjects with sufficiently good health to allow participation in all study-related procedures and complete the study follow-up period (based on medical records).
7. Ability to undergo a vitreoretinal surgical procedure under monitored anesthesia care.
8. Blood counts, blood chemistry, coagulation and urinalysis without abnormal significance.
9. Negative for HIV, HBC, and HCV. Negative for CMV IgM and EBV IgM.
10. Willing to defer donation of blood and tissues.
11. Able to understand study procedures and willing to sign informed consent

8.2.2 Exclusion Criteria

1. Evidence of neovascular AMD by history, as well as by clinical exam, fluorescein angiography (FA), or ocular coherence tomography (OCT) at baseline in either eye.
2. History or presence of diabetic retinopathy, vascular occlusions, uveitis, Coat's disease, uncontrolled glaucoma, cataract or media opacity preventing posterior pole visualization or any significant ocular disease other than AMD that has compromised or could compromise vision in the study eye and confound analysis of the primary outcome.
3. History of retinal detachment repair in the study eye.
4. Axial myopia greater than -6 diopters.
5. At least 2 months following cataract removal in the study eye and Yttrium Aluminum Garnet (YAG) laser capsulotomy in the study eye in the past 4 weeks and any other ocular surgery in the study eye in the past 3 months prior to OpRegen implantation.
6. History of cognitive impairments or dementia.
7. Contraindication for systemic immunosuppression.
8. History of any condition other than AMD associated with choroidal neovascularization in the study eye (e.g. pathologic myopia or presumed ocular histoplasmosis).
9. Any type of systemic disease or its treatment, in the opinion of the Investigator, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.
10. For female subjects; pregnancy or breastfeeding.
11. Current participation in another clinical study. Past participation (within 6 months) in any clinical study of a drug administered systemically or to the eye.
12. Currently receiving aspirin, aspirin-containing products and/or any other coagulation modifying drugs which cannot be discontinued 7 days prior to surgery.
13. History of cancer (other than a non-melanoma skin cancer). For cancers in remission more than five years, enrollment is allowed with concurred documented approval of principal investigator and oncologist prior to enrollment.[5]

Note: "Live" *attenuated vaccination is prohibited during active systemic immunosuppression.*

[5] In the case of any suspected malignancies at screening, patient should be referred to appropriate medical specialist.

8.3 ELIGIBILITY CRITERIA FOR COHORT 4

8.3.1 Inclusion Criteria

1. Age 50 and older.
2. Diagnosis of dry (non-neovascular) AMD in both eyes.

[redacted]

11. BCVA letter score of ≥ 29 letters and ≤ 64 letters (Snellen equivalent of 20/64 – 20/250) in treated eye using ETDRS charts at starting distance of 4m.
12. Visual acuity as measured by ETDRS in the non-operated eye must be better than or equal to that in the operated eye.
13. Subjects with sufficient good health that can participate in all study-related procedures and complete the study follow-up period (based on medical records).
14. Ability to undergo a vitreoretinal surgical procedure under monitored anesthesia care.
15. Blood counts, blood chemistry, coagulation and urinalysis without abnormal significance.
16. Negative for TB, HIV, HBC, and HCV. Negative for acute or reactivated CMV IgM and EBV IgM or asymptomatic in the opinion of the investigator.
17. Willing to defer donation of blood and tissues.
18. Able to understand study procedures and willing to sign informed consent.

8.3.2 Exclusion Criteria

1. Evidence of neovascular AMD by history, as well as by clinical exam, fluorescein angiography (FA) at ocular coherence tomography (OCT) at baseline in either eye.

[redacted]

8. At least 2 months following cataract removal in the study eye and Yttrium Aluminum Garnet (YAG) laser capsulotomy for both eyes. Any other ocular surgery in either eye in the past 3 months prior to OpRegen implantation.
9. Current participation in another clinical study of an active drug (placebo and sham will be allowed). Past participation (within 6 months) in any clinical study of a drug administered systemically (except for vitamins and minerals) or to the eye.
10. History of cognitive impairment or dementia

11. Contraindication for systemic immunosuppression
12. Any type of systemic disease or its treatment, in the opinion of the Investigator, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.
13. For female subjects; pregnancy or breastfeeding
14. Currently receiving aspirin, aspirin containing products and/or any other coagulation modifying drugs which cannot be discontinued 7 days prior to surgery
15. History of cancer (other than a non-melanoma skin cancer). For cancers in remission more than five years, enrollment is allowed with concurred documented approval of principal investigator and oncologist prior to enrollment.[6]
16. Known allergy to any of the study medications or formulation.
17. Inability to comply with study or follow-up procedures
18. Inability to obtain CFP, FAF, OCT/OCTA and microperimetry of sufficient quality to be analyzed and graded by the Central Reading Center

Note: "Live" attenuated vaccination prohibited during active systemic immunosuppression.

Final decision for subject eligibility upon confirmation of Central Reading Center and the Sponsor.

9. CONCOMITANT MEDICATIONS AND SUPPORTIVE CARE

9.1 PREVIOUS MEDICATIONS

All medications taken by/given to the subject, as a treatment for the primary and concomitant diseases within two weeks prior to the subject screening visits, will be recorded in the case report form (CRF). Change in these medications should be recorded during each subsequent subject evaluation.

9.2 DISALLOWED CONCOMITANT MEDICATIONS

The subjects should be instructed to discontinue medications that may alter coagulation, including aspirin and aspirin-containing medications, 7 days prior to the implantation of OpRegen. They should be guided to discuss the risks associated with this discontinuation with their primary physician. Decisions regarding the timing of restarting these medications will be at the discretion of the Principal Investigator.

Anti VEGF intraocular injections are contraindicated when given as a treatment for Wet AMD. However, if subject was treated with Anti VEGF intraocular injections as a short-term therapy for an indication other than Wet AMD (or disease which is defined as exclusion criteria) more than

[6] In the case of any suspected malignancies at screening, patient should be referred to appropriate medical specialist.

12 months prior to study baseline, patient may be eligible after being discussed with Study Medical Monitor.

9.3 PER PROTOCOL STUDY MEDICATIONS

9.3.1 Immunosuppressive Medications

Subjects undergoing an allogeneic cell transplantation procedure may develop an immune response towards these cells, thereby limiting their survival and functionality. Therefore, the subjects will receive systemic immunosuppression therapy [redacted] and long-term systemic treatment.

9.3.1.1 [redacted]

9.3.1.2 Systemic (PO) tacrolimus

Systemic (PO) tacrolimus 0.01 mg/kg daily [redacted] up to 6 weeks post-transplantation, [redacted]

9.3.1.3 Systemic (PO) mycophenolate mofetil,

Systemic (PO) mycophenolate mofetil, up to 2gr/per day, [redacted] for at least three months [redacted] post-transplantation, [redacted]

9.3.2 Pupillary Dilation

It is recommended that all subjects whenever possible will undergo a pupillary dilation to a minimum of 8 mm during ophthalmological assessment. This will allow better quality imaging. A proven method is the instillation of 1-2 drops of 0.5% tropicamide (or equivalent) followed by 1 drop of 10% phenylephrine (or equivalent). Subjects with heavily pigmented irises will take longer to achieve full dilation.

9.3.3 Prophylaxis and Treatment of Infections

Institution guidelines will be followed to provide prophylaxis for infections. Strict guidelines for hygiene and care will be applied. Topical antibiotic treatment as customary following vitrectomy procedure will be given, including a course of topical antibiotic drops (ofloxacin or equivalent 4 times daily) beginning the day after surgery and over the course of up to 6 weeks.

Subjects subjected to the immunosuppressive treatment outlined in this study may develop immunodeficiency. Therefore, the approach to the diagnosis and treatment of fever in such subjects should be an aggressive one. If any infections occur, they will be treated per institutional practice and will be documented as adverse events (AEs).

9.3.4 Contrast Imaging Drug

Fluorescein a 5 cc (ml) solution of 10% sodium fluorescein will be given prior to FA imaging. The injection should be performed in an antecubital vein with a 19 or 21-gauge butterfly infusion. A vein in the hand may be used if no access can be obtained in the antecubital region.

9.3.5 Supportive Care

Subjects should receive full supportive care according to the Institution's practice patterns and clinical guidance, including analgesic, antibiotic, anti-inflammatory and antipyretic medications, or any other supportive care according to clinical judgment.

[redacted]

All concomitant medications administered, from time of signature on the informed consent and until the end of the study, will be recorded in the CRF and the reason for administration should be clearly stated in the indications and if needed also documented as AEs.

Rescue equipment (oxygen) and drugs such as hydrocortisone, epinephrine (or other inotropic agents), and antihistamines should be available at the surgery unit and will be administered per investigator discretion.

9.3.6 Per Protocol Medication Return

Every effort will be done to assure that subjects return any unused per protocol medications to the site.

10. STUDY DESIGN

This clinical trial will evaluate the safety, tolerability and preliminary efficacy of subretinal implantation of OpRegen to subjects with advanced form of dry-AMD. The study will consist of four cohorts. The first 2 cohorts, 3 subjects each, legally blind with best corrected visual acuity of 20/200 or worse in the study eye, will receive a single subretinal implantation of OpRegen. The third cohort will include up to 6 subjects, with BCVA of 20/200 or worse in the study eye, will receive a single subretinal implantation of OpRegen. The fourth cohort will include approximately 12 subjects with BCVA between 20/64-20/250, of whom 6 will receive a targeted single subretinal implantation of OpRegen [redacted]. Staggered intervals within and between cohorts will be applied, as described in Sections 6.5 and 10.1. The study is being conducted in participants with confirmed bilateral GA (Study Eye and Non-Study Eye). Between cohorts, and subjects if applicable, the next step to proceed will occur per DSMB recommendation, based on accumulated safety data.

Cell suspension will be delivered into the subretinal space in the macular area as described in the IFU and operating manuals for each delivery device. A total volume of up to [redacted] cell suspension (depending on the dose) will be implanted in single area at potential risk for GA expansion. Along with the relevant surgical procedure, the subjects will receive systemic immunosuppression [redacted], as described in Section 9.3.

During Part 1 of the study, subjects will be assessed at pre-scheduled intervals, as shown in Table 2 using methods and techniques described in Table 1. The study evaluation plans are designed to assess occurrence of systemic adverse events and to detect potential toxicities in different organ systems. Furthermore, ophthalmological examination and visual and retinal functional and structural examinations will be performed as part of baseline assessment and during follow-up, in order to collect initial data about the efficacy of OpRegen.

An end of Part 1 of the study visit is planned at [redacted] after the implantation of OpRegen.

[redacted]

10.1 DOSE ESCALATION AND STAGGERED INTERVALS

Staggered intervals between subjects within each cohort and between cohorts were designed in order to allow monitoring and investigation of adverse events, prior to exposing additional subjects to the product.

The safety data gathered from each cohort will be reviewed by the independent Data Safety Monitoring Board (DSMB, see Section 20.2). Depending on the safety data there will be a DSMB recommendation to pursue one of the following alternatives: proceed to the next higher dose; stop dose escalation; investigate a lower dose; or repeat a dose level.

The staggered procedure that will be followed in this study is described below.

[redacted]

[redacted]

10.2 DOSE LIMITING TOXICITY (DLT) AND STOPPING RULES

Potential toxicities and safety issues associated with the surgical procedure and of the investigational product will be carefully monitored during this study.

