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Supplementary information

Partial recovery of visual function in a blind patient after optogenetic therapy

In the format provided by the authors and unedited

Supplementary Text

To assess safety, we performed combinations of five different tests during 15 patient visits over a period of 84 weeks. There were four visits before vector injection, one visit at injection, and ten visits after injection. The timing of the visits (in weeks) relative to vector injection was -4, -3, -2, -1, 0, 1, 2, 4, 9, 13, 17, 25, 38, 52, and 80, as shown in Extended Data Figure 2.

(1) We performed ocular examinations at every visit. This consisted of slit-lamp examination before and after pupil dilation of eyelids, eyelashes, palpebral and bulbar conjunctiva, cornea, anterior chamber, lens, and vitreous; tonometry measurement of intraocular pressure before pupil dilation; and funduscopy after pupil dilation. On each of the 15 visits, the results of the ophthalmic examinations were as follows: Keratic precipitates: not present; Anterior chamber: calm; Anterior chamber cell grade: 0 (scale from 0 to 4+, based on the recommendation of the Standardization of Uveitis Nomenclature (SUN) Working Group [1]); Anterior chamber flare grade: 0 (from 0 to 4+, SUN Working Group); Vitreous: normal; Vitreous cells grade: 0 (scale from 0 to 4+, SUN Working Group). There were no ocular adverse events.

(2) We examined the anatomy of the retina using spectral-domain Optical Coherence Tomography (OCT) at weeks -4, -3, -2, 1, 2, 4, 9, 13, 17, 25, 38, 52, and 80. The OCT images from all follow-up visits after injection were graded by the reading center (Coimbra Ophthalmology Reading Center) as similar (grade 0) to those from visits before injection (Grades: 0-Approximately the same, 1-Better, 2-Worse, 3-Not applicable). Note that there were similar hypo-reflective cyst-like spaces in both the fellow eye and the treated eye both before and after injection (Extended Data Figures 3-6). The hypo-reflective cyst-like spaces

are not considered as “true” intraretinal cysts and are commonly observed in late-stage retinitis pigmentosa as a consequence of outer retinal degeneration (degenerative loss of outer retinal cells).

(3) We examined the anatomy of the retina on color fundus photographs (CFP) at weeks -4, 25, and 52. On CFP images (and at funduscopy), retinal vasculature with retinal vessel attenuation was visible (as part of the degenerative condition) before and after injection. There was no sign of vasculitis at any time point. Optic disc pallor and bone spicule hyperpigmentation were noted in both eyes before injection and this did not change after injection. Vitreous haze based on CFP was grade 0 (scale of 0 to 4+, National Institutes of Health grading system [2]).

(4) We examined the anatomy of the retina on fundus autofluorescence (FAF) images at weeks -4, 25, and 52 and we found no changes, as assessed by the investigator and graded by the reading center (Coimbra Ophthalmology Reading Center). The evaluation of the reading center at each of these three visits was: hypofluorescence compatible with bone spicule hyperpigmentation, no central hyperautofluorescence, and no parafoveal hyperautofluorescent ring.

(5) We performed a general physical examination and a 12-lead electrocardiogram at weeks -4 and 52. Vital signs (systolic and diastolic blood pressure, pulse rate) were recorded at weeks -4, 0, 1, 2, 4, 9, 13, 17, 25, 38, 52, and 80. The results of the physical examinations, vital signs, and 12-lead electrocardiograms were normal on all occasions.

In summary, there were no ocular or systemic adverse events at any of the visits. In addition, there were no self-reported adverse events, anomalies, or changes in health status of the patient at any time.

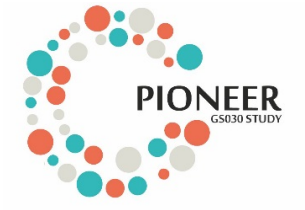
The OCT, CFP, and FAF images obtained are available to readers as a downloadable directory from:
https://passageinnovation-my.sharepoint.com/:f:/g/personal/mtaiel_gensight-biologics_com/EkUITiEa4AxNs_YryLq7fT8BGpdYkXZMWWtDK6Wg-fcQfA

References

1. Jabs, D. A., Nussenblatt, R. B., Rosenbaum, J. T., & Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* **140**, 509–516 (2005).
2. Nussenblatt, R. B., Palestine, A. G., Chan, C. C. & Roberge, F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology* **92**, 467–471 (1985).

CLINICAL STUDY PROTOCOL

A Phase 1/2a, Open-Label, Non-Randomized, Dose-Escalation Study to Evaluate the Safety and Tolerability of GS030 in Subjects with Retinitis Pigmentosa

Protocol Number:	GS030_CLIN_001
EudraCT Number:	2017-002204-27
Study Name/Logo	
Investigational Product:	GS030 Active substance: GS030-Drug Product (GS030-DP) - recombinant adeno-associated viral vector, derived from serotype 2 (rAAV2.7m8), containing the optimized channelrhodopsin ChrimsonR-tdTomato gene under the control of the ubiquitous CAG promoter (rAAV2.7m8-CAG-ChrimsonR-tdTomato). Associated Device: Visual Interface Stimulating Glasses (GS030-Medical Device [GS030-MD]).
Phase:	Phase 1/2a
Sponsor:	GenSight Biologics 74 Rue du Faubourg Saint-Antoine 75012 Paris France
Contract Research Organization:	ICON Clinical Research Ltd South County Business Park Leopardstown, Dublin 18 D18 X5R3 Ireland
Protocol Date	12 MAY 2020
Protocol Version:	Final V5.0

CONFIDENTIAL

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 1/2a, Open-Label, Non-Randomized, Dose-Escalation Study to Evaluate the Safety and Tolerability of GS030 in Subjects with Retinitis Pigmentosa

Protocol Number: GS030_CLIN_001

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation guidelines for current Good Clinical Practice and applicable regulatory requirements.

Sponsor Signatory

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Signature 

Date 12 May 2020

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SYNOPSIS

Protocol Number:

GS030_CLIN_001

Title:

A Phase 1/2a, Open-Label, Non-Randomized, Dose-Escalation Study to Evaluate the Safety and Tolerability of GS030 in Subjects with Retinitis Pigmentosa

Investigational Treatment: GS030

- Active Substance: GS030-Drug Product (GS030-DP)
- Medical Device: GS030-Medical Device (GS030-MD)

Phase:

Phase 1/2a

Objectives:

Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of escalating doses of GS030-DP administered via a single intravitreal injection (IVT) and repeated light stimulation using GS030-MD in subjects with non-syndromic retinitis pigmentosa (RP).

Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the treatment effect of GS030 as assessed by vision and ocular measures, including visual acuity, visual function, orientation and mobility, and quality of life (QoL).
- Compare visual acuity, visual function, orientation and mobility before and after gene transfer, with and without GS030-MD
- Evaluate immune response (humoral and cellular) to recombinant adeno-associated viral vector derived from serotype 2 (rAAV2.7m8), and to ChrimsonR-tdTomato (ChR-tdT) expressed protein.

Study Design:

This is a multicenter, Phase 1/2a, open-label, non-randomized, dose-escalation, safety and tolerability study.

Number of Subjects:

- Screening: 30 subjects
- Treated: 12 to 18 subjects (dose-escalation cohorts + extension cohort)
- There will be 3 dose-escalation cohorts with 3 subjects per each cohort. A traditional 3 + 3 dose-escalation design will be implemented. A fourth extension cohort will be enrolled using the highest well-tolerated dose.

Treatment: GS030

GS030-DP:

The doses to be studied are:

- Cohort 1: Low dose ~ 5.0×10^{10} vector genomes (vg) in treated eye
- Cohort 2: Medium dose ~ 1.5×10^{11} vg in treated eye
- Cohort 3: High dose ~ 5.0×10^{11} vg in treated eye

Doses are administered via a single IVT injection in a volume of 100 µL.

GS030-MD

The GS030-MD will be used to deliver light stimulation to the retina.

Study Duration:

- Study duration for each subject: 5 years after GS030-DP IVT
- Planned study initiation date: 2018
- Planned study completion: 2025

Study Population:

This study will include adult subjects with documented diagnosis of non-syndromic RP, which has been confirmed by means of full-field electroretinogram (ERG; any previously performed ERG is acceptable).

Targeted Level of Visual Function

To mitigate risk, the dose-escalation cohorts will include subjects with very severe vision loss:

- No light perception (NLP) level of visual acuity
- Light perception (LP) level of visual acuity

NLP and LP levels of visual acuity will be included in the dose-escalation cohort.

If safety is confirmed in subjects with NLP and LP upon Data Safety Monitoring Board review, and provided there is an early indication of the potential for vision restoration at the end of the dose-escalation portion of the study, the extension cohort may include subjects with less severe vision loss (hand motion or counting fingers [CF]).

Selection of Study Eye

If both eyes meet all inclusion criteria and no exclusion criteria, investigators will select the worse-seeing eye per subject perception for treatment. If the subject perceives no difference between the visual function of both eyes, the eye with worst visual acuity as assessed at the screening visit will be selected for treatment. If visual acuity is identical in both eyes, the right eye will be selected as the study eye.

Selection Criteria

Subjects must meet all selection criteria:

1. Signed informed consent form (ICF).
2. Age ≥18 years to ≤75 years at the time of ICF signature.
3. Diagnosis of non-syndromic RP defined as:
    a. Clinical diagnosis of non-syndromic RP based on history, mid-peripheral visual dysfunction, and fundoscopic appearance.
    b. Diagnosis of non-syndromic RP is confirmed on full-field ERG (any previously performed ERG is acceptable).

4. Visual acuity:
    a. Visual acuity in the dose-escalation cohorts of no better than LP.
    b. Visual acuity in the extension cohort of no better than CF pending review of dose-escalation cohort data by the DSMB.
5. Relatively preserved ganglion cell layer volume and retinal nerve fiber layer thickness, as measured with spectral domain optical coherence tomography (SD-OCT).
6. Retains memory of former useful vision.
7. Ability to obtain adequate pupillary dilation to permit thorough ocular examination and testing.
8. Negative serum pregnancy test for women of childbearing age only.
9. Female subjects (if of childbearing potential) must agree to use highly effective methods of birth control up to 12 months after GS030-DP IVT, and male subjects must agree to use condoms for up to 12 months after GS030-DP IVT. (Highly effective methods of birth control include: combined (estrogen and progesterone containing) hormonal contraception (oral, injectable or transdermal) associated with inhibition of ovulation; progesterone-only hormonal contraception (oral, injectable or transdermal) associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner (provided that partner is the sole sexual partner of the woman of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success); true sexual abstinence, when consistent with the preferred and usual lifestyle of the subject (sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).
10. Ability to wear, utilize, and follow all instructions on proper use of the GS030-MD.
11. Interpupillary distance of ≥51 mm and ≤72 mm.
12. Refractive error of the study eye between -9 diopters and +6 diopters.

Non-Selection Criteria

Subjects must not meet any non-selection criteria:

1. Prior receipt of any gene therapy.
2. Subjects participating in another clinical trial and receiving an investigational medicinal product within 90 days prior to Visit 1.
3. Subjects with systemic disease or other pathology other than that related to diagnosis of non-syndromic RP whose symptoms or associated treatments may affect vision, for example cancers or pathology of the central nervous system.
4. Subjects with systemic disease or other medical or psychiatric conditions that preclude safe participation in the study.
5. Subjects who are taking photosensitizing drugs used in psoralen plus ultraviolet light (PUVA) therapy for psoriasis, eczema, vitiligo, and other similar diseases, such as psoralens (also known as psoralene or methoxsalen) or photosensitizing drugs used for photodynamic therapy in the treatment of cancer or eye diseases, such as porfimer sodium (Photofrin®), aminolevulinic acid (Levulan®), or the methyl ester of aminolevulinic acid (Metvixia® cream), and other similar photosensitizing drugs/agents.
6. Subjects receiving immunosuppressive therapies, other than the immune modulating regimen described in this protocol.
7. Subjects of reproductive potential unwilling to use effective contraception for the 12 months after administration of GS030-DP.
8. Subjects who are pregnant or breastfeeding.
9. Subjects who are unwilling or unable to comply with the study protocol.
10. Subjects with any condition that would not allow them to complete follow-up examinations during the study and, in the opinion of the investigator, would make them unsuitable for the study.
11. Subjects who are human immunodeficiency virus (HIV) positive.
12. Subjects with known allergy to corticosteroids, or who will be unable to tolerate the corticosteroid regimen, or with an active intercurrent infection contraindicating treatment
13. Subjects who have undergone significant ocular surgery (per investigator determination) within 3 months prior to Visit 1.
14. Presence of narrow iridocorneal angles contraindicating pupillary dilation.

15. Presence of disorders of the ocular media which interfere with visual acuity and other ocular assessments, including SD-OCT, during the study period.
16. Presence of any systemic or ocular diseases, or pathologies, other than non-syndromic RP, or their associated therapies, that can cause or have the potential to cause vision loss.
17. Prior vitrectomy or vitreomacular surgery.
18. Presence of vitreo-macular adhesion or traction, epiretinal membrane macular pucker and macular hole, evident by ophthalmoscopy and/or by SD-OCT examinations and assessed by the investigator to significantly affect central vision.
19. Current evidence of retinal detachment assessed by the investigator to significantly affect central vision.
20. Active ocular inflammation or recurrent history of idiopathic or autoimmune-associated uveitis.
21. Hypersensitivity to GS030-DP or to any of the ingredients.
22. Presence of an Active Implantable Medical Device.
23. Subjects who have undergone thermal laser procedure to the retina within 3 months of trial entry, or any prior thermal laser procedure to the macular region.

Inclusion Criteria

Subjects must meet all inclusion criteria:

1. Review of all selection criteria to ensure continued compliance from Visit 2 through Visit 4.
2. Have a negative urine pregnancy test at Visit 4 for women of childbearing potential (women who are 2 years post-menopausal or surgically sterile are not considered to be of childbearing potential).
3. Have a negative test result for infection with HIV (results from test performed at Visit 1).
4. Ability to tolerate repeated light stimuli produced by the GS030-MD, as assessed in the inclusion phase (Visit 2 through Visit 4).

Exclusion Criteria

Subjects must not meet any exclusion criteria:

1. Any non-selection criteria which become applicable after the selection visit.
2. Presence, at the time of study inclusion, of infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
3. Presence of systemic illness, including alcohol and drug abuse (except nicotine), or medically significant abnormal laboratory values that are deemed by the investigator to preclude the subject's safe participation in the study.
4. Presence of illness or disease that, in the opinion of the investigator, include symptoms and/or associated treatments that can alter visual function, for instance cancers or pathology of the central nervous system.
5. Any medical or psychological condition that, in the opinion of the investigator, may compromise the safe participation of the subject in the study or would preclude compliance with the study protocol or ability of the subject to successfully complete the study.
6. The subject is unable or unwilling to comply with the protocol requirements.
7. Failure to demonstrate presence of either ganglion cell layer or recognizable retinal nerve fiber layer.

Replacement of Subjects:

Subjects may be replaced, if subject withdrawal occurs post-injection.

Withdrawal Criteria:

Subjects unable to tolerate, wear, or appropriately use GS030-MD at screening (Visit 1) and at all 3 inclusion visits (Visit 2 through Visit 4) will not continue in the study and will not receive GS030-DP.

Primary Safety Endpoint:

Safety and tolerability of GS030 treatment at Week 52/Year 1 based on local and systemic safety issues, specifically those related to IVT of GS030-DP and the subsequent repeated use of GS030-MD, as assessed by incidence of adverse events (AEs).

Secondary Endpoints:

  - Assessment of the treatment effect on visual function, functional vision and mobility, with the change from baseline to Week 52 of parameters measured with FrACT, Humphrey visual field 10-2, full-field threshold stimulus test (FST), Grating visual Acuity Test (GAT) square localization test, direction of motion test, door task, line task, visual perception tests, eye-hand coordination, and, visual exploration and relative position

- Assessment of the treatment effect on structural changes of the posterior pole of the fundus from baseline to Week 52 with parameters measured with SD-OCT, color fundus photography, and fundus auto fluorescence (FAF).
- Assessment of the treatment effect on QoL changes from baseline to Week 52 with the Visual Function Questionnaire-25 (VFQ-25) and Short-Form Survey 36 Version 2 (SF-36v2).
- Humoral and cellular immune responses to rAAV2.7m8 and ChR-tdT expressed protein.

Safety Assessments:

- General ocular assessments:
  - Slit-lamp biomicroscopy (pre- and post-pupil dilation)
  - Intraocular pressure measurement
- Ocular imaging assessments:
  - Color fundus photography
  - Fundus autofluorescence
  - SD-OCT
- Adverse events
- Serious adverse events
- Adverse device effects
- Serious adverse device effects
- Laboratory parameters (hematology and clinical chemistry)
- Vital signs
- Physical examination
- 12-lead electrocardiogram
- Concomitant medications
- Testing for bio-dissemination (blood, urine, tears)
- Immune response will be evaluated by:
  - Humoral response to rAAV2.7m8 and ChR-tdT protein
  - Cellular response to rAAV2.7m8 and ChR-tdT protein

Assessments of Treatment Effect:

Vision and Ocular Assessments

- Perceptual Threshold:
  - Full field threshold stimulus test
- Visual field assessments:
  - Humphrey visual field 10-2
- Visual acuity assessments:
  - Freiburg Visual Acuity Test
  - Grating visual Acuity Test
- Visual function assessments:
  - Square localization
  - Direction of motion
- Orientation and mobility assessments:
  - Door task
  - Line task
  - Visual perception tests, eye-hand coordination
  - Visual exploration and relative position

Quality of Life Assessments

- Visual Function Questionnaire-25
- Short-Form Survey 36 Version 2

Statistical Analysis:

Safety:

All subjects treated with GS030-DP and GS030-MD will be evaluated for safety. No statistical tests will be performed; all safety assessments will be summarized in a descriptive manner.

Detection of Treatment Effect:

All subjects treated with GS030-DP and GS030-MD with baseline assessments of treatment effect will be evaluated at Week52/Year 1 (Visit 14). Treatment effect will be summarized in a descriptive manner. If feasible, statistical tests will be performed to compare treated and non-treated eyes within subjects.

Interim Analysis:

Interim analyses might be performed to support planning of further clinical development.