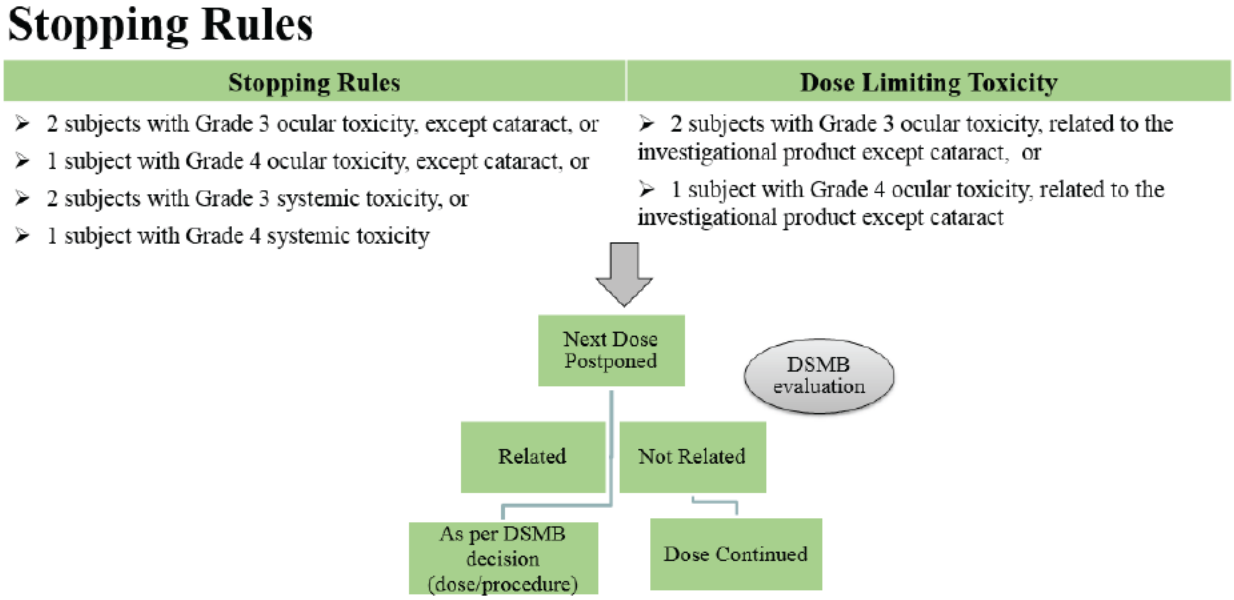


Figure 2: Stopping Rules

Based on the toxicity scales presented in Section 21.1.7 (see Table 6 and Table 7), the stopping rules (Figure 2) are defined as follows:

- 2 subjects with Grade 3 ocular toxicity, except cataract, or
- One (1) subject with Grade 4 ocular toxicity, except cataract, or
- 2 subjects with Grade 3 systemic toxicity, or
- One (1) subject with Grade 4 systemic toxicity

Based on the ocular toxicity scale presented in Section 21.1.7 (see Table 6) the dose limiting toxicity are defined as follows:

- 2 subjects with Grade 3 ocular toxicity, related to the investigational product except cataract, or
- One (1) subject with Grade 4 ocular toxicity, related to the investigational product except cataract

In case a Grade 3-4 toxicity occurs during the dosing within a cohort, as defined above, in accordance with the stopping rule, the dosing of the next subjects will be postponed until a decision is made by the DSMB regarding the relation of the SAE to OpRegenand to the surgical procedure. If, according to the DSMB opinion, the SAE is not related to the investigational product and the implantation procedure, the dosing schedule of the next subjects will be continued according to the

study plan. In case the event is related to the investigational product and the implantation procedure (dose limiting toxicity), dose adjustment and/or surgical procedure modification will be performed in accordance with recommendations of the DSMB.

The study sponsor is ultimately responsible for all decisions.

10.3 STUDY METHODS AND TECHNIQUES

In addition to the standard medical and laboratory assessments, the subjects will undergo specific systemic and ophthalmological examinations. The methods and techniques that will be used in this clinical trial are listed below in Table 1.

Table 1. Study Assessments

Assessment	Time points	Primary Endpoints/ Safety	Efficacy Endpoints of Clinical Relevance
Best-Corrected Visual Acuity (BCVA)-ETDRS Retro illuminated 4-meter ETDRS Chart "R" for refraction followed by Chart "1" and "2" BCVA is reported in number of letters read correctly. First, the right eye is tested with Chart 1 and then the left eye is tested with Chart 2. Must be conducted by trained examiner (technician acceptable) and as per "BCVA Instructions Manual".	[redacted]	√	√
Low Luminance Best Corrected Visual Acuity LL BCVA is measured by placing a 2.0-log-unit neutral density filter over the trial frame in front of the study eye and having the participant read the normally illuminated ETDRS chart using a different version of the chart. This test is optional as subjects with low vision will not be able to perform this test and is not applicable for Cohorts 1-3.	[redacted]		√
Spectral Domain Optical Coherence Tomography (SD-OCT) Images obtained by certified examiner (technician acceptable). Reading of images done by central reading center. Refer to Central Reading manual for instructions.	[redacted]	√	√

Assessment	Time points	Primary Endpoints/ Safety	Efficacy Endpoints of Clinical Relevance
[redacted]	[redacted]	√	
Dilated Fundus Examination (peripheral retina, macula, choroid, optic nerve, retinal/detachment, retinal or vitreous hemorrhage, vitreous hemorrhage density, vitreous cells.)	[redacted]	√	
Microperimetry Automated microperimetry to be performed in Cohort 3 (optional) and in Cohort 4. Must be conducted by certified examiner (technician is acceptable). Reading of images done by central reading center. Refer to Central Reading manual for instructions.	[redacted]	√	√
Fluorescein Angiography (FA) Standard procedure for detection of CNV. Must be conducted by certified examiner (technician is acceptable): at [redacted] to verify dry AMD and absence of neovascular (wet) AMD, and on final exam at end of study; optional FA during follow-up in cases of suspected conversion to wet AMD	[redacted]	√	
Intraocular Pressure (IOP) One IOP measurement per eye	[redacted]	√	
Slit Lamp Examination (Lids/Lashes, Conjunctiva, Cornea, Iris, Aqueous Cells, Aqueous Flare and Lens) Must be conducted by certified examiner (technician is acceptable)	[redacted]	√	
Physical Examination including ECG, Vital Signs Clinical evaluation by the study-dedicated investigator or designee will be performed at several time points to evaluate pre- and post-implantation subject condition including immunosuppression treatment safety (see below)**	[redacted]	√	
Malignancy Assessment In the case of any suspected malignancies at screening, subject should be referred to appropriate medical specialist.	[redacted]	√	
Complete Blood count (including differential) / Chemistry (including Serum Electrolytes)/ Coagulation / Urinalysis	[redacted]	√	

Assessment	Time points	Primary Endpoints/ Safety	Efficacy Endpoints of Clinical Relevance
Serology Assessment including testing for HIV, CMV, EBV, HBV and HCV	[redacted]	√	
[redacted]	[redacted]	√	
Immunology HLA-typing will be performed during [redacted] or during one of the subsequent visits if not performed during [redacted]	[redacted]	√	
[redacted]	[redacted]	√	
QuantiFERON (state of inoculation) To detect tuberculosis (TB) disease	[redacted]	√	
[redacted]	[redacted]	√	
Fundus Autofluorescence Imaging (FAF) Images obtained by certified examiner (technician acceptable). Reading of images done by central reading center. Images are done by using blue light Heidelberg instrumentation. Each assessment for each subject must be done with the same camera used at Screening. Refer to Central Reading manual for instructions.	[redacted]	√	√
Color Fundus Photography (CFP) Images obtained by certified examiner (technician acceptable). Reading of images done by central reading center. Color Images are done by using Zeiss instrumentation. Each assessment for each subject must be done with the same camera used at Screening. Refer to Central Reading manual for instructions.	[redacted]	√	√
Reading Speed Test This test is mandatory for subjects are proficient in English.	[redacted]		√
NEI VFQ-25 Quality of Life (examiner version) 25 item subject reported outcome. Scores range from 0-100 with the higher score indicating better visual function.	[redacted]		√

Assessment	Time points	Primary Endpoints/ Safety	Efficacy Endpoints of Clinical Relevance
Functional Reading Independence (FRI) Index The FRI index is a patient-reported outcome measure developed specifically for use in GA subjects. Scores derived from the index range from 1 (unable to do) to 4 (total independence) and may be analyzed as either categorical (which is preferred from a regulatory perspective) or continuous variables. This test should be administered in the subject's mother tongue language and is not applicable for Cohorts 1-3	[redacted]		√

The schedule of assessments for screening and first year during the study are detailed in Table 2. The schedule of assessments for long-term follow-up is detailed in Section 15.

Table 2. Study Evaluations and Examinations Schedule

Visit #	[redacted]
Day (or M=month=28)	
Informed Consent	
General	
Eligibility Criteria	
Vital signs (including smoking habits)	
Medical History	
AMD Medical History Lesion Characteristics by Eye Involvement, Localization, and Focality	
Demographics	
Physical examination	
Dilated Fundus Examination	
Intraocular Pressure (IOP)	
Slit Lamp Exam	
[redacted]	
Immunosuppression assessment[11]	
[redacted]	

[9] All testing for Visit #3 should be done prior to surgery.

[redacted]

[11] Immunosuppression treatment will be given as follows: [redacted] Systemic; (PO) tacrolimus 0.01 mg/kg daily [redacted] until up to 6 weeks post transplantation, [redacted] Systemic (PO) mycophenolate mofetil, total up to 2 grams/ day, [redacted] 3 months [redacted] post transplantation, [redacted]

Visit #	[redacted]
Day (or M=month=28)	
General (continued)	
General safety assessment (AEs and concomitant medication)	
Surgery of OpRegen® implantation	
Investigators global evaluation of device performance	
Intraoperative Video/OCT Imaging	
Discharge from the hospital[15]	
Functional Testing	
BCVA	
Low Luminance BCVA[16]	
SD- OCT (central reading)	
Fundus Autofluorescence (FAF) (central reading)	
Color Fundus Photography (CFP) (central reading)	
Microperimetry[17] (central reading)	
Fluorescein Angiography (FA) (central reading)	

[13] The eye chosen for OpRegen implantation will be the eye with worse visual function.

[14] Investigators global evaluation will be determined pre- and post-implantation for participants in cohort 4 who receive subretinal cell delivery of OpRegen via [redacted]

[15] Hospitalization is not applicable for U.S subjects.

[16] Performance of Low Luminance BCVA is dependent on subject's BCVA. This test is optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3.

[17] Microperimetry for cohort 3 [optional], but is required for all [redacted] subjects and all cohort 4 US-treated subjects

Visit #	[redacted]
Day (or M=month=28)	
Functional Testing (continued)	
NEI-VFQ25 (interviewer version)	
Functional Reading Independence (FRI) Index[18]	
Reading speed test[19]	
Laboratory Tests	
Complete Blood count (including differential)	
Chemistry (including Serum Electrolytes)	
Coagulation	
Urinalysis	
Serology	
Rheumatology (including ESR and CRP)	
[redacted]	
QuantiFERON (state of inoculation)	
ECG	
Malignancy assessment[21]	
HLA typing[22]	

X – Mandatory test/evaluation O - Optional test/evaluation

[18] This test should be administered in the subject's mother tongue language and is not applicable for Cohorts 1-3

[19] This test is mandatory for subjects proficient in English

[redacted]

[21] In the case of any suspected malignancies at screening, patient should be referred to appropriate medical specialist.

[22] Will be performed during [redacted] or during one of the subsequent visits if not performed during [redacted]

11. DETAILED STUDY PLAN

11.1 PRE-SCREENING ACTIVITIES

A printed version of the IRB approved Informed Consent will be provided to potential subjects and their families in order to allow them to review and understand all necessary information about the study and the investigational product prior to making a decision about their participation in the trial. The Principal Investigator and the clinical trial team should provide complete explanations and answer all questions raised by the potential participant, including explanation that the participation is voluntary, and they will be able to terminate their participation at any time, without any prejudice.

The informed consent must be signed and dated by the subject before the subject can undergo any study-related activities.

[redacted]

The screening period is up to [redacted] before implantation of the investigational product. During this visit the informed consent form is read and signed by the subject and screening measurements are taken as detailed in Table 2.

The informed consent procedure will ensure that subjects are adequately informed about the risks and benefits associated with study procedures and interventions. No study related procedures including weaning subjects from medications such as aspirin, will be done prior to completion of the informed consent signing procedure. A copy of the signed and dated informed consent must be provided to the subject.

A detailed medical history, including "live" attenuated vaccination, should be obtained from each subject during the screening period, to ensure that he/she is not subject to exclusion. A complete physical examination will be performed, including vital signs measurements. A 12-lead ECG will be performed. A complete blood count (including differential), serum biochemistry panel, coagulation, urinalysis, rheumatology (including ESR and CRP), serology as well as malignant hematological transformation and Quantiferon (state of inoculation) will be performed at a central laboratory (for detailed list of laboratory parameters please refer to Section 24.1).

In the case of any suspected malignancies at screening, subject should be referred to appropriate medical specialist.

During the [redacted], the subjects will be asked to complete the NEI-VFQ25 (interviewer version) questionnaire and Functional Reading Independence (FRI) index.

Immunosuppression assessment will be performed by the study investigator, to ensure that the subject's medical condition allows immunosuppression therapy.

At screening, a full ocular history will be obtained and an ophthalmic examination including the following assessments will be performed, as detailed in Table 2:

- Demographics
- Inclusion/Exclusion Criteria
- BCVA
- Low Luminance BCVA (optional)
- SD-OCT (central reading)
- Microperimetry (central reading) cohort 3 [optional], but is required for all [redacted] subjects and all cohort 4 US-treated subjects and Cohort 4)
- Fluorescein Angiography (FA) (central reading)
- Fundus Autofluorescence (FAF) (central reading)
- Color Fundus Photography (CFP) (central reading)
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Reading Speed Test (for subject's proficient in English)

Final decision for subject eligibility upon confirmation of Central Reading Center and the Sponsor.

Immunosuppression therapy will be prescribed, if subject is eligible for enrollment, as detailed in Section 9.3.1. [redacted] will be measured during the [redacted].

General Safety Assessment including prior and concomitant medications and adverse events will be performed during all visits.

[redacted]

- LOCS III (baseline 1)

[redacted]

11.3.1 [redacted]

The subjects can be hospitalized (if country specific requirement) [redacted] per investigator discretion. The following procedures and assessments will be performed on the [redacted]:

- General safety assessment (AEs and concomitant medication)
- Vital signs
- Medical History
- Physical examination
- Dilated Fundus Examination
- IOP

- Slit Lamp Exam
- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading)
- Immunosuppression assessment
- [redacted]
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)
- Complete Blood count (including differential)
- Chemistry (including Serum Electrolytes)
- Coagulation – and confirmation that aspirin/aspirin containing drugs and other coagulation modifying drugs were discontinued
- Urinalysis
- Reading speed test, if not performed during Screening for subject's proficient in English
- HLA-typing will be performed during [redacted] or during one of the subsequent visits if not performed during [redacted].

[redacted]

The results will be reviewed by the associated principal investigator to re-confirm subject's eligibility.

[redacted]

The following procedures and assessments will be performed on the [redacted] prior to implantation:

- General safety assessment (AEs and concomitant medication)
- Vital signs
- Dilated Fundus Examination (optional)
- IOP (optional)
- Slit Lamp Exam (optional)
- [redacted]

Additional Day of Implantation Assessments [redacted]

11.3.2.4 Surgical Procedure and Implantation of OpRegen®

The eye chosen for OpRegen® implantation will be the eye with worse visual acuity. The surgery will be performed by retro-bulbar or peri-bulbar anesthetic block or monitored intravenous sedation or by general anesthesia, at the discretion of the surgeon and in discussion with the subject. The eye undergoing surgery will be prepped and draped in sterile fashion according to the institutional protocol.

OpRegen® Subretinal Implantation with Vitrectomy

[redacted]

Vitrectomy procedure is required in the majority of cases in which retinal or sub-retinal intervention is performed. It is a routine procedure, with a low incidence of complications. The procedure involves formation of three small sclerotomies, removal of the vitreous gel, and then immediate implantation of the OpRegen® into the subretinal space via a very small caliber cannula.

The subretinal implantation as described following vitrectomy is schematically depicted in Figure 3[23] below.

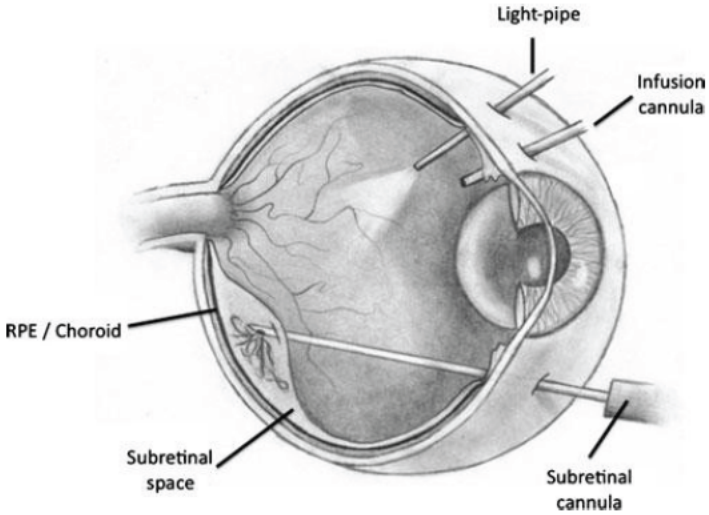


Figure 3: Subretinal Implantation After Vitrectomy

A surgical procedure manual describes the details of the procedures for vitrectomy and OpRegen® subretinal implantation.

[23] From (Stout JT 2011). (Note that in this schematic drawing, placement of the surgical ports is not anatomically accurate).

OpRegen® will be implanted into the subretinal space at a predetermined site (if applicable) within the posterior pole, [redacted] OpRegen® will be implanted into the subretinal space via formation of a small bleb, with a volume of [redacted] Subconjunctival antibiotics and steroids (maxitrol ophthalmic ointment (neomycin sulfate 3.5mg in 1g, polymyxin b sulfate 10000 [usp'u] in 1g, dexamethasone 1mg in 1g) or other equivalent generic drugs) will be administered. The eye will be covered with a patch and plastic shield. The surgical implantation procedure will be video-recorded.

[redacted]

[redacted]

Detailed surgical procedure manuals provided to the sites describe the specifics of the individual procedures. All surgical implantation procedures will be video-recorded for subsequent analyses.

11.3.2.5 Post-Implantation Activities and Follow-Up

The surgery report and required procedure documentation will be completed, and the clinical trial records will be updated to accurately reflect the outcome of the transplantation. [redacted]

Following OpRegen® implantation, subjects will remain in the recovery room or return to the ophthalmology department for close monitoring for safety until the subject is stable and meets all criteria for discharge.

The flowchart below (Figure 5) schematically shows the activities for OpRegen® implantation following vitrectomy as described above.

[redacted]

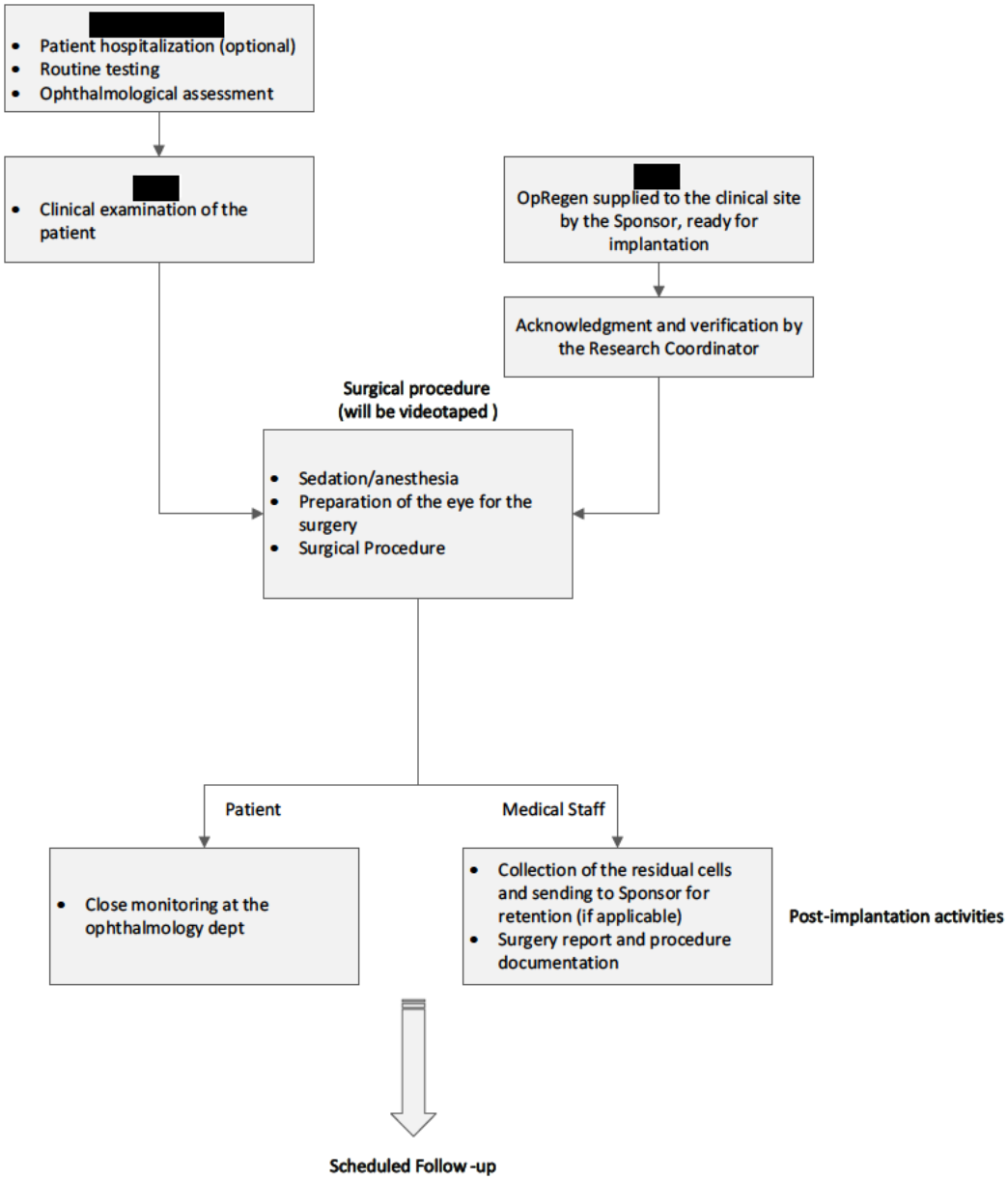


Figure 5: [redacted] activities flowchart

Following OpRegen® implantation, using either surgical procedure, the subject may be hospitalized (if country specific requirement) for up to three days, per investigator discretion. After the surgery, the subject will be followed up for general health/ophthalmological complaints and safety. Any changes in overall health will be assessed and treated, as needed.

Post-surgery discharge will be performed at the discretion of the investigator according to the subject's general and ophthalmological condition. During the post procedure period and until end of study, a total of 14 visits will be performed. A total of 12 visits will be performed at site and two visits will be telephone visits (and).

, the following assessments will be performed at :

- General safety assessments (AEs and concomitant) medications

- Vital Signs
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- SD-OCT (central reading)
- Color Fundus Photography (central reading)
- Discharge from the hospital (optional), as per investigator discretion, in countries or institutions requiring hospitalization
- Subject will be instructed to take "per protocol medications" and to contact the site in case of any general or ophthalmological conditions.