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAV	Adeno-associated virus
ADE	Adverse Device Effect
ADL	Activities of daily living
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
CAG	CMV enhancer + chicken β-actin promoter
CF	Counting fingers
ChR-tdT	ChrimsonR-tdTomato
CRO	Contract Research Organization
CTCAE	Common terminology criteria for Adverse Events
DD	Device Deficiency
DLT	Dose-limiting toxicity
DP	Drug Product
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERG	Electroretinogram
FAF	Fundus autofluorescence
FDA	Food and Drug Administration
FrACT	Freiburg visual acuity test
FST	Full-field threshold stimulus test
FU	Follow-up
GAT	Grating visual Acuity Test
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HU	Home Use
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IOP	Intraocular pressure
IRB	Institutional Review Board

IRD	Inherited Retinal Disease
IVT	Intravitreal injection
LP	Light perception
MD	Medical Device
MTD	Maximum tolerated dose
NLP	No light perception
QoL	Quality of Life
rAAV2.7m8	Recombinant adeno-associated viral vector, derived from serotype 2
RGC	Retinal ganglion cells
RP	Retinitis Pigmentosa
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD-OCT	Spectral-domain optical coherence tomography
SF-36v2	Short form survey 36 version 2
SUN	Standardization of uveitis nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
VFQ-25	Visual function questionnaire-25
vg	Viral genomes
VMD2	Vitelliform macular dystrophy

DEFINITION OF TERMS

GS030-DP	GS030-Drug Product (GS030-DP) - Recombinant adeno-associated viral vector, derived from serotype 2 (rAAV2.7m8), containing the optimized channelrhodopsin ChrimsonR-tdTomato gene under the control of the ubiquitous CAG promoter (rAAV2.7m8-CAG-ChrimsonR-tdTomato)
GS030-MD	Visual Interface Stimulating Glasses (GS030-Medical Device [GS030-MD]) that amplify the external visual stimulus to the optogenetically engineered retina

5 INTRODUCTION

5.1 Disease and Indication

Retinitis pigmentosa (RP) is a class of inherited retinal diseases (IRD) involving progressive degeneration of the rod and cone photoreceptors of the eye, typically starting in the mid-periphery and advancing towards the macula and fovea. In RP, rods are affected by mutations leading to night blindness (Hartong et al 2006). These cells degenerate from the periphery towards the center of the retina, resulting in tunnel vision. In late-stage RP, cone photoreceptors lose their outer segments, become light insensitive, and degenerate, causing loss of central visual acuity and eventually blindness (Hartong et al 2006; Fahim et al 2017; Klapper et al 2016).

RP is a genetically heterogeneous disease, affecting over 1 million individuals worldwide, with an estimated prevalence of 1 in 4,000 (Hartong et al 2006). IRD are a leading cause of blindness in individuals aged 65 years and younger in developed countries, and RP is the most common inherited retinal disorder (Hartong et al 2006; Liew et al 2014; Daiger et al 2014).

5.2 Current Treatment

Currently, no drug treatment is approved for RP in the United States (US) or Europe. One vision-restoring device is CE Marked for marketing in RP (March 2011): the Argus II Retinal Prosthesis System (Second Sight Medical Products, Inc, Sylmar, CA, US; H110002, February 2013). This device is also approved as a Humanitarian Use Device in the US. Similar to GS030, this device incorporates stimulating glasses, but the Argus II requires surgery to place an implant (retinal prosthesis) into the eye.

The eye is a relevant target for researchers developing innovative stem cell and gene therapies because it is small, easily accessible, and biologically well-understood and transparent, so the effect of treatment can be evaluated non-invasively. There are several gene therapies under development targeting the eye (Cookson 2016).

The most popular delivery vector for gene therapies is the adeno-associated virus (AAV) (Cookson 2016). An example of AAV ocular gene therapy showing success to date is the gene replacement therapy for *RPE65* (retinal pigment epithelium-specific 65kDa protein) in Leber's congenital amaurosis type 2, an early onset form of autosomal recessive retinal degeneration caused by mutations in the *RPE65* gene. Based on promising data from non-clinical studies, clinical trials were initiated involving subretinal administration of AAV2-h*RPE65* vectors. Based on Phase 3 trial results, AAV2-h*RPE65* became the first approved ophthalmic gene therapy product in the US and Europe (Petit et al 2016, Russell et al 2017).

AAV gene replacement therapies in clinical development, include treatments for MERTK RP, rab escort protein 1 choroideremia, and cyclic nucleotide-gated channel beta 3 achromatopsia. In the first clinical safety study for MERTK RP, 6 subjects received a subretinal injection of AAV-mediated gene therapy for retinal dystrophy (AAV2-VMD2-hMERTK), in which the MERTK cDNA was expressed under the control

of the promoter of the retinal pigment epithelium specific vitelliform macular dystrophy (VMD2) gene. Three subjects displayed improved visual acuity in the treated eye within the first week/month post-intervention, but the improvement declined to baseline 2 years post-treatment in 1 of the subjects. It is possible that the quality of treatment, including the number of cells treated and expression levels of MERTK, may have been too low to promote long-term benefits (Petit et al 2016).

In addition to the gene replacement therapies, mutation-independent therapies are under development for entire families of retinal degenerative diseases. Mutation-independent therapies have been in clinical studies for wet age-related macular degeneration and late-stage RP. Diseases that benefit the most from a mutation-independent approach are those associated with photoreceptor loss, in particular RP. This disease context is attractive for a mutation-independent treatment approach because, in the vast majority of cases the genetic defects are specific to rod photoreceptors, even though cones die as well. This secondary loss of cones causes severe visual disabilities and complete blindness in humans, so gene therapies that prolong cone function and survival could maintain the temporal window of useful vision (Petit et al 2016).

Optogenetic-based gene therapy is a mutation-independent therapy. It is a potential therapeutic technology currently explored for vision restoration in RP and other inherited retinal diseases. Optogenetics is a biological technique that uses light to control cells in living tissues. Neuronal cells are typically targeted for control through genetic modification leading to the expression of light-sensitive ion channels.

5.3 Investigational Product and Mechanism of Action

GenSight Biologics is developing GS030 as a therapeutic treatment based on an optogenetic gene therapy product targeting RGCs and encoding an optimized form of the channelrhodopsin Chrimson (ChrimsonR-tdTomato [ChR-tdT]) derived from the green algae *Chlamydomonas noctigama*.

Considering its mechanism of action, GS030 is expected to show a potential effect in subjects with a functional RGC layer amenable to GS030-Drug Product (GS030-DP) administration and stimulation with the Visual Interface Stimulating Glasses (GS030-Medical Device [GS030-MD]). Considering their persistence throughout the disease course, RGCs are an attractive target to restore light sensitivity in diseased retinas of subjects with inherited retinal photoreceptor dystrophies. Indeed, RGCs persist in the retina upon photoreceptor degeneration, and only modest remodeling is reported (Marc et al 2003; Jones et al 2016).

The GS030-DP is intended to deliver a photoactivatable protein to RGCs to restore photosensitivity that together with the stimulating device will lead to restoration of visual perception. GS030-DP will be delivered as a single administration by intravitreal injection (IVT). As a well-studied gene therapy vector, its expression is expected to be long-lasting.

The light sensitivity of the ChR-tdT opsin is lower than that of human opsins and cannot respond to natural light intensity. Therefore, a medical device is needed to provide a light source of appropriate intensity and wavelength to allow adequate light stimulation of the channelrhodopsin protein. Light intensity at the appropriate wavelength provided by the Visual Interface Stimulating Glasses (GS030-MD) is greater than what is naturally encountered in most normal lighting conditions. Therefore, the GS030 treatment combines the simultaneous action of 2 components: a drug product, GS030-DP (the gene therapy) and a medical device, GS030-MD (Visual Interface Stimulating Glasses).

Specifically, the GS030-MD:

- Performs visual image processing
- Provides the adapted light intensity needed to stimulate ChR-tdT
- Provides the adapted wavelength needed to stimulate ChR-tdT

5.4 Key Findings from Non-Clinical Studies

Key findings from non-clinical studies of GS030 that support the clinical program are described in detail in the investigator's brochure. Pharmacological and toxicological studies were conducted to demonstrate the safety and tolerability of IVT administration of the GS030-DP, as well as subsequent light stimulation of the transgene protein product. Preclinical proof-of-concept, product-optimization, and selection studies have been conducted in 2 animal models. The murine *rd1* model was used as it is a relevant and common retinal degeneration model mimicking the human RP condition, and remains the most relevant model in rodents. A cynomolgus monkey model was used because its eye size and retinal organization are similar to those of a human.

A 6-month Good Laboratory Practice (GLP) study addressing toxicity, biodistribution, and immunogenicity of GS030-DP in cynomolgus monkeys allowed the start of a Phase 1/2a clinical trial in RP. The study employed bilateral IVT administration at 2 dose levels, including the maximum feasible dose (7.21×10^{10} and 7.84×10^{11} viral genome [vg]/eye).

Results showed that single bilateral IVT administration of GS030-DP in cynomolgus monkeys at levels of 7.21×10^{10} and 7.84×10^{11} vg/eye followed by a 3-month or 6-month observation period primarily resulted in a dose-dependent inflammatory response, including findings of anterior segment cells, flare, fibrin, corneal keratic precipitates and/or corneal oedema, as well as perivascular retinal opacities (retinal sheathing) and vitreal opacities. This inflammation generally started at Day 3 and peaked at Day 28, with slight to severe inflammation in high-dose animals and very mild to moderate inflammation in low-dose animals, and showed resolution over the remaining of the observation period.

Associated minor changes in clinical pathology were present, mainly at the high dose, on Day 3 that were consistent with an inflammatory response, including mild to moderate increase in neutrophils and monocytes along with mild reductions in red cell mass and mild to moderate increases in fibrinogen. These changes were generally reversed by Day 7.

At necropsy (3 or 6 months after dose administration), GS030-DP-related microscopic findings occurred in the eye and optic nerve, generally in a dose-dependent manner and graded as minimal. Findings included mononuclear cell infiltration (graded minimal) in the retina, vitreous body, ciliary body, anterior or posterior chamber, filtration angle (trabecular meshwork and Schlemm's canal), and optic disc at both GS030-DP doses.

No GS030-DP-related changes were observed in clinical signs, body weight, food intake, electroretinogram (ERG), spectral domain optical coherence tomography (SD-OCT) imaging, clinical chemistry, urinalysis, cardiovascular, respiratory, and neurological endpoints. Periocular clinical signs and reductions in intraocular pressure (IOP) observed following injection of the high dose of the GS030-DP were considered to be secondary to the ocular inflammation induced by GS030-DP and/or associated with veterinary treatment. No specific treatment for ocular inflammation was given to the animals.