[redacted]

The visit and following assessments are optional and will be performed per investigator discretion:

- General safety assessments (AEs and concomitant medications)
- Vital Signs
- Dilated Fundus Examination (optional)
- IOP (optional)
- Slit Lamp Exam (optional)
- SD-OCT (central reading)
- [redacted]
- SD-OCT (central reading)
- Discharge from the hospital (optional), as per investigator discretion, in countries or institutions requiring hospitalization
- Subject will be instructed to take "per protocol medications" and to contact the site in case of any general or ophthalmological conditions.

[redacted]

The visit and following assessments are optional and will be performed per investigator discretion:

- General safety assessments (AEs and concomitant medications)
- Vital Signs
- Dilated Fundus Examination (optional)
- IOP (optional)
- Slit Lamp Exam (optional)
- SD-OCT (central reading)
- Discharge from the hospital (optional), as per investigator discretion, in countries or institutions requiring hospitalization
- Subject will be instructed to take "per protocol medications" and to contact the site in case of any general or ophthalmological conditions.

[redacted]

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Physical examination
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Immunosuppression assessment
- [redacted]
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)
- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading)
- Microperimetry (central reading) cohort 3 [optional], but is required for all [redacted] subjects and all cohort 4 US-treated subjects

[redacted]

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Physical examination
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Subject will be instructed to take "per protocol medications" and to contact the site in case of any general or ophthalmological conditions.
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)
- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading) – optional, as per investigator discretion.
- CBC (including differential)
- Chemistry (including Serum Electrolytes)
- Coagulation
- Urinalysis
- Rheumatology (including ESR and CRP)
- HLA typing if not done previously

[redacted]

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Immunosuppression assessment
- [redacted]
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)
- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading)
- Microperimetry (central reading) cohort 3 [optional], but is required for all [redacted] subjects and all cohort 4 US-treated subjects
- CBC (including differential)
- Chemistry (including Serum Electrolytes)
- Coagulation
- Urinalysis
- Rheumatology (including ESR and CRP)
- HLA typing if not done previously

[redacted]

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Immunosuppression assessment
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)
- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading) – optional, as per investigator discretion

[redacted]

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Physical examination
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Immunosuppression assessment
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)
- Microperimetry (central reading) cohort 3 [optional], but is required for all [redacted] subjects and all cohort 4 US-treated subjects
- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading)
- [redacted]
- CBC (including differential)
- Chemistry (including Serum Electrolytes)
- Coagulation
- Urinalysis
- Rheumatology (including ESR and CRP)
- Malignant hematological transformation
- HLA typing if not done previously

[redacted]

[redacted]

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Physical examination
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Immunosuppression assessment
- BCVA

- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)

[redacted]

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Physical examination
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Immunosuppression assessment [redacted]
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)
- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading)
- Microperimetry (central reading) cohort 3 [optional] but is required for all [redacted] subjects and all US-treated cohort 4 subjects
- Reading speed test
- CBC (including differential)
- Chemistry (including Serum Electrolytes)
- Coagulation
- Urinalysis
- Rheumatology (including ESR and CRP)
- Malignant hematological transformation
- HLA typing if not done previously

[redacted]

This visit will be a telephone visit during which the subject will be asked general questions regarding his/her health and visual condition. Following phone safety assessment, the subject may be invited to perform further systemic and/or ocular testing, as required. These visits will be defined as unscheduled visits.

[redacted]

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam

- Immunosuppression assessment (optional, only if subject is still prescribed mycophenolate mofetil, per investigator discretion)
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)
- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading)
- CBC (including differential)
- Chemistry (including Serum Electrolytes)
- Coagulation
- Urinalysis
- Rheumatology (including ESR and CRP)
- HLA typing if not done previously

[redacted]

This visit will be a telephone visit during which the subject will be asked general questions regarding his/her health and visual condition. Following phone safety assessment, the subject may be invited to perform further systemic and/or ocular testing, as required. These visits will be defined as unscheduled visits.

[redacted] END OF STUDY/ EARLY DISCONTINUATION

This visit is for subjects who completed the whole study duration of [redacted] post-implantation of OpRegen®, or for subjects who prematurely discontinued planned [redacted] study (early termination criteria, see Section 12).

- General safety assessments (AEs and concomitant medications)
- Vital signs
- Physical Examination
- Dilated Fundus Examination
- IOP
- Slit Lamp Exam
- Immunosuppression assessment [redacted]
- BCVA
- Low Luminance BCVA (optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3)

- SD-OCT (central reading)
- FAF (central reading)
- CFP (central reading)
- Microperimetry for cohort 3 [optional], but is required for all [redacted] subjects and all cohort 4 US-treated subjects
- NEI-VFQ25 (interviewer version)
- Functional Reading Independence (FRI) index
- Reading speed test
- Fluorescein Angiography (central reading)
- CBC (including differential)
- Chemistry (including Serum Electrolytes)
- Coagulation
- Urinalysis
- Rheumatology (including ESR and CRP)
- Malignant hematological transformation
- HLA typing, if not done previously
- ECG

[redacted]

12. CRITERIA FOR EARLY TERMINATION/ DISCONTINUATION

Subjects who discontinue early or are prematurely discontinued from the study should be followed and treated by the study Investigator in a customary manner. All of the Early Discontinuation assessments (Section 11.7) should be performed before discontinuation of the subject, if possible.

All subjects have the right to withdraw consent and discontinue participation without prejudice at any time during the study. The Investigator, in conjunction with the Sponsor, may also discontinue the subject from participation in the study at any time if both consider discontinuation to be in the subject's best interest.

Reasons for withdrawal of the subject prior to [redacted] must be stated in the CRF and in the source documentation for all study subjects who were enrolled in the study.

A subject may withdraw or be withdrawn from the study for the following reasons:

1. Subject withdrawal of consent
2. Sponsor requests subject to be withdrawn
3. Request of primary care physician or investigator
4. Non-compliance

5. Protocol Violation of inclusion or exclusion criteria, if, in the opinion of the Investigator and the Sponsor, the violation would significantly compromise data interpretation
6. Loss to follow-up/failure to return
7. AE/Experience
8. Subject requires additional therapy which is prohibited according to the protocol
9. Disease progression
10. Death
12. Termination of the study by the Sponsor
11. Other

13. UNSCHEDULED VISITS

An unscheduled visit may be performed at any time during the study at the subject's request, or as deemed necessary by the study Investigator. The date and reason for the unscheduled visit will be recorded. Vital signs, adverse events and concomitant medications will be recorded, and the ocular condition will be assessed as per reason for unscheduled visit.

14. STUDY ASSESSMENTS

14.1 SAFETY ASSESSMENTS

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study. The investigator remains responsible for following through an appropriate health care option, AEs that are serious or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or becomes chronic or stable.

For the purpose of this study, the safety of the investigational product and surgical procedure will be assessed during and after surgery by the investigator observed by ocular examinations and imaging techniques. Any observed changes will be reported as adverse events.

Ocular toxicity and Systemic toxicity will be reported as per definitions in the section 21.1.7.

Imaging assessments will be analyzed by central reading center(s) designated by the Sponsor.

Safety parameters will also be assessed by laboratory tests (e.g., hematology, serum chemistry, and urinalysis), ocular examinations, physical examinations. Concomitant medications and AEs will be monitored and tracked.

The Study Schedule provides timing of all specimen collections while Protocol Attachment 1 defines the clinical laboratory tests to be performed during the study. The actual date and timing (24-hour clock time) of each sampling will be recorded by site personnel.

Unless otherwise noted in the Protocol Attachment 1 (Section 24.1), laboratory tests will be analyzed by a central laboratory designated by Sponsor and will be used for data analysis purposes. Investigators must document their review of each laboratory report and evaluate out-of-range results to determine if clinically significant and record as AEs.

14.1.1 Assessment of Ocular Toxicity

Routine eye examination will be performed before and after implantation of OpRegen®. The Investigator will be alert to possible intra-operative complications. Clinical ocular examinations for toxicity will include slit lamp examination, applanation tonometry, and gonioscopy (if needed), and examination of the vitreous and fundus. The list of potential ocular toxicities and grading is shown in Section 21.1.7.

14.1.2 Assessment of Systemic Toxicity

Physical examination at regularly-scheduled time points will be performed by the clinical trial medical personnel to allow detection of and response to any acute symptoms. Complete blood count with differential, INR, PTT, serum chemistry, measures of hepatocellular integrity and renal function (including BUN and creatinine) and urinalysis will be performed during the [redacted], serving as a baseline, pre-implantation evaluation, and during post-treatment evaluations. These tests will allow detection of toxicity in a number of organ systems. In addition, safety information will be obtained by specific questioning. Systemic toxicity will be graded based on the scale shown in Section 21.1.7.

14.2 ASSESSMENT OF POTENTIAL OPHTHALMOLOGICAL CLINICAL EFFECT

Visual assessments will be performed prior to and after OpRegen® implantation in order to determine whether OpRegen® implantation has an effect on visual parameters.

Potential efficacy will be evaluated, but not limited by determining the rate of the GA progression, retinal sensitivity to light in the engrafted regions and changes in visual acuity.

15. POST-STUDY LONG TERM FOLLOW-UP

Long-term follow-up will occur for up to [redacted]

During the long-term follow up the subjects will undergo routine testing including vital signs and general physical examination and clinical eye examination including IOP, slit lamp and dilated fundus examination. An optional malignant hematological transformation test and immunosuppression assessment may be performed at the [redacted] to follow-up for potential adverse reactions associated with immunosuppression therapy. Routine laboratory tests will be performed at each visit, including blood count, chemistry (serum electrolytes), urinalysis, and rheumatology (including ESR and CRP). Also, functional eye testing will be performed, as described in Section 10.3. All AEs and concomitant medications should be reported over the course of the long-term follow-up period. Table 3 summarizes the evaluations that will be performed during the long-term follow up.

Table 3. Evaluations and examinaions schedule during long-term follow-up.

Procedure/Visit #/Day	[redacted]
Routine Testing	
Vital signs	
Physical examination	
Dilated Fundus Examination (optional)	
IOP (optional)	
Slit Lamp Exam (optional)	
Immunosuppression toxicity assessment	
Functional Testing	
BCVA	
Low Luminance BCVA[24]	
SD-OCT	
FAF	
CFP	
Microperimetry[25]	
NEI-VFQ25 (interviewer version)	
Functional Reading Independence (FRI) index[26]	
Fluorescein Angiography[27]	
Reading speed test[28]	
Routine Lab Tests	
CBC (including differential)	
Chemistry (including Serum Electrolytes)	
Rheumatology (including ESR and CRP)	
Urinalysis	
Additional Systemic Screening	
[redacted]	

[redacted]

[24] Performance of Low Luminance BCVA is dependent on subject's BCVA. This test is optional for cohort 4 subjects with low vision who are not able to perform this test and is not applicable for cohorts 1-3..

[25] Microperimetry for cohort 3 [optional], but is required for all [redacted] subjects and all cohort 4 US-treated subjects

[26] Not applicable for Cohorts 1-3.

[27] If not done at [redacted], perform at [redacted]. Fluorescein 5 cc (ml) solution of 10% sodium fluorescein will be given prior to FA imaging

[28] This test is mandatory for subjects proficient in English

[redacted]

16. SUBJECT CONFIDENTIALITY AND DISCLOSURE OF DATA

The Investigator must ensure that each subject's anonymity is maintained as described below. On the CRFs or other documents submitted to the Sponsor and/or its designee, subjects must only be identified by study, Subject Identification Number, and demographics, subject to restrictions of local regulations. No other personal identifiers will be used, and data will be de-identified in a manner compliant with applicable privacy laws and regulations. Documents that are not for submission to the Sponsor and/or its designee (e.g., signed Informed Consent Forms [ICF]) should be kept in strict confidence by the Investigator in compliance with applicable laws and regulations and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. The Investigator and institution must permit authorized representatives of the Sponsor and/or its designee, national and local health authorities, and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator is obligated to inform the subject in the ICF that his/her study-related records will be reviewed by the above-named representatives.

Subjects will be informed that data will be held on file by the Sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and applicable regulatory authorities. All subject data will be held in strict confidence, as allowed by law.

Upon the subject's permission, medical information may be given to the subject's personal physician or other appropriate medical personnel responsible for the subject's welfare.

At the time of death, no matter the cause, permission for an autopsy will be requested from the subject's family. Subjects will be asked to advise their families of this request and of its scientific and medical importance. If an autopsy is performed, a copy of the autopsy report should be obtained by the site and provided to the Sponsor and/or designee.

17. DATA REPORTING AND MONITORING

The clinical trial at site will be managed by the Principal Investigator who will ensure that systems are in place so that the rights of the subjects are respected and protected while quality is implemented in all aspects of the trial.

Copies of the processing documents, labels, temperature recordings, relevant batch certificates-of-analysis, chain-of-custody documents, or other official papers will be stored with the clinical trial or subject-specific records.

All data and observations will be documented in CRF (electronic) using the source documentation generated at the clinical site. The CRF will be maintained on each subject and will be the primary data collection instrument for this study. CRFs will be completed and signed by the study Investigator as information becomes available.

The procedures outlined in the protocol and the CRFs will be carefully reviewed by the study Investigator and clinical staff prior to study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol should be made,

except in emergency situations when alternative treatment is necessary for the protection, proper care and well-being of the subjects.

Protocol amendments will be submitted to the institutional IRB for review and approval prior to implementation. In case the amendment substantially alters the study design or increases the potential risk to the subjects, the Informed Consent and supporting documentation should be revised and subjects consent to participate in the study will be obtained, if applicable.

In case of a significant protocol deviation, an investigation should be initiated and completed in a timely manner. The Sponsor should be notified immediately. A deviation report should be filled out and sent to the Sponsor, including corrective actions suggested for prompt implementation to avoid recurrence of the incident.

18. STUDY MEDICATION

18.1 DESCRIPTION

OpRegen® is a cell-based product composed of RPE cells, derived from hESCs through a process of directed differentiation. OpRegen® can be implanted as a single cell suspension to form a targeted suspension of $50x10^3$ to $200x10^3$ [redacted] in either an ophthalmic [redacted]

18.2 MANUFACTURING AND SHIPMENT

A full description of OpRegen® manufacturing are provided in Section 2.5.2 and 2.5.3 of the Investigator's Brochure.

On the day of the implantation, OpRegen® formulated in [redacted] and prepared to provide a targeted clinical dose of $50x10^3$ or up to $200x10^3$ viable cells in [redacted] of injection solution. [redacted]

The cell suspension should be loaded to the intended delivery device in accordance with the Sponsor's Surgical Procedure Instructions and immediately implanted into the subject's eye.

18.3 QUALITY CONTROL

OpRegen® is manufactured under GMP manufacturing conditions, in compliance with the manufacturing instructions and procedures as provided by the Sponsor. In case OpRegen® final dose preparation is required it is being carried out in designated cell facilities/laboratories approved by the Sponsor's Quality Assurance department.

Quality control (QC) tests are performed throughout the course of the batch manufacturing and on the final product and their results are documented. The QC tests have pre-defined specifications and the product release tests should be within the specification range.

The product specifications include tests performed on the final product at the end of each batch production (representatively), and tests performed on the final

formulation, in case washing and replacement of the medium is required to prepare the dose.

The release tests and product specifications will appear in the product Certificate of Analysis (CoA). Current OpRegen® release criteria are summarized in Table 4, below.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

18.4.1 [redacted]

[redacted]

[redacted]

[redacted]

19. RISK ASSESSMENT

19.1 POTENTIAL RISK ASSOCIATED WITH IMPLANTATION OF THE INVESTIGATIONAL PRODUCT

Preclinical safety studies of OpRegen® in [redacted] and [redacted] (referenced earlier in Section 5) did not reveal any serious safety concerns associated with subretinal implantation of OpRegen®.

A summary of potential expected risks is discussed in Section 5.1 of the Investigator's Brochure. This study is an ongoing safety study, so refer to the most recently published DSUR and EC updates for the latest and up to date information.

19.2 POTENTIAL RISKS ASSOCIATED WITH THE STUDY PROCEDURES

Potential risks of OpRegen are divided into 1) the risks associated with the product; and 2) risks associated with the administration procedure (described in further detail in Section 20.2). These risks are based on the data from similar studies and data from OpRegen clinical study CCN_CT02. The summary of potential risks is presented in Table 5 below. Overall and per patient assessment of each risk mentioned below and any new unexpected adverse events is performed continuously. The summary provided below is being updated with progression of the clinical investigation and product development.

19.3 [redacted]

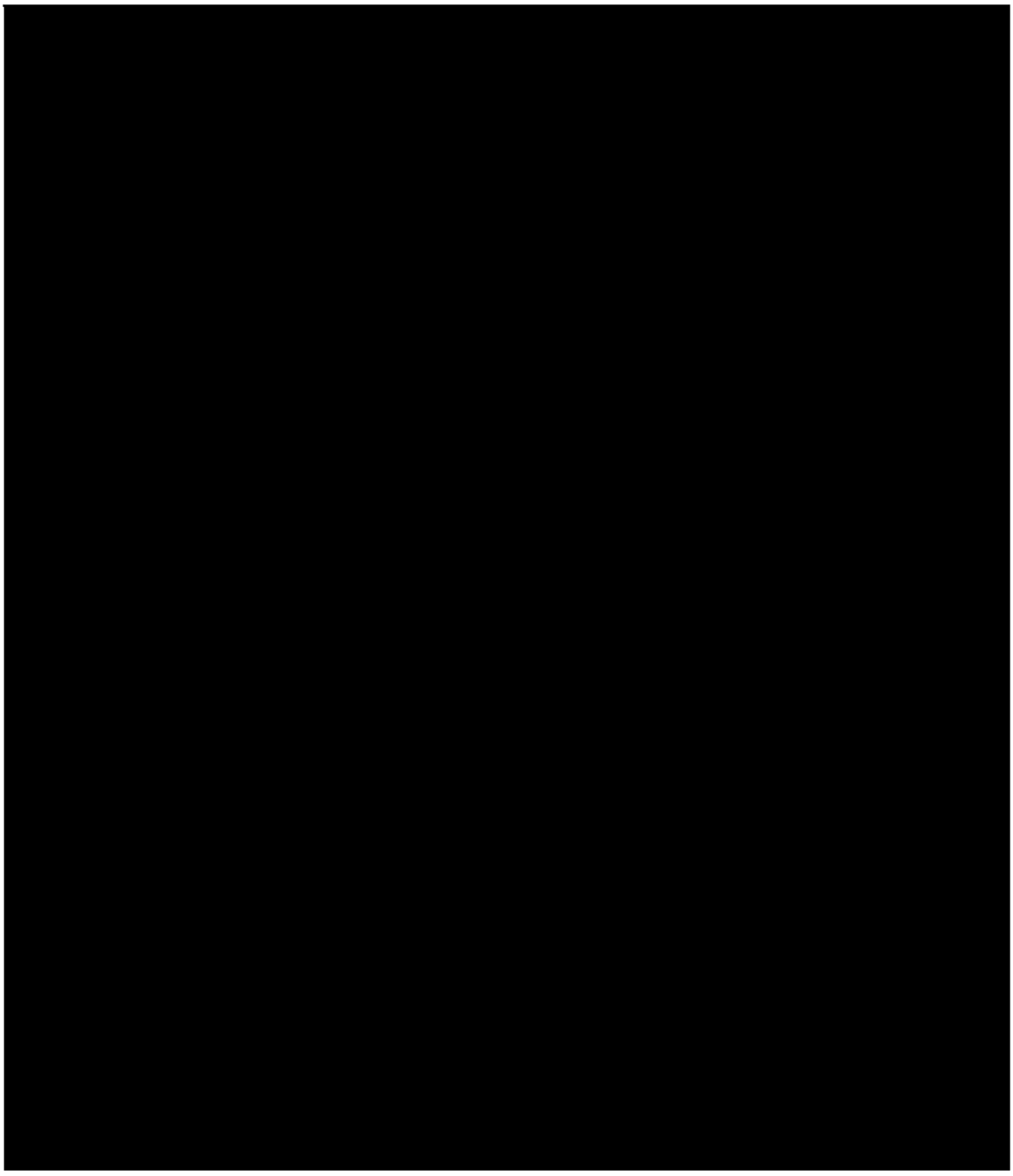
[redacted]

[redacted]

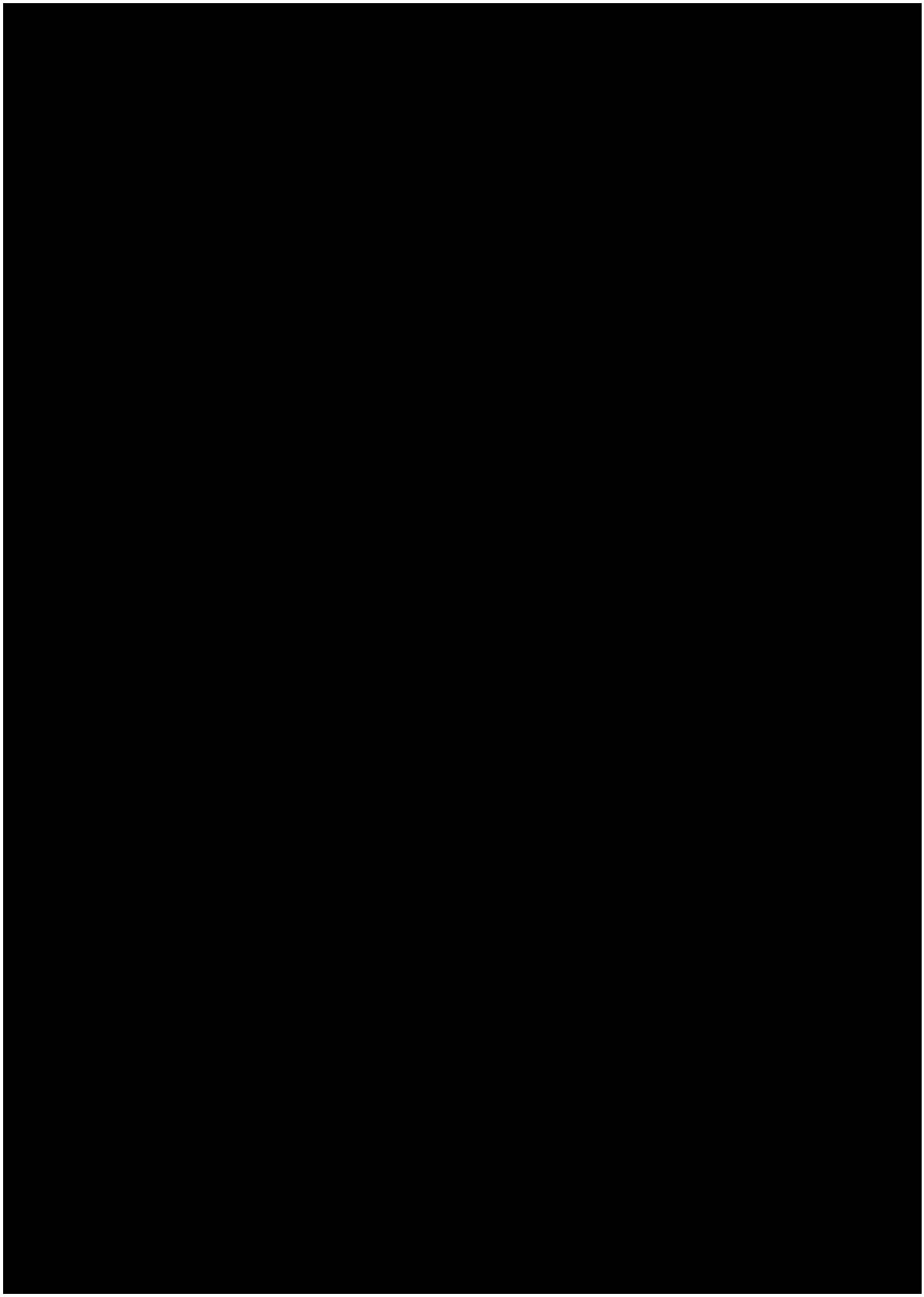
19.4 [redacted]