In conclusion, single bilateral intravitreal injection administration of GS030-DP in cynomolgus monkeys at levels of $7.21x10^{10}$ and $7.84x10^{11}$ vg/eye was overall well-tolerated over a 6-month observation period. The main event was dose-dependent ocular inflammation which showed signs of recovery during the 6-month observation period and was not associated with any retinal tissue destruction/reorganization or deleterious functional changes. Therefore, in the absence of adverse toxicological effects and since the ocular inflammation was less pronounced at the low dose, $7.21x10^{10}$ vg/eye, the no-observed-adverse-effect level (NOAEL) of a single bilateral intravitreal administration of GS030-DP in the cynomolgus monkeys was considered to be $7.21x10^{10}$ vg/eye.

Another GLP study was conducted to evaluate the potential retinal toxicity of 580-610 nm LED light in *rd1* blind mice treated with GS030-DP (7.84×10^{9} vg/eye) given by single bilateral intravitreal injection, approximately 5 weeks prior to 580-610 nm LED light exposure during 2 hours at two intensity levels (1.4×10^{16} and 1.7×10^{17} photons/cm^2/s). Animals were evaluated for at least 14 days following the 2-hour LED light exposure period.

No clinical observations were considered related to test article treatment during the pre-light or post-light exposure period. Ophthalmic findings in eyes administered with GS030-DP at 7.84×10^{9} vg/eye were comparable with those observed in control eyes prior to and following light exposure. Microscopic evaluation did not identify GS030-DP-related findings in the eyes or optic nerves, and no 580-610 nm LED light-related findings were identified in the retina.

In conclusion and within the context of this study, an approximate 2-hour exposure to 580-610 nm LED light at a nominal intensity up to 1.7×10^{17} photons/cm^2/s did not cause evidence of retinal toxicity in *rd1* mice that expressed ChR-tdT, following intravitreal administration of GS030-DP at a dose of 7.84×10^{9} vg/eye. We have designed the GS030MD such that the total exposure (dose) received by the human retina through GS030-MD light stimulation per period of 48 hours will not exceed the dose received by the mouse retina during the 2-hour light exposure.

Dose selection

For this first-in-human study, the three doses that will be evaluated (low, medium and high) have been selected based on preclinical pharmacodynamic results obtained in the non-human primate (NHP) dose-ranging pharmacological study (GS030_NC_PHAR_004) and on safety results obtained in the NHP preclinical toxicology studies (GS030_NC_TOX_001 and GS030_NC_TOX_004). These studies are detailed in the non-clinical IMPD submitted within the CTA package.

GS030-DP dose selection has been based on experimental data obtained in non-human primates (NHP) for the following reasons: (1) NHP and human ocular structure and organization are similar. These two species are the only ones having a macula and fovea pit; (2) Vitreous volume of macaque eye is only ~ 40% smaller than the human one; (3) Upon intravitreal injection of an AAV2.7m8 vector, transduction is strong in the non-human primate fovea, a region essential for high-acuity vision, as well as numerous regions beyond the fovea, and is increased compared to its parental serotype AAV2 (Dalkara *et al*. 2013).

The three clinical doses selected for the GS030_CLIN_001 study correspond to safe and underactive/active doses in non-human primates.

5.5 Known Potential Risks and Benefits

The known potential risks and benefits of GS030 are described in detail in the investigator's brochure. Briefly, the GS030-DP is intended for a single administration per eye, and the safety of AAV vectors is becoming increasingly well-known. It is expected that the primary adverse reaction to GS030-DP administration will be ocular inflammation, and that management of inflammation will be a standard component of pre- and post-administration care. In this study, a systemic immune modulating regimen will be utilized to prevent or reduce the extent of ocular inflammation from the GS030-DP (see Section 7.5.8). The dose response of inflammatory effects can be assessed in this study by inclusion of single escalating doses.

Another potential risk of the IVT is related to the localized administration of the AAV vector in the eye.

There is a potential - though likely limited - risk of the GS030-DP IVT to negatively affect vision. This risk would be greatest in subjects with better visual function, particularly those in the early stages of RP. This risk is mitigated by targeting low-vision subjects in this study. In low-vision subjects, GS030 is a restorative therapy and not a therapy intended to prevent decline or reverse pathology. It circumvents the pathology, thus targeting subjects who have already lost vision. The dose-escalation cohorts will include subjects with very severe vision loss (no light perception [NLP] and light perception [LP]). If safety is confirmed in subjects with NLP and LP upon Data Safety Monitoring Board (DSMB) review, and provided there is an early indication of the potential for vision restoration at the end of the dose-escalation portion of the study, the

extension cohort may include subjects with less severe vision loss (hand motion or counting fingers [CF]). The Freiburg Visual Acuity Test (FrACT) (with larger Landolt C optotypes for lower visual acuity subjects) and Grating visual acuity test (GAT) will be used to confirm hand motion and CF.

A long-term follow-up phase is included to continue to assess safety for up to 5 years post-GS030-DP IVT so that extensive, long-term follow-up data can be obtained on all subjects, and so that subjects can continue to use GS030-MD. The study follow-up period of 5 years post-GS030-DP IVT should be more than adequate to monitor the safety of GS030 use in subjects over time. Subjects will require training with GS030-MD to ensure that they understand proper handling of the device and potential device failures.

A treatment is currently available for RP, it is the medical device Argus II, which not only provides a lower resolution image than the one expected from the GS030 treatment, but also requires a surgical implant. GS030-DP is administered via IVT and is therefore less invasive than implant surgery, which could be an advantage of the product over the Argus II.

5.6 Rationale for the Study Design

GS030 is being developed for the treatment of inherited retinal disorders with an initial focus on RP. Because there are very few approved treatments for RP, there is limited need from a marketing or regulatory perspective to make special claims (e.g. safety, ease of use) beyond establishing safety and effectiveness in the target populations. The study protocol will allow for a robust analysis of the safety and tolerability of GS030. The planned clinical study endpoints assess visual function in the targeted indication. The study endpoints selected are standard visual, safety, and quality of life (QoL) assessments used in clinical trials. An optimized version of GS030-MD, that can be used at home, is introduced in the course of the clinical trial to assess the impact and potential benefits of GS030-MD use on a patient's real life In addition, giving the possibility to use the optimized GS030-MD at home may contribute to increasing the patient's adherence to treatment. Sample sizes are also consistent with previous studies of gene therapy starting in orphan indications.

6 STUDY OBJECTIVES

6.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of escalating doses of GS030-DP administered via a single IVT and repeated light stimulation using GS030-MD in subjects with non-syndromic RP.

6.2 Secondary Objectives

- Evaluate the treatment effect of GS030 as assessed by vision and ocular measures, including visual acuity, visual function, orientation and mobility, and QoL.
- Compare visual acuity, visual function, orientation and mobility before and after gene transfer, with GS030-MD and without GS030-MD.
- Evaluate immune response (humoral and cellular) to recombinant adeno-associated viral vector, derived from serotype 2 (rAAV2.7m8) and to the expressed ChR-tdT protein.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan: Description

Study GS030_CLIN_001 is a multicenter, Phase 1/2a, open-label, non-randomized, dose-escalation, safety and tolerability study of GS030-DP in association with GS030-MD in subjects with non-syndromic RP that is confirmed by full-field ERG. The study design will include a dose escalation of the vector encoding the ChR-tdT. This first-in-human study design will evaluate the safety and tolerability of GS030, the associated GS030-MD and GS030-DP, which is the treatment to be developed and considered for marketing.

The total study duration for 1 subject is up to 5 years post-GS030-DP IVT:

- Screening (Visit 1; up to 9 weeks before Visit 5; see Section 8.1)
- Inclusion Phase (Visit 2 through Visit 4; over 8 weeks; 3 separate visits; see Section 8.2)
- GS030-DP IVT Visit (Visit 5; 1 day; see Section 8.3)
- Post-GS030-DP Treatment Phase (Visit 6 through Visit 14; over 1 year; see Section 8.4)
- Long-Term Follow-up Phase: (Visit 15 through Visit 19; up to 5 years post-GS030-DP IVT (see Section 8.5)
- Home-use monitoring phase: When GS030-MD optimized for home use is available and the patient qualified to use it (see Sections 7.1.4.2 and 7.1.4.3), a monitoring phase will be organized over 6 months (see Table 2). Subjects will be then monitored according to the long-term follow-up phase schedule (*e.g.* starting at 1.5 Year-visit if the subject started using GS030-MD at home after completion of Week 24 Visit). Phone calls are added to the long term follow-up phase at Year 2.5, Year 3.5 and Year 4.5 (see Table 1 and Figure 3). The phone-call questionnaire will be provided in the Clinical Operation Manual.

  The GS030-MD optimized for home use consists of an optimised version of the GS030-MD complying with technical/regulatory requirements enabling its use at home (e.g. compliance with IEC 60601-1-11 standard).

Figure 2 shows the dose-escalation cohorts, the timing of dosing within each cohort, and dose escalation between each cohort.

Figure 3 shows the GS030_CLIN_001 study design.

The schedule of planned study assessments is shown in Table 1.

7.1.1 Screening (Visit 1)

Prior to undergoing any screening procedures, each subject or their legally authorized representative must sign and date the Informed Consent Form (ICF). Since subjects are severely visually impaired, the ICF should be read to the subject in addition to providing them with a printed copy of the document, as well as an audio version. An impartial witness must observe the consent process and must sign and date the ICF.