[redacted]

[redacted]



[redacted]



19.5 ADEQUACY OF PROTECTION AGAINST RISKS

The following procedures are likely to minimize the potential risks associated with study procedures:

- The medical history and physical examination performed prior to the implantation of OpRegen® will identify subjects with medical or ophthalmic conditions that would increase the risks associated with the study procedures. These subjects will not be enrolled to the study.
- The surgical procedures and implantation of the investigational product will be performed in standard fashion by highly experienced retinal surgeons and with strong attention to the risks described above.
- To minimize the risks associated with systemic immunosuppression, assessment of the subjects will be performed by the study-dedicated investigator or designee in order to evaluate whether the subject's medical condition is appropriate for immunosuppression and in order to follow up after potential adverse reactions associated with immunosuppression (see Section 10.3).
- To minimize the risks associated with severe immunological reaction, monitoring for the presence of an immune response to the transplanted cells will be performed.
- Topical administration of antibiotics and steroids is planned to minimize the risk of local inflammation.
- To minimize the risk of potential acute adverse events, the subjects may be hospitalized for up to three days (per investigator discretion) following implantation of OpRegen® and will be examined frequently on an ambulatory basis thereafter.
- Results of all laboratory and safety examinations of each subject will be reviewed by the study Investigator throughout the study. In addition, an independent medical monitor will evaluate the records.
- Results of all laboratory and safety examinations of each cohort will be periodically reviewed by the independent DSMB.

Informed Consent and supporting study documentation include thorough explanation of the study procedures and related risks and benefits. All documentation will be approved by the relevant ethical and regulatory authorities, to ensure maximal protection of the subjects.

During the enrollment process, and the study itself, the subjects will receive all information from the study Investigator and designated Research Coordinators. The Investigator and Research Coordinators will be available to address all questions and concerns arising regarding possible effects of OpRegen® during the enrollment and during the study. The subjects will be provided with contact information of the study Investigator and the Research Coordinators and will be encouraged to contact them in case of any emergency.

Participation in this study is completely voluntary and great care will be taken to ensure that individuals do not feel coerced to participate. All subjects will be able to terminate their participation at any time, without prejudice.

Confidentiality of the study subjects and their medical information will be maintained by coding data collection forms.

19.6 POTENTIAL BENEFITS

This Phase I/II clinical trial will define the safety and tolerability of OpRegen®, implanted into one eye of subjects with advanced dry-AMD. No direct clinical benefit to the study subjects is expected. The results of this trial will be helpful in understanding of potential clinical benefit of OpRegen® in dry-AMD subjects and in planning of the future clinical trials in this and other indications.

20. STUDY MONITORING

Site visits will be conducted by the Sponsor and/or designee to inspect study data, subject medical records, and CRFs in accordance with current US GCP and the respective local and national government regulations and guidelines, as applicable per the study Monitoring Plan. The Investigator will permit authorized representatives of the Sponsor, the FDA, the IRB/IEC and appropriate national or local health authorities access to all relevant study information.

SAEs or other safety concerns will be evaluated immediately by the Medical Monitor as well as the DSMB (see Section 20.2).

20.1 MEDICAL MONITOR, CRO AND CRA MONITORING VISITS

The safety medical monitoring for this trial will be provided either by the Sponsor or its designee. The Medical Monitor (MM) should be adequately qualified, will follow the study specific monitoring plan and current guidelines for the safety monitoring of clinical investigations.

The Clinical Research Organization (CRO) will be designated by the Sponsor (if applicable) and will be responsible for regular monitoring of study data at the clinical site and for ensuring compliance with the regulatory requirements, including ICH guidelines and adherence to the study protocol. The clinical site will be monitored to verify that enrollment rate, data recording, and protocol adherence are satisfactory. The frequency of monitoring individual sites may fluctuate depending upon enrollment rate, quantity of data collected and the complexity of the study.

These monitoring visits will be performed for the purposes of verifying adherence to the protocol and the completeness and accuracy of data entered in the CRF. During these visits, the clinical research associate (CRA) will verify CRF entries by comparing them with the primary source documents (hospital/clinic/office records), which will be made available for this purpose. The CRA will review the maintenance of regulatory documentation and drug accountability. The CRA will review the progress of the study with the Investigator and other site personnel on

a regular basis. CRF sections will be recorded by the site personnel and verified by the CRAs during these visits. At the end of the study, a closeout monitoring visit will be performed. CRA monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the CRA to review CRFs and relevant source documents. The Study Coordinator and/or Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits will be made available by the Investigator.

20.2 DATA SAFETY MONITORING BOARD

The DSMB will be composed of independent physicians with expertise in ophthalmology/clinical trials in the targeted population, and a statistician. A DSMB Charter specifying role, process, and constitution of the DSMB will be prepared and signed by all members. The DSMB will receive safety data of each study cohort periodically, carefully review it and forward to the Sponsor its recommendations regarding study continuation. It will have the right to recommend discontinuation of the trial for safety reasons or for overwhelming clinical effect.

The DSMB members will communicate with the Sponsor with regards to issues resulting from the conduct and clinical aspects of the trial. The Sponsor will work closely with the board to provide the necessary data for review.

The justification for lack of sponsor blinding of the data provided to the DSMB is based on the fact that the study is an open label and single-arm design; therefore, safety monitoring is of major importance.

21. SAFETY REPORTING

21.1 ADVERSE EVENTS DEFINITION

A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to a drug or drug delivery system, or due to per protocol medications received.

A lack of drug effect is not an AE in clinical trials because the purpose of clinical trials is to establish whether there is drug effect and the nature of that effect or lack thereof.

AEs may be either spontaneously reported or elicited during questioning and examination of the subject. The occurrence of an AE will be determined on the basis of observed or volunteered signs and symptoms and changes in the subject's physical examination and laboratory test results.

During the study, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs on the source documents and on the appropriate AE CRF. AE is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study or through the long-term follow up period. Intercurrent illness or injuries will be considered as AEs. Abnormal results of diagnostic procedures will be considered as AEs if the abnormality:

- Results in study withdrawal

- Is associated with SAE
- Is associated with clinical sign or symptom
- Leads to additional treatment or to further diagnostic tests
- Is of clinical significance, as considered by the study Investigator

Preexisting condition is one that is present at the start of the study. Preexisting conditions will be recorded as AEs if their frequency and/or intensity worsens during the study period. At baseline evaluations, any clinically significant abnormality will be recorded as a preexisting condition at medical history. All new signs and symptoms will be reported as AEs.

The recording period for AEs starts at the time of written informed consent until the subject completes the study, unless an unresolved AE is still being followed-up. For all subjects who took at least one dose of study drug/ per protocol medications – whether they completed the treatment period or not – the recording period ends 4 weeks/28±4 days after study termination/completion.

All AEs will be evaluated by the Investigator for seriousness, severity, relationship to study drug, and outcome. All AEs with ongoing/unknown outcomes require follow-up. Outcome information will be pursued until resolution or until the last batch of queries (after the last subject's last visit). For adverse events that are serious or medically relevant, additional follow up will continue beyond last batch of queries under the responsibility of the Sponsor/Delegate safety department. Such events will be followed until resolution or stabilization.

Any changes in subject condition reported spontaneously or observed during and after surgery will be documented as AE, if the condition meets criteria for AE.

Surgical procedures will not be reported as an outcome of AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

21.1.1 Clinical Laboratory Abnormalities

Clinical laboratory abnormalities will be documented as an AE if one or more of the following conditions are met:

- It is associated with a specific medical condition (defined as a diagnosis or clinically significant signs or symptoms)
- It required medical intervention (e.g., treatment discontinuation, new/change in concomitant medications).
- The laboratory abnormality is clinically significant and confirmed in a repeat test
- The abnormality suggests disease and/or organ toxicity

The test will be repeated and the subject will be followed-up until the test value has returned to the normal range, or the Investigator has determined that the abnormality is chronic or stable. The Investigator will exercise medical judgment in deciding whether abnormal values are clinically significant.

21.1.2 Serious Adverse Events

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or the Sponsor, it is characterized by any of the following:

- Results in death
- Is life-threatening (i.e., in the view of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization (i.e., the AE requires at least a 24-hour inpatient hospitalization or prolongs a hospitalization beyond the expected length of stay.) Hospitalization, prolonged hospitalization or surgery will not be reported as SAE if related to diagnostic or elective surgical procedures for a preexisting condition. (Note: complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious)
- Results in a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in a subject's offspring (i.e., if it is suspected that exposure to a study drug [in male or female subjects] may have resulted in a congenital anomaly in the child)
- Other important medical event (i.e., events may not be immediately life-threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent another serious outcome)

All SAEs (DLTs refer to section 10.2) will be carefully monitored throughout the course of the study. Collection of SAE information will begin upon the subject's signing of the informed consent through the end of the long-term follow-up period, or for as long as is necessary per the Investigator's discretion (whichever is later). SAEs may be either spontaneously reported or elicited during questioning and examination of the subject. All identified SAEs must be recorded and described in the subject's source records. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. All SAEs will be classified as related or not related to the study drug. All SAEs must be reported to the Sponsor as soon as possible and no later than 24 hours after the Investigator has knowledge of the event. Serious adverse events will be reported by completing the SAE form provided by the Sponsor. Refer to the Safety Management Plan for procedures and reporting requirements.

If a subject terminates study participation early after receiving any amount of study drug/SAEs will be collected for at least 12 weeks after the last dose

of per protocol drug, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug/per protocol medication, or a protocol procedure.

21.1.3 Suspected Adverse Reaction and Causality

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drugs/per protocol drug and adverse event.

The Investigator will use the following question when assessing causality of an adverse event to study drug: Is there a reasonable possibility that the drug caused the event? An affirmative answer designates the event as a suspected adverse reaction.

21.1.4 Relationship of Adverse Events and Serious Adverse Events to Study Drug

AEs that occur during clinical studies can be significant enough to lead to changes in the drug development program (e.g., changes in dose, changes in study population, or changes in the information given to subjects in the informed consent form.) Such changes are particularly possible with AEs that are suspected to be related to the study drug and with AEs that, in their most severe form, are life-threatening. It is therefore very important for the Investigator to give an opinion on the cause-effect relationship between an AE and the study drug.

Causality must be assessed when reporting the AE in the AE CRF and SAE forms. Only AEs judged by the Investigator, by the Sponsor, or by the Sponsor's legal representative as having a reasonable, suspected, causal relationship to the study drug will be considered to be suspected adverse drug reactions. In general, the expression "reasonable, causal relationship" means that there is evidence or arguments to suggest a causal relationship.

21.1.5 Event Expectation

Unexpected: An event is considered "unexpected" when its nature (specificity) or severity is not consistent with the list of potential adverse reactions included in the current Investigator's brochure.

Expected: An event is considered "expected" when its nature and severity are consistent with the list of potential adverse reactions included in the current IB.

21.1.6 Recording of Adverse Events

At each contact with the subject the study Investigator or his/her designee will seek information on AEs by specific questioning and examination. Information on all AEs will be immediately recorded in the source document and the data will be transferred to the CRF. All clearly related signs, symptoms and abnormal results will be recorded in the source document. The CRF will include a description, onset and resolution date, duration, maximum severity, assessment of causality, other suspected agent, subject's preexisting disease, action taken and outcome.

All AEs occurring during the study and long-term follow up period will be recorded and graded as described in Section 21.1.7. The clinical course of each event will be followed until resolution, stabilization or until it has been reported as non-related to the investigational product.

21.1.7 Toxicity Grading

The AEs will be graded using NCI's CTCAE.

The list of potential ocular toxicities and their grading is shown in Table 6. This list is a modification of the Ocular/Visual Adverse events v.3.0 (CTCAE), considering the specific subject population and the circumstances of the intervention.

The following AEs are defined as ocular toxicity and are to be assessed for grading as follows:

Table 6. Ocular toxicity scale

Toxicity	Grade 1	Grade 2	Grade 3 SAE	Grade 4 SAE
Keratitis (corneal inflammation/cornea ulceration)	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic; Medical intervention indicated	Symptomatic; Surgical intervention indicated	Perforation or blindness (worse than baseline visual function)
Glaucoma	Elevated intraocular pressure (EIOP) warranting topical agent for intervention	EIOP requiring topical agents and oral agents for intervention	EIOP requires operative intervention	Uncontrolled EIOP, resulting in blindness (worse than baseline visual function)
Cataract	Mild change from baseline, detected on ophthalmologic examination, not warranting intervention	Moderate change from baseline, detected on ophthalmologic examination, not warranting intervention	Severe change from baseline, detected on ophthalmologic examination, not warranting intervention **NOT SAE**	Severe change warranting operative intervention **NOT SAE**
Uveitis	Mild anterior uveitis, not warranting intervention	Moderate anterior uveitis, warranting intervention	Severe posterior or pan-uveitis, warranting medical intervention	Severe uveitis warranting operative intervention and threating ocular integrity
Vitreous hemorrhage	Mild hemorrhage detected on ophthalmologic examination, not warranting intervention	Moderate hemorrhage not warranting intervention	Severe hemorrhage warranting vitrectomy	Uncontrolled vitreous hemorrhage, threatening ocular integrity
Retinal detachments/PVR (Proliferative vitreoretinopathy)	Localized, peripheral intervention not indicated	Not resolving; intervention not indicated	Operative intervention indicated	Operative failure, threatening ocular integrity

Systemic toxicity will be graded based on the scale, shown in Table 7.

The following AEs are defined as systemic toxicity and are to be assessed for grading as follows:

Table 7. Systemic toxicity scale

Grade	Definition
1	Mild toxicity, usually transient, requiring no special treatment and generally not interfering with daily activities.
2	Moderate toxicity which may be ameliorated by simple therapeutic maneuvers, and impairs usual activities
3 **SAE**	Severe toxicity which requires therapeutic intervention and interrupts usual activities. Hospitalization may or may not be required.
4 **SAE**	Life-threatening toxicity which requires hospitalization

21.1.8 Severity Grading

The severity assessment is determined by the Investigator and is based on the definitions below. The maximum severity observed is to be recorded.

21.1.8.1 MILD: Subject is aware of event or symptom but event/symptom is easily tolerated.

21.1.8.2 MODERATE: Subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

21.1.8.3 SEVERE: Significant impairment of functioning; subject is unable to carry out usual activities and/or the subject's life is at risk from the adverse event.

21.2 DEVICE SAFETY

[redacted]

These potential events will be collected and reported to be consistent with 21CFR803, which notes that a user facility must report device related serious injury to the manufacturer.

The AEs that are attributed to device will be graded using a modification of NCI CTCAE (see Table 5). This list is a modification of the Ocular/Visual Adverse events v.3.0 (CTCAE), considering the specific subject population and the circumstances of the intervention.

The list of AESI is shown in Table 8.

21.2.1 Device Adverse Events of Special Interest

When present at the time of surgery the following AESI may be assessed for grading as follows:

21.2.1.1 MILD: Subject is aware of event or symptom but event/symptom is easily tolerated.

21.2.1.2 MODERATE: Subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

21.2.1.3 MODERATELY SEVERE: Subject experiences impairment (e.g. vision loss up to 3 lines) or a related event that may require an additional procedure

21.2.1.4 SEVERE: Significant impairment of functioning; subject is unable to carry out usual activities and/or the subject's life is at risk from the adverse event.

21.2.2 Device Adverse Events of Special Interest

Table 8. Device Adverse Events of Special Interest

Grade	1	2	3	4
Event	**Mild**	**Moderate**	**Moderately Severe**	**Severe/significant**
• Endophthalmitis	any occurrence resolving no change in vision	any occurrence not resolving vision loss up to 2 lines ETDRS	any occurrence not resolving vision loss up to 3 lines ETDRS	Panophthalmitis Or significant >3 lines vision loss ETDRS
• Retinal detachment	Localized, peripheral, intervention not planned	Not resolving, intervention not indicated	Operative indication indicated	Operative failure, threatening ocular integrity
• Choroidal hemorrhage*	Localized subretinal/subRPE hemorrhage	Not resolving, localized subretinal/subRPE hemorrhage	Operative indication indicated diffuse subretinal/sub RPE hemorrhage	Choroidal effusion, Choroidal rupture, Expulsive choroidal hemorrhage, and Unspecified choroidal hemorrhage
• Perforation of retina			Yes, any occurrence Operative indication indicated	Yes, any occurrence Operative failure

Grade	1	2	3	4
Event	**Mild**	**Moderate**	**Moderately Severe**	**Severe/significant**
• Cell egress			Yes, any occurrence Operative indication indicated	Yes, any occurrence Operative failure Significantly decreased vision
• Failure to deliver cells	•	•	Yes, any occurrence Operative indication indicated	Yes, any occurrence Operative failure Significantly decreased vision
• Unplanned vitrectomy	•	•	Yes, any occurrence	Yes, any occurrence Operative failure Significantly decreased vision

*Significant choroidal hemorrhage includes the following medical codes: choroidal effusion, choroidal rupture, expulsive choroidal hemorrhage, and unspecified choroidal hemorrhage

21.3 SAFETY EXPEDITED REPORTING

21.3.1 Reporting to the IRB/IEC

All serious and unexpected AEs including grade 3-4 toxicities based on Table 6, Table 7 and Table 8 will be reported to the IRB and to the FDA and other relevant regulatory authorities.

It is the responsibility of the study Investigator or his/her designee to comply with applicable local regulatory requirements for the reporting of SAEs to the IRB/IEC. Investigators should immediately forward to the IRB/IEC any written safety report or update provided by the Sponsor in accordance with local regulatory requirements (e.g., safety report, IB, safety amendments, and updates).

A special SAE report will be created for this purpose and will include the following information:

- Subject number
- Description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event was classified as serious
- Investigator's assessment of causality

All SAEs must be reported to the Sponsor as soon as possible and no later than 24 hours after study Investigator or his/her designee has knowledge of the event.

When an SAE occurs, the Investigator must do the following:

- Note in the subject's medical file the date on which the Investigator or site staff first learned of the event by any route (e.g., at a follow-up visit with the subject, by telephone with the subject, or from a third party).
- Immediately complete an AE CRF and an SAE form, without waiting for the clinical outcome or for the results of further investigation.
- Send to the assigned Medical Monitor (MM) de-identified copies of pertinent records, as soon as such copies are available, for example:
    - Hospital admission reports
    - Reports of further consultations
    - Laboratory test reports
    - Reports from other examinations aiding diagnosis
    - Results from pre-treatment assessments for comparison with the results obtained under treatment
    - Autopsy report, if an autopsy is performed
- Fulfill regulatory requirements for reporting to the IRB/IEC.

If an AE initially judged non-serious worsens and becomes serious, the Investigator must follow the procedure described above.

21.3.2 Reporting to the DSMB

The reporting rule described in Section 21.3.1 should be applied for reporting to the DSMB. All serious and unexpected AEs including grade 3-4 toxicities based on Table 6 and Table 7 above should be reported to the DSMB. The SAE report created for notification of the IRB and regulatory authorities should be sent to the DSMB members within 48 hours from the event.

21.3.3 Medical Monitoring Review

The MM (see Section 20.1), CRA and the Sponsor should be notified about SAE by the study Investigator or his/her designee, by email or fax, as soon as possible and not later than 24 hours after the event.

The MM is responsible for initial review of these events within two (2) days of the notification. The MM review will be documented. If the MM requires additional information to make an assessment, the clinical site will have two (2) days to respond to the request. Most information should be available within four (4) days of the site's knowledge of the event.

21.3.4 Reporting to Regulatory Authorities

The Sponsor or his authorized representative will notify the FDA or any other relevant regulatory authorities of any unexpected, serious adverse event or fatal or life-threatening experience associated with study procedures as soon as

possible, in accordance with regulatory requirements. As per 21 CFR 312.32, unexpected fatal or life-threatening suspected adverse reactions are reported by telephone or fax no later than seven (7) calendar days after knowledge of the event. All serious, unexpected, suspected adverse reactions and Grade 3-4 ocular toxicities (except cataract) related to the investigational product, such as intraocular infection, inflammation, retinal detachment, tumor/ectopic tissue formation will be reported to the FDA via a written report within fifteen (15) days of receipt of the information.

21.4 FOLLOW-UP OF THE ADVERSE EVENTS

Subjects who experienced AEs will be followed until resolution or stabilization. SAEs that are ongoing at the end of the study period will be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to study participation will be recorded and reported immediately.

22. STATISTICAL METHODOLOGY

22.1 STUDY DESIGN AND SAMPLE SIZE

As this is an open-label, phase I/IIa dose escalation, safety, tolerability and preliminary efficacy study, neither power assessment, nor formal hypotheses testing are currently planned for study outcome measures.

Detailed methodology for data summary and analyses will be documented in a Statistical Analysis Plan (SAP). This document may modify the plans outlined in the protocol; however, any major modification of the outcome measures and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

The planned sample size of approximately 24 eyes for 4 study cohorts to be treated with targeted OpRegen® doses of $50x10^3$ and up to $200x10^3$ cells, is considered clinically appropriate for further characterization of the safety, tolerability and preliminary efficacy of OpRegen® in the treatment of subjects with subjects with advanced dry-form AMD with GA.

22.2 ANALYSIS SETS

22.2.1 Modified Intent-to-Treat (mITT) Analysis Set

The Modified Intent-to-Treat (mITT) analysis set will consist of all subjects who have been enrolled to the trial and received the OpRegen® implantation. This analysis set, which will include all data captured in database for these subjects, will serve as the primary Analysis Set for inference.

22.2.2 Per Protocol (PP) Analysis Set

The Per Protocol (PP) analysis set is a subset of the mITT Analysis Set and will consist of all subjects who have been enrolled into the trial, received the OpRegen® implantation and violated none of the major protocol guidelines.

22.3 SIGNIFICANCE LEVEL

No formal hypothesis testing is planned for this study. However, a significance level of 0.05 using two-tailed tests will be utilized in the case that exploratory significance testing will be performed.

22.4 INTERIM REPORTS

Comprehensive interim reports of accumulated safety, tolerability and preliminary available efficacy data will be presented to the independent Data Safety Monitoring Board (DSMB).