After providing informed consent via a signed ICF, all subjects will undergo a standardized screening visit to ensure that all selection (Section 7.4.2) and non-selection (Section 7.4.3) criteria defined in Section 7.4 are met. At this visit, subjects will undergo general assessments, vision and ocular assessments, measurement of physical features to assess ability to wear GS030-MD, measurement of distance between centre of selected eye and middle of nose bridge, and optical aberrations of the study eye (Section 8.1). Subjects who meet all selection and non-selection criteria, including ability to wear and utilize the GS030-MD, and follow all instructions regarding its proper use, will proceed to the inclusion phase after their study eye is identified. Subjects unable to physically tolerate, wear, or appropriately use GS030-MD will not continue in the study and will not receive GS030-DP.

7.1.2 Inclusion Phase (Visit 2, Visit 3, Visit 4)

The inclusion phase includes 3 visits that must be completed over an 8-week period; timing of visits over this 8-week period will be at the discretion of the subject and the investigator. Each visit can be performed over one or two days. The inclusion phase will ensure compliance with all inclusion/exclusion criteria (see Section 7.4.4 and Section 7.4.5, respectively), including the ability to tolerate GS030-MD and comply with all protocol requirements, in order to confirm eligibility to receive GS030-DP.

Baseline measurements as well as assessment of photophobia and the predefined GS030-MD stimulation parameters will be obtained (see Section 8.2). A standard procedure describing predefined GS030-MD stimulation parameters and assessment of photophobia will be provided in a separate Clinical Operations Manual.

One assessment to establish baseline vision values and one assessment to assess photophobia and tolerance to GS030-MD stimulating light may be performed on the same day, allowing for all 3 assessments for each to be completed within 3 visits. The baseline value for comparison to post-GS030-DP treatment outcomes will be the mean value of the 3 baseline vision tests performed during the inclusion phase.

All subjects will give blood samples for genotyping at Visit 4, since having an identified mutation is not a requirement at inclusion.

A systemic immune modulating regimen will be administered to prevent or reduce the extent of ocular inflammation from GS030-DP (see Section 7.5.8).

If subjects are deemed fully eligible at the end of the last inclusion phase visit (Visit 4), the subject will be considered fully qualified to receive GS030-DP at the GS030-DP IVT Visit (Visit 5, see Section 8.3).

7.1.3 GS030-DP IVT (Visit 5)

After confirming that all selection and non-selection criteria and inclusion and exclusion criteria continue to be met, all scheduled assessments will be performed as listed in the Schedule of Assessments for Visit 5 (see Table 1; see Section 8.4). Upon completion of the Visit 5 assessments, each subject will receive a single administration of GS030-DP in a volume of 100 µL in the study eye, following standard IVT preparation and administration procedures (Avery et al 2014). GS030-DP dosing at Visit 5 will occur according to the subject's assigned dose escalation cohort (see Section 7.2 below for the description of dose escalation).

A standard guidance for IVT of the GS030-DP preparation and administration will be provided in a separate Clinical Operations Manual.

7.1.4 Post-GS030-DP Treatment Phase (Visits 6 through 14)

After GS030-DP IVT, subjects will participate in the post-GS030-DP treatment phase from Visit 6 through Visit 14 over a period of 1 year post-GS030-DP IVT. Subjects will undergo ongoing safety and tolerability evaluations, vision and ocular assessments (including visual acuity, visual function, and orientation and mobility) and assessment of QoL according to the Schedule of Assessments (see Table 1; see Section 8.4). A specific monitoring phase will start at Week 24 or later on, once the patient is qualified to use GS030-MD at home (see Table 2).

GS030-MD use will begin at Week 8 (Visit 9), to allow for maximum transgene expression after GS030-DP IVT. During this period, subjects will complete all vision and ocular assessments with and without the GS030-MD so that direct, controlled comparisons can be achieved.

7.1.4.1 Training Sessions

Beginning at Week 12 (Visit 10), subjects will also participate in a minimum of 6 visual training sessions between Week 12 and Week 24 (Visit 10 through Visit 12). The training program will be proposed to subjects who demonstrate at least LP visual ability after GS030-DP IVT, utilizing the GS030-MD. Additional training sessions may be scheduled at the discretion of the training specialist (by following GS030-MD user manual) and the investigator if deemed useful for the subject. These sessions will be separate from scheduled study visits and will allow subjects to learn to better utilize theGS030-MD and to learn to appreciate and interpret visual perceptions provided by GS030. No visual, ocular, or orientation and mobility test results will be documented during the visual training sessions; however, orientation and mobility exercises will be included in the training program. Orientation and mobility exercises will be performed with the Visual Interface Stimulating Glasses (GS030-MD).

The GS030-MD optimized for home use will be provided to qualified subjects. Qualified subjects must have participated in a minimum of 2 training sessions with GS030-MD optimized for home use and utilization of the GS030-MD outside of the investigation site

must be deemed appropriate and safe by the investigator and training specialist. Use of the GS030-MD by the subject outside of the investigation site will not commence before completion of the Week 24 study visit; after Week 24 visit, additional training sessions may be needed for the patient to qualify.
A standard procedure for the visual training sessions will be provided in a separate Clinical Operation Manual.

7.1.4.2 GS030-MD for Home Use

The GS030 MD will be provided for home use to qualified subjects (see Section 7.1.4.2). A monitoring phase will be organized over 6 months once the subject starts using the GS030-MD at home. We note T1 as the first day the subject uses the device at home. The safety and tolerability of the use of the device at home will be assessed by the following seven scheduled visits post T1: Day 4; Week 1; Week 2; Week 4; Week 8; Week 16 and Week 24 (see Table 2). After Week 24 Visit post T1, the subject will get into the long-term follow-up phase with visit time points calculated post D0, D0 corresponding to the GS030-DP IVT.

In other words, a subject starting using GS030-MD at home after completion of Week 24 visit, will be monitored for 24 Weeks post T1 as previously described (7 scheduled visits post T1; see Table 2) and will enter into the long term follow-up period at 1.5 Years Visit (calculated post D0, D0 corresponding to the GS030-DP IVT).

User manuals for GS030-MD home use will be provided as separate documents:

- A User Manual for clinical sites,
- A Patient Manual for the patient in paper and audio formats.

The home-use monitoring visits over 24 weeks might be combined with scheduled study visits of the post-treatment phase or of the long-term follow-up phase if the timing corresponds. The study coordinator will make phone calls to the subject to check the use of the device at home, in terms of observance, technical aspects, practicality and comfort for the patient. The phone calls are scheduled post T1 at Week 3, Week 6 and Week 12. A home use questionnaire will be provided to run the phone calls and the visits in a consistent way over all sites. Phone calls are added in the long-term follow-up phase at Year 2.5, Year 3.5 and Year 4.5 (see Table 1 and Figure 3).

The home use questionnaire will be provided in the Clinical Operation Manual.

From the start of the GS030-MD home use, and until the end of subject participation in the study, the subject's ability to use the device will be assessed by the investigator at study visits/phone calls, and retraining may be decided at the investigator's discretion. For more information, please refer to the Clinical Operation Manual.

7.1.4.3 Interim Analysis

Interim analyses might be performed to support planning of further clinical development.

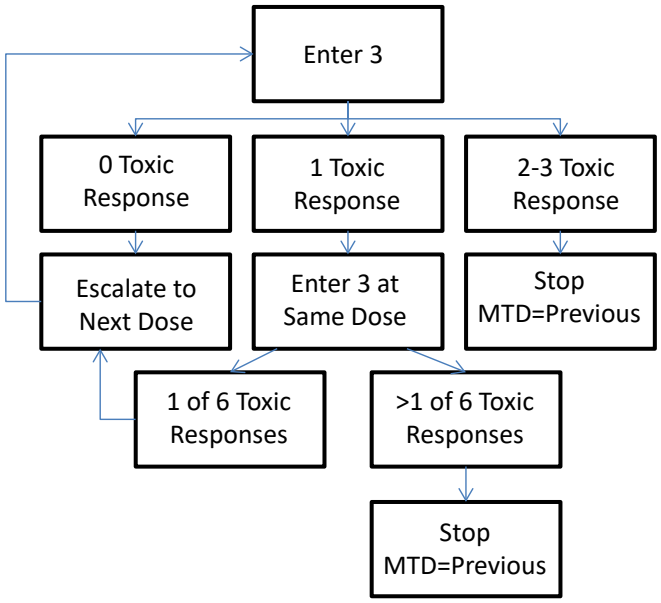
7.1.5 Long-Term Follow-up Phase (Visits 15 through 19)

To allow for extensive data collection and monitoring for all subjects, 5 follow-up visits will be conducted 1.5, 2, 3, 4, and 5 years post-GS030-DP IVT. Ongoing safety and tolerability assessments, vision and ocular assessments (including visual acuity, visual function, and orientation and mobility), and assessment of QoL will occur according to the Schedule of Assessments (see Table 1). Furthermore, once the patient uses GS030-MD at home, phone calls are added at Year 2.5, Year 3.5 and Year 4.5 (see Table 1 and Figure 3).

7.2 Description of Dose Escalation

GS030-DP will be administered via IVT at Visit 5 according to the subject's assigned dosing cohort. There will be 3 dose escalation cohorts with 3 subjects per each cohort to determine the maximum tolerated dose (MTD). A traditional 3 + 3 dose-escalation design will be implemented (Figure 1). A fourth extension cohort will be enrolled to further assess the safety of the highest well-tolerated dose.

Figure 1. 3 + 3 Dose-Escalation Design



Abbreviation: MTD = maximum tolerated dose.

Doses will include:

- Cohort 1: Low dose ~5.0×10^{10} vector genomes (vg) in treated eye
- Cohort 2: Medium dose ~1.5×10^{11} vg in treated eye
- Cohort 3: High dose ~5.0×10^{11} vg in treated eye
- Cohort 4: Extension cohort

- If the highest dose of ~5.0 × 10^{11}vg does not raise any safety concerns, additional subjects will be further enrolled at that dose.
- Otherwise, 3 to 9 subjects in the extension cohort will receive a single IVT of GS030-DP at the highest well-tolerated dose.

7.2.1 Safety Intervals within Each Cohort

There will be a 4-week interval between dosing in Subject 1 and the 2 following subjects (Subject 2/Subject 3) of each dosing cohort, in order to allow the principal investigator to make the decision to proceed to GS030-DP IVT in the second and third subjects of the cohort, based on the results of safety and tolerability of GS030-DP in the first subject (Figure 2).

7.2.2 Safety Intervals between Each Cohort and DSMB

A minimum of a 4-week interval will be maintained between the IVT in the last subject of a cohort and the cut-off for data collection for DSMB review (Figure 2). During this time, screening of subjects (i.e. Visit 1 only) may continue in accordance with the visit windows of the study schedule. No additional subjects will be treated with the GS030-DP until recommendations by the DSMB are received.

Safety data will be provided to the DSMB. The DSMB will periodically convene to review accumulating safety data and to provide a recommendation on study continuation (e.g. enrolling the next dose level) or early termination in the case of a safety concern. Details of data outputs provided for the meetings will be specified in the DSMB Charter.

See Section 7.4.7.1 for a description of dose-limiting toxicities (DLTs), dose escalation, and study stopping rules.

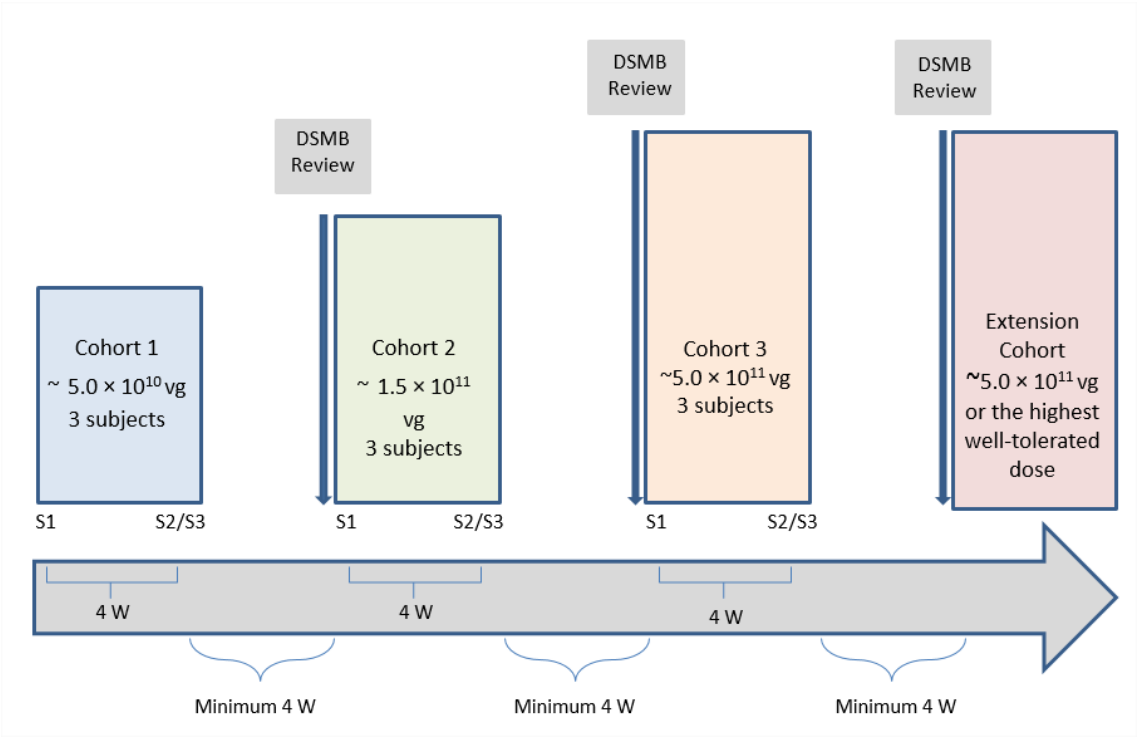
7.3 Study Design and Schedule of Assessments

Figure 2 shows the dose-escalation cohorts, the timing of dosing within each cohort, and dose escalation between each cohort.

Figure 3 shows the GS030_CLIN_001 study design.

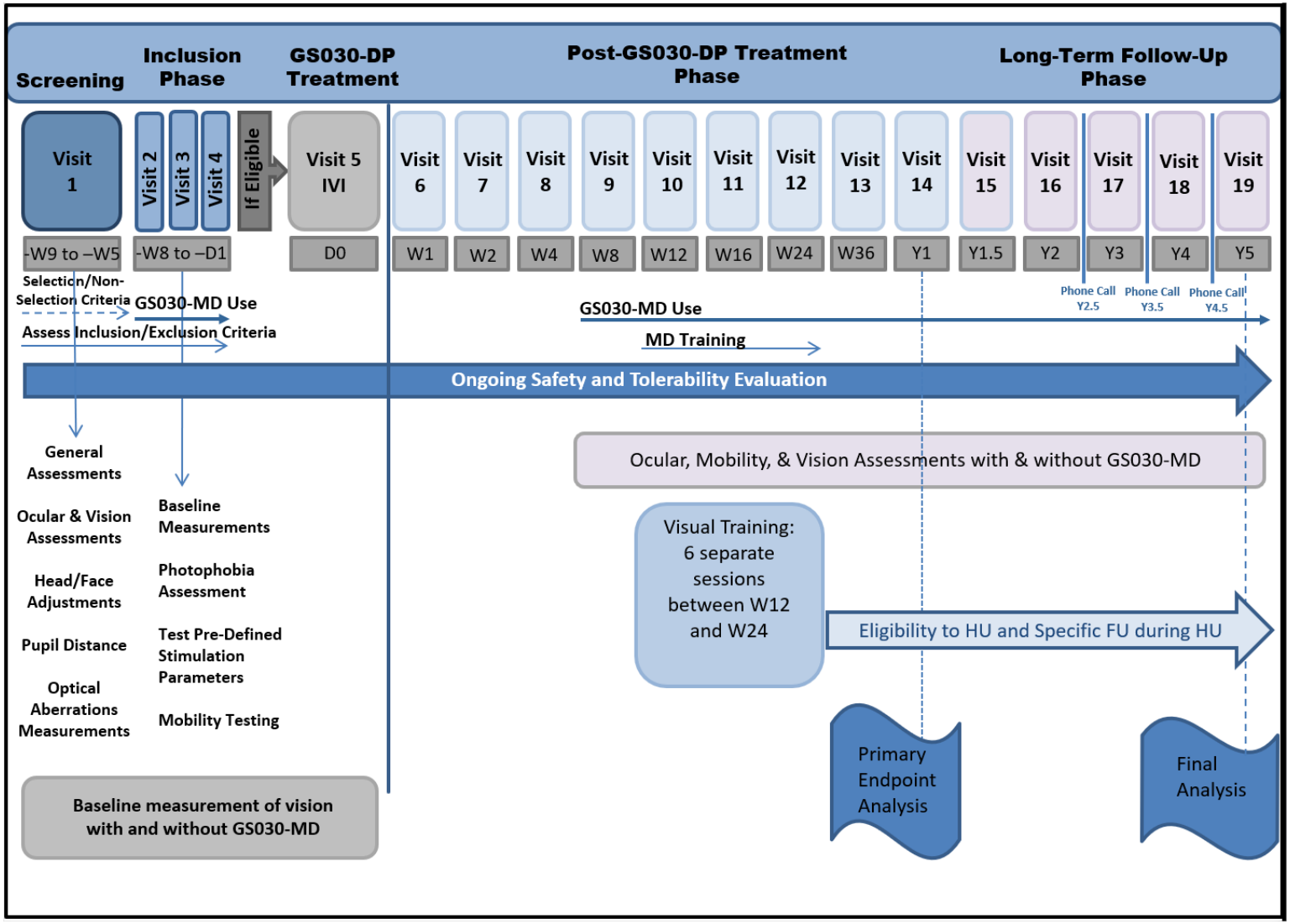
The schedule of planned study assessments is shown in Table 1.

Figure 2. Cohorts for Study GS030_CLIN_001.



Abbreviations: DSMB = Data Safety Monitoring Review Board; S = subject; vg = viral genomes; W = week

Figure 3. GS030_CLIN_001 Study Diagram.



Abbreviations: D = day; GS030-DP = GS030-Drug Product; GS030MD = GS030-Medical Device; IVT = intravitreal injection; W = week; Y = year.