Depending on the safety data available, there will be a DSMB recommendation to pursue one of the following alternatives: proceed to the next higher dose; stop dose escalation; investigate a lower dose; or repeat a dose level.

22.5 DESCRIPTIVE STATISTICS

All measured variables and derived parameters will be listed individually and if appropriate, presented in summary tables by dose regimen group and overall, providing sample size, absolute and relative frequency for categorical variables, or sample size, arithmetic mean, standard deviation, median, minimum and maximum for continuous variables. Confidence intervals will be presented for the efficacy endpoints for exploratory purposes only.

22.6 MISSING DATA

Every effort will be made to complete follow-up for all subjects and avoid missing data, in particular regarding essential items. For other cases of missing data, the "last observed value" (LOV) approach will be used when appropriate.

22.7 SUBJECT DISPOSITION

Data from subjects who are screened but not treated, subjects in the mITT and PP Analysis Sets, as well as trial withdrawals from study follow-up will be summarized using descriptive statistics.

22.8 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics, baseline data as well as disease prognostic factors, medical history, and prior medications will be summarized for the mITT analysis set using descriptive statistics.

22.9 CONCOMITANT MEDICATIONS USE

The WHO drug dictionary will be used to classify medications verbatim for Concomitant Medication and Pre-Trial Medications.
Analysis of concomitant drug use will be performed in the following manner:

- Pre-Study IP Implantation Medications Use: Analyses will include coded medications that were initiated prior to study IP implantation, regardless stopping date. An incidence table including patient counts (no. of subjects) and percentages broken down by Medication Class and Preferred Term will be provided.
- Concomitant Medications Use (Post-Study IP Implantation): Analyses will include only coded medications that were consumed following study IP implantation, regardless if drug initiation date was before or after it. An incidence table including patient counts (no. of subjects) and percentages broken down by Medication Class and Preferred Term will be generated.

22.10 EVALUATION OF SAFETY

22.10.1 Treatment Emergent Adverse Events (TEAEs)

AEs will be recorded from the time a subject has signed the Informed Consent. All AEs reported by the investigators will be coded according to the current version of the MedDRA dictionary.
The following will be incorporated into the analysis of AEs:

- All analyses to be provided will include coded AEs.
- AEs analyses will include only the TEAEs, namely, those events which started following study IP implantation. Listings of both TEAEs and non-TEAES will be provided.
- Summary tables of TEAEs will be provided by Study Cohort and overall.
- The incidence (no. of subjects) and frequency (no. of events) of TEAEs will be provided when broken down by System Organ Class (SOC) and by Preferred Term (PT) according to MedDRA dictionary.
- Breakdowns of TEAEs by all of the AEs attributes (e.g. seriousness, severity) will also be provided.
- Breakdowns of TEAEs by age and sex will also be provided.
- The derived dictionary used in the analyses displaying the MedDRA System Organ Class (SOC), the Preferred Term (PT), and the AE Verbatim Term as specified by the Investigator, will be provided.

22.10.2 Safety Laboratory Tests

Analyses of safety laboratory data will be performed in the following manner:

- Summary tables of safety laboratory parameters will be provided by Study Cohort and overall.
- Box-Plots of laboratory measurements before study IP administration and afterwards by scheduled visit and will be provided. In this analysis baseline values are the measurements taken up study IP administration,

while "during trial" evaluations are the measurements taken after that time point.

- Descriptive statistics of quantitative tests results and changes from baseline by scheduled visit will also be provided. The analysis algorithm as described for the above Box-Plots assessments will be used for this analysis as well.
- Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal, or High. Shift analysis of the categorical change from baseline to each scheduled visit and to the last observed assessment will also be performed.
- A list of parameters and related cut-off values defining the potentially clinically significant (PCS) abnormal values will be outlined by the Sponsor. Measurements used in the analysis are those taken following study IP administration. The incidence tables of PCS lab values as well as the individual patient listing will be provided using the denominator which is the number of subjects with at least one post-baseline administration of trial medication. Individual subjects' listings of PCS measurements will also be presented.

22.10.3 Vital Signs

Analyses of vital signs (blood pressure, pulse, temperature, and respiration rate) will be performed in the following manner:

- Summary tables of vital signs will be provided by Study Cohort and overall.
- Box-Plots of vital signs before study IP administration and afterwards by scheduled visit and will be provided. In this analysis baseline values are the measurements taken up study IP administration, while "during trial" evaluations are the measurements taken after that time point.
- Descriptive statistics of quantitative tests results and changes from baseline by scheduled visit will also be provided. The analysis algorithm as described for the above Box-Plots assessments will be used for this analysis as well.
- A list of parameters and related cut-off values defining the potentially clinically significant (PCS) abnormal values will be outlined by the Sponsor. Measurements used in the analysis are those taken following study IP administration. The incidence tables of PCS lab values as well as the individual patient listing will be provided using the denominator which is the number of subjects with at least one post-baseline administration of trial medication. Individual subjects' listings of PCS measurements will also be presented.

22.10.4 ECG Assessments

As only qualitative ECG assessments are planned, any clinically relevant changes occurring from screening until the last trial visit will be recorded as an adverse event.

22.10.5 Physical Examination

Any clinically relevant changes occurring from screening until the last trial visit will be recorded as an adverse event.

22.11 TOLERABILITY ASSESSMENTS

Tolerability analysis will be based on the number and percent of subjects who failed to reach the [redacted] due to adverse events and overall discontinuation rate. The time to withdrawal due to adverse events and overall discontinuation rate, starting from the day of study IP administration will be presented using Kaplan-Meier curves.

A similar analysis approach will be repeated for the study Part 2 duration.

22.12 EVALUATION OF PRELIMINARY EFFICACY

The below listed endpoints will be used to evaluate the preliminary efficacy of OpRegen® treatment. Descriptive statistics will be used to assess the changes in these parameters and an attempt to assess potential dose response relationships in these metrics will be done.

22.12.1 Efficacy Endpoints of Clinical Relevance

Preliminary efficacy assessments will utilize the below listed parameters:

- Directional change in the GA lesion area over time
- Overall change in the GA lesion area of the study eye over time using SD-OCT and FAF
- Change from baseline over time in BCVA as measured by ETDRS chart
- Change from initial assessment over time in retinal sensitivity (as assessed by microperimetry)
- Change from baseline over time in Reading Speed Test
- Change from baseline over time in Low Luminance BCVA
- Correlation assessment between quantitative metrics derived from FAF images, SD-OCT images and CFP images
- Correlation assessment between functional and structural changes
- Change over time in NEI VFQ-25 Quality of Life score
- Change over time in Functional Reading Independence (FRI) Index score

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

22.13 HYPOTHESIS

The primary hypothesis is that there will be no dose-limiting toxicity (DLT) and that implantation of OpRegen® to subjects with progressive dry-form AMD with GA will be safe and well-tolerated.

For the purpose of this study DLT is defined as an SAE determined to be product-related.

A secondary null hypothesis is that there will be no difference in disease progression, as measured by retinal function and structure, between the treated and untreated regions in the treated eye and between treated and untreated eye of a subject.

22.14 STATISTICAL METHODS

For the primary hypothesis the dose will be defined to exceed the maximally tolerated dose (MTD) if at least two of the subjects in a cohort have DLT.

If the dose has not exceeded the MTD in Cohort 1, the study will proceed to Cohort 2, pending the DSMB review. If the dose has not exceeded the MTD in Cohort 2, the study will proceed to Cohort 3, pending the DSMB review of data from Cohorts 1 and 2. Enrollment of Cohort 4 will proceed only after review of the accumulated safety data by the DSMB.

For the secondary hypothesis concerning changes in retinal structure and function following OpRegen® implantation, the small number of subjects (3 per cohort in Cohorts 1 and 2, up to 6 in Cohort 3 and approximately 12 in Cohort 4) precludes any definitive assessment of change through formal statistical testing. However, the following data analytical techniques will be used to describe the retinal structure and function results: assessing the changes in treated eyes will involve comparing the magnitude of observed changes in retinal structure and function to the distribution of changes between visits in a given subject (including historical data, when available), and will be also compared to the same measures gathered from previously studied populations of similarly affected subjects.

Measurements of retinal structure and function made on the non-treated eye of each subject will also be examined in the same way as for the treated eye to evaluate the extent to which placebo effects or unexpected temporal trends may be contributing to observed changes in retinal function. The non-treated eyes form a good comparison group for the fellow treated eyes in terms of rate of enlargement of GA.

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24. PROTOCOL ATTACHMENTS

24.1 LABORATORY TESTS

Laboratory Tests Detailed List					
Immunology	**Performed by**	**Malignant Hematological Transformation**	**Performed by**	**Serology**	**Performed by**
HLA Typing	Central Lab	[redacted]	Central Lab	Hepatitis B Surface Ag	Central Lab
Complete Blood Count	**Performed by**	[redacted]	Central Lab	HCV Ab	Central Lab
White Blood Cells	Central Lab	[redacted]	Central Lab	HIV	Central Lab
Red Blood Cells	Central Lab	**Automated Differential ***	**Performed by**	EBV	Central Lab
Hemoglobin	Central Lab	Neutrophils	Central Lab	CMV	Central Lab
Hematocrit	Central Lab	Lymphocytes	Central Lab	**Rheumatology**	**Performed by**
MCV	Central Lab	Monocytes	Central Lab	ESR	Central Lab
MCH	Central Lab	Eosinophils	Central Lab	CRP	Central Lab
MCHC	Central Lab	Basophils	Central Lab	**Drug Levels**	**Performed by**
Platelets	Central Lab	Large Unstained Cells	Central Lab	[redacted]	External Lab
Coagulation	**Performed by**	Neutrophils Abs	Central Lab	**Tuberculosis**	**Performed by**
PT_sec	Central Lab	Lymphocytes Abs	Central Lab	Quantiferon Gold	Central Lab
INR	Central Lab	Monocytes Abs	Central Lab		
APTT_Sec	Central Lab	Eosinophils Abs	Central Lab		
Chemistry	**Performed by**	Basophils Abs	Central Lab		
Glucose	Central Lab	LUC Abs	Central Lab		
Phosphorus	Central Lab	**Hematology**	**Performed by**		
Uric Acid	Central Lab	ESR	Central Lab		
Creatinine Serum	Central Lab	**Urinalysis ****	**Performed by**		
BUN	Central Lab	Specific Gravity	Central Lab		
Total Protein	Central Lab	pH	Central Lab		
Albumin	Central Lab	Protein	Central Lab		
SGOT(AST)	Central Lab	Glucose	Central Lab		
SGPT(ALT)	Central Lab	Ketones	Central Lab		
Gamma GT	Central Lab	Bilirubin	Central Lab		
Alkaline Phosphatase	Central Lab	Leucocytes	Central Lab		
Bilirubin Total	Central Lab	Erythrocytes	Central Lab		
Calcium	Central Lab	Nitrites	Central Lab		
Sodium	Central Lab	Urobilinogen	Central Lab		
Potassium	Central Lab				
Chloride	Central Lab				
IGA Quant	Central Lab				
IGG Quant	Central Lab				
IGM Quant	Central Lab				
LDH LTOP	Central Lab				
CPK	Central Lab				

* When Large unstained cells are high or equal to 4.5% than the following microscopic parameters will be tested: atypical lymphocytes (% and abs), bands (% and abs), basophils (% and abs), eosinophils (% and Abs), neutrophils (% and abs.), monocytes (% and abs.), lymphocytes (% and abs.), Metamyelocytes (% and abs.), Myelocytes (% and abs.), NRBC (% and abs.), Promyelocytes (% and abs.).

**When urinalysis positive for Protein, WBC, or RBC, the following microscopic parameters will be tested: Leucocytes, Erythrocytes, Granular-Casts, Hyaline-Casts, Mucus, Crystals, and Bacteria