Table 1. Schedule of Assessments

Assessment	**Screening**	**Inclusion Phase[a]**			**GS030-DP IVT**	**Post-GS030-DP Treatment Phase**									**Long-Term Follow-up Phase**							
Visit / Phone call (P)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**P1**	**17**	**P2**	**18**	**P3**	**19 EOS**
Study Time Point	**-W9 to -W5**	**-W8 to -D1**			**D0**	**W1**	**W2**	**W4**	**W8[b]**	**W12**	**W16**	**W24[n]**	**W36**	**W52/Y1**	**Y1.5**	**Y2**	**Y2.5**	**Y3**	**Y3.5**	**Y4**	**Y4.5**	**Y5**
Visit Window	**±3 D**	**±3D**		**-4D**		**±2D**	**±2D**	**±2D**	**±1W**	**±1W**	**±1W**	**±2W**	**±2W**	**±2W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**
Informed Consent	X																					
Selection/Non-Selection Criteria	X																					
Inclusion/Exclusion Criteria		X[c]			X																	
Diagnosis and Disease History	X																					
Prior Medications	X																					
Demographic Data (age, sex, year of birth, weight and height)	X																					
Medical/Surgical History	X																					
Physical Examination	X													X								X
12-Lead ECG	X													X								X
Vital Signs	X				X	X	X	X	X	X	X	X	X	X	X	X		X		X		X
Assessment of Physical Features for Ability to Wear GS030-MD[d]	X																					
Photophobia questionnaire	X	X[e]												X								
Home Use questionnaire																	X		X		X	
GS030-DP Administration					X																	
Training Sessions										X[f]												
Ocular and Vision Assessments[g]																						
BCVA[o]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Iris Color	X[q]																					
FrACT	X[h]	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
GAT		X	X	X					X	X	X	X	X	X	X	X		X		X		X
Humphrey Visual Field 10-2		X	X	X				X		X		X		X		X		X		X		X
Full field threshold stimulus test		X	X	X					X	X	X	X	X	X	X	X		X		X		X
Square Localization		X	X	X		X	X	X	X	X	X	X	X	X	X	X		X		X		X
Direction of Motion		X	X	X		X	X	X	X	X	X	X	X	X	X	X		X		X		X

Assessment	**Screening**	**Inclusion Phase[a]**			**GS030-DP IVT**	**Post-GS030-DP Treatment Phase**									**Long-Term Follow-up Phase**							
Visit / Phone call (P)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**P1**	**17**	**P2**	**18**	**P3**	**19 EOS**
Study Time Point	**-W9 to -W5**	**-W8 to -D1**			**D0**	**W1**	**W2**	**W4**	**W8[b]**	**W12**	**W16**	**W24[n]**	**W36**	**W52/Y1**	**Y1.5**	**Y2**	**Y2.5**	**Y3**	**Y3.5**	**Y4**	**Y4.5**	**Y5**
Visit Window	**±3 D**	**±3D**		**-4D**		**±2D**	**±2D**	**±2D**	**±1W**	**±1W**	**±1W**	**±2W**	**±2W**	**±2W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**
Full field electroretinogram (ERG)	X[m]																					
Slit-Lamp Examination – Pre- and Post-Pupil Dilation - Funduscopy	X				X[i]	X	X	X	X	X	X	X	X	X	X	X		X		X		X
Tonometry for IOP Measurement	X				X[i]	X	X	X	X	X	X	X	X	X	X	X		X		X		X
Color Fundus Photography	X											X		X								X
FAF	X											X		X		X		X		X		X
SD-OCT	X	X	X			X	X	X	X	X	X	X	X	X	X	X		X		X		X
Orientation and Mobility Assessments																						
Door Task			X							X	X	X		X		X		X		X		X
Line Task			X							X	X	X		X		X		X		X		X
Visual perception tests, eye-hand coordination			X							X	X	X		X		X		X		X		X
Visual Exploration and relative position			X							X	X	X		X		X		X		X		X
MD Usability Assessment																						
Medical Device Survey												X		X[p]								
Quality of Life Assessments[j]																						
VFQ-25				X								X		X		X		X		X		X
SF-36v2				X								X		X		X		X		X		X
Safety Assessments																						
Adverse Events/SAE	X																					
ADE/SADE	X																					
Prior/Concomitant Medications	X																					
Assess Ocular Inflammation (Treated Eye)						X	X	X	X	X	X	X	X	X								
Laboratory Assessments																						

Assessment	**Screening**	**Inclusion Phase[a]**			**GS030-DP IVT**	**Post-GS030-DP Treatment Phase**									**Long-Term Follow-up Phase**							
Visit / Phone call (P)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**P1**	**17**	**P2**	**18**	**P3**	**19 EOS**
Study Time Point	**-W9 to -W5**	**-W8 to -D1**			**D0**	**W1**	**W2**	**W4**	**W8[b]**	**W12**	**W16**	**W24[n]**	**W36**	**W52/Y1**	**Y1.5**	**Y2**	**Y2.5**	**Y3**	**Y3.5**	**Y4**	**Y4.5**	**Y5**
Visit Window	**±3 D**	**±3D**		**-4D**		**±2D**	**±2D**	**±2D**	**±1W**	**±1W**	**±1W**	**±2W**	**±2W**	**±2W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**	**±4W**
Hematology/Clinical Chemistry	X						X	X	X			X	X	X	X	X		X		X		X
Serum HIV Test	X																					
Serum Pregnancy Test	X																					
Urine Pregnancy Test[k]				X																		
Humoral Immune Response Against rAAV2.7m8 and ChR-tdT Protein				X		X	X	X	X	X	X	X	X	X								
Cellular Immune Response Against rAAV2.7m8 and ChR-tdT Protein				X		X	X	X	X	X	X	X	X	X								
Sample for Bio-Dissemination (Blood, Urine, Tears)				X	X[l]	X	X	X	X	X		X										
Genotyping				X																		

Abbreviations: ADE=adverse device effect; AE=adverse event; ChR-tdT=ChrimsonR-tdTomato; D=day; DOB=date of birth; ECG=electrocardiogram; EOS=end-of-study; FAF=Fundus autofluorescence; FrACT=Freiburg Visual Acuity Test; GAT=Grating Visual Acuity Test; GS030-DP =GS030-Drug Product; GS030-MD = GS030-Medical Device; HIV=human immunodeficiency virus; IOP=intraocular pressure; IVT=intravitreal injection; rAAV7.2m8=recombinant adeno-associated viral vector, derived from serotype 2; SADE=serious adverse device effect; SAE=serious adverse event; SD-OCT=spectral domain optical coherence tomography; SF-36v2=Short Form Survey 36 Version 2; VFQ-25=Visual Functioning Questionnaire-25; W=week; Y=year.

[a] The inclusion phase will be composed of 3 visits. Each visit can be performed over one or two days. One assessment to establish baseline vision values and one assessment to assess photophobia and tolerance to GS030-MD stimulating light may be performed on the same day, allowing for all 3 assessments for each measure to be completed within 3 visits. These 3 visits must occur within an 8-week period of time.

[b] After IVT of the GS030-DP subjects will begin to utilize the GS030-MD at study visits starting at Week 8. During this period, subjects will complete all vision and ocular assessments with the GS030-MD and without GS030-MD so that direct, controlled comparisons can be achieved.

[c] Inclusion/exclusion criteria will be assessed over the inclusion phase visits.

[d] This includes but is not limited to measurement of head-breadth, interpupillary distance, and optical aberrations. See separate user's manual for details.

[e] Determination of tolerance to the GS030-MD stimulating light will be performed over the inclusion phase visits.

[f] Subjects will undergo at least 6 visual training sessions, performed as separate visits from study visits, commencing at Week 12 and continuing through Week 24.

[g] All ocular and vision assessments will be performed on the treated and non-treated eye.

[h] Includes assessment of visual level for satisfying inclusion criterion for level of vision for study eligibility.

[i] The schedule for slit-lamp examination and IOP measurement is provided in the separate Clinical Operations Manual.

[j] Quality of life assessments must be performed prior to any ocular, vision, or mobility testing.

[k] Test must occur by Visit 4. Results must be available before the end of Visit 4.

[l] To be checked 4 hours post-IVT.

[m] Test must not be repeated if a previous ERG is already available.

[n] Use of the GS030-MD by the subject outside of the investigation site will not commence before completion of the Week 24 study visit and could start just after Week 24 visit completion or at later time point if additional training and/or training sessions are needed.

[o] Best Corrected Visual Acuity (BCVA) performed on the treated and non-treated eyes

[p] The Medical Device Survey will be replaced by the Home Use Questionnaire when the patient will use the GS030-MD at home

[q] Determination of iris color will be done on the first visit following the approval of the protocol amendment 4

Table 2 - Monitoring Phase during home use

Assessment	**Home-Use Monitoring Phase – Start just after Week 24 visit completion or at later time point**									
Study Time Point since Home Use start (T1)	Day 4 Visit	Week 1 Visit	Week 2 Visit	Week 3 Phone Call	Week 4 Visit	Week 6 Phone Call	Week 8 Visit	Week 12 Phone Call	Week 16 Visit	Week 24 Visit
Visit Window	± 1D	± 2D	± 2D	± 2D	± 1W	± 1W	± 1W	± 1W	± 1W	± 2W
Home Use Questionnaire	X	X	X	X	X	X	X	X	X	X
Ocular and Vision Assessments[b]										
BCVA[a]	X	X	X		X		X		X	X
FrACT	X				X				X	X
GAT	X				X				X	X
Full field threshold stimulus test	X				X				X	X
Slit Lamp Examination – Pre and post pupil Dilation - Funduscopy	X	X	X		X		X		X	X
Tonometry for IOP Measurement	X	X	X		X		X		X	X
FAF	X				X				X	X
SD-OCT	X	X	X		X		X		X	X
Safety Assessments										
Adverse Events/SAE/ADE/SADE	X									
Prior/Concomitant Medications	X									
Assess Ocular Inflammation	X	X	X		X		X		X	X

Abbreviations: H-U=Home-Use; ADE=adverse device effect; AE=adverse event; D=day; FAF=Fundus autofluorescence; FrACT=Freiburg Visual Acuity Test; GAT=Grating Visual Acuity Test; IOP=intraocular pressure; SADE=serious adverse device effect; SAE=serious adverse event; SD-OCT=spectral domain optical coherence tomography; W=week.

[a] BCVA performed on the treated and non-treated eyes
[b] Ocular and vision assessments will be performed on the treated eyes, except for BCVA performed on both eyes; ocular and vision assessments of the treated eye will be performed with and without the GS030-MD when applicable

7.4 Selection of Study Population

This study will include adult subjects with documented diagnosis of non-syndromic RP, which has been confirmed by means of full-field electroretinogram (ERG; any previously performed ERG is acceptable).

Targeted Level of Visual Function

To mitigate risk, the dose-escalation cohorts will include subjects with very severe vision loss:

- No light perception (NLP) level of visual acuity
- Light perception (LP) level of visual acuity

NLP and LP levels of visual acuity will be included in the dose-escalation cohort.

If safety is confirmed in subjects with NLP and LP upon DSMB review, and provided there is an early indication of the potential for vision restoration, at the end of the dose-escalation portion of the study, the extension cohort may include subjects with less severe vision loss (hand motion or counting fingers [CF]).

Selection of Study Eye

If both eyes meet all inclusion/exclusion criteria, investigators will select the worse-seeing eye per subject perception for treatment. If the subject perceives no difference between the visual function of both eyes, the eye with worst visual acuity as assessed at the screening visit will be selected for treatment. If visual acuity is identical for both eyes, the right eye will be selected as the study eye.

7.4.1 Number of Planned Subjects

Approximately 30 subjects are planned for screening in this study, with 12 to 18 subjects planned for treatment (dose-escalation cohorts + extension cohort) (see Section 10.2). It is estimated that 3 study sites in 3 countries will participate in this study.

Subjects who do not meet selection and non-selection criteria may be rescreened within 30 days. In this case, full screening procedures will be repeated and a new subject number will be assigned. Rescreening can only occur if GS030-DP has not been administered.

Refer to Section 10.2 for statistical considerations regarding sample size.

7.4.2 Selection Criteria

Subjects must meet all selection criteria:

1. Signed informed consent form (ICF).
2. Age ≥18 years to ≤75 years at the time of ICF signature.
3. Diagnosis of non-syndromic RP defined as:
    a. Clinical diagnosis of non-syndromic RP based on history, mid-peripheral visual dysfunction, and fundoscopic appearance.
    b. Diagnosis of non-syndromic RP is confirmed on full-field ERG (any previously performed ERG is acceptable).
4. Visual acuity:
    a. Visual acuity in the dose-escalation cohorts of no better LP.
    b. Visual acuity in the extension cohort of no better than CF pending review of dose-escalation cohort data by the DSMB.
5. Relatively preserved ganglion cell layer volume and retinal nerve fiber layer thickness, as measured with SD-OCT.
6. Retains memory of former useful vision.
7. Ability to obtain adequate pupillary dilation to permit thorough ocular examination and testing.
8. Negative serum pregnancy test for women of childbearing age only.
9. Female subjects (if of childbearing potential) must agree to use highly effective methods of birth control up to 12 months after GS030-DP IVT and male subjects must agree to use condoms for up to 12 months after GS030-DP IVT. (Highly effective methods of birth control include: combined (estrogen and progesterone containing) hormonal contraception (oral, injectable or transdermal) associated with inhibition of ovulation; progesterone-only hormonal contraception (oral, injectable or transdermal) associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner (provided that partner is the sole sexual partner of the woman of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success); true sexual abstinence, when consistent with the preferred and usual lifestyle of the subject (sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).
10. Ability to wear, utilize, and follow all instructions on proper use of the GS030-MD.
11. Interpupillary distance of ≥51 mm and ≤72 mm.
12. Refractive error of the study eye between -9 diopters and +6 diopters.

7.4.3 Non-Selection Criteria

Subjects must not meet any non-selection criteria:

1. Prior receipt of any gene therapy.
2. Subjects participating in another clinical trial and receiving an investigational medicinal product within 90 days prior to Visit 1.

3. Subjects with systemic disease or other pathology other than that related to diagnosis of non-syndromic RP whose symptoms or associated treatments may affect vision, for example cancers or pathology of the central nervous system.
4. Subjects with systemic disease or other medical or psychiatric conditions that preclude safe participation in the study.
5. Subjects who are taking photosensitizing drugs used in psoralen plus ultraviolet light therapy for psoriasis, eczema, vitiligo, and other similar diseases, such as psoralens (also known as psoralene or methoxsalen) or photosensitizing drugs used for photodynamic therapy in the treatment of cancer or eye diseases, such as porfimer sodium (Photofrin®), aminolevulinic acid (Levulan®), or the methyl ester of aminolevulinic acid (Metvixia® cream), and other similar photosensitizing drugs/agents.
6. Subjects receiving immunosuppressive therapies, other than the immune modulating regimen described in this protocol.
7. Subjects of reproductive potential unwilling to use effective contraception for the 12 months after administration of GS030-DP.
8. Subjects who are pregnant or breastfeeding.
9. Subjects who are unwilling or unable to comply with the study protocol.
10. Subjects with any condition that would not allow them to complete follow-up examinations during the study and, in the opinion of the investigator, would make them unsuitable for the study.
11. Subjects who are human immunodeficiency virus (HIV) positive.
12. Subjects with known allergy to corticosteroids, or who will be unable to tolerate the corticosteroid regimen or having an active intercurrent infection contra-indicating treatment
13. Subjects who have undergone significant ocular surgery (per investigator determination) within 3 months prior to Visit 1.
14. Presence of narrow iridocorneal angles contraindicating pupillary dilation.
15. Presence of disorders of the ocular media which interfere with visual acuity and other ocular assessments, including SD-OCT, during the study period.
16. Presence of any systemic or ocular diseases, or pathologies, other than non-syndromic RP, or their associated therapies, that can cause or have the potential to cause vision loss.
17. Prior vitrectomy or vitreomacular surgery.
18. Presence of vitreo-macular adhesion or traction, epiretinal membrane, macular pucker and macular hole, evident by ophthalmoscopy and/or by SD-OCT examinations and assessed by the investigator to significantly affect central vision.
19. Current evidence of retinal detachment assessed by the investigator to significantly affect central vision.
20. Active ocular inflammation or recurrent history of idiopathic or autoimmune-associated uveitis.
21. Hypersensitivity to GS030-DP or to any of the ingredients.
22. Presence of an Active Implantable Medical Device.

23. Subjects who have undergone thermal laser procedure to the retina within 3 months of trial entry, or any prior thermal laser procedure to the macular region.

7.4.4 Inclusion Criteria

Subjects must meet all inclusion criteria:

1. Review of all selection criteria to ensure continued compliance from Visit 2 through Visit 4.
2. Have a negative urine pregnancy test by Visit 4 for women of childbearing potential (women who are 2 years post-menopausal or surgically sterile are not considered to be of childbearing potential).
3. Have a negative test for infection with HIV (results from test performed at Visit 1).
4. Ability to tolerate repeated light stimuli produced by GS030-MD, as assessed during the inclusion phase (Visit 2 through Visit 4).

7.4.5 Exclusion Criteria

Subjects must not meet any exclusion criteria:

1. Any non-selection criteria that become applicable after the selection visit.
2. Presence, at the time of study inclusion, of infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
3. Presence of systemic illness, including alcohol and drug abuse (except nicotine), or medically significant abnormal laboratory values that are deemed by the investigator to preclude the subject's safe participation in the study.
4. Presence of illness or disease that, in the opinion of the investigator, include symptoms and/or associated treatments that can alter visual function, for instance cancers or pathology of the central nervous system.
5. Any medical or psychological condition that, in the opinion of the investigator, may compromise the safe participation of the subject in the study or would preclude compliance with the study protocol or ability of the subject to successfully complete the study.
6. The subject is unable or unwilling to comply with the protocol requirements.
7. Failure to demonstrate presence of either ganglion cell layer or recognizable retinal nerve fiber layer.

7.4.6 Replacement of Subjects

Subjects may be replaced if subject withdrawal occurs post-injection.

7.4.7 Withdrawal of Subjects from the Study

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal, when provided, will be documented in the electronic case report form (eCRF).

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data for subjects who withdrew from the study in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of serious AEs (SAEs) and serious Adverse Device Effects (SADEs), or if special circumstances concerning the GS030 IMP or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

7.4.7.1 Dose-Limiting Toxicity, Dose Escalation, and Study Stopping Rules

Every AE recorded in this study must be assessed by the investigator to determine whether it meets the definition of a dose-limiting toxicity (DLT).

A DLT is defined as any toxicity determined by the investigator to be RELATED to the study drug and/or medical device (*i.e.* GS030-MD) and deemed serious or sufficiently severe to preclude dose escalation.

For the purposes of this study, any event of grade 4 or 5 (per the Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) that is assessed as possibly, probably, or definitely related to the study drug and/or medical device (*i.e.* GS030-MD) will be considered to be a DLT.

7.4.7.2 Removal of Subjects

Subjects unable to tolerate, wear, or appropriately use GS030-MD at screening (Visit 1) and at all 3 inclusion visits (Visit 2 through Visit 4) will not continue in the study and will not receive GS030-DP.

7.5 Investigational Products

7.5.1 Identity of Investigational Products

GS030 treatment combines the simultaneous action of 2 components: a drug product GS030-DP (gene therapy) and a medical device, GS030-MD (Visual Interface Stimulating Glasses).

7.5.1.1 GS030-DP

The active substance is GS030-DP, a recombinant adeno-associated viral vector, derived from serotype 2 (rAAV2.7m8), bearing the optimized channelrhodopsin ChrimsonR-tdTomato gene, under the control of the ubiquitous CAG promoter (rAAV2.7m8-CAG-ChrimsonR-tdTomato).

GS030-DP is a sterile suspension of purified viral vector formulated in phosphate buffer solution (PBS) plus 0.001% Pluronic F68®. It is filled in vials and stored frozen at ≤ -70°C ready for intended medical use. Please refer to the Clinical Operations Manual for full details.

GS030-DP will only be dispensed with the written authorization of the investigator or a specifically designated delegate of the investigator. Please refer to the Clinical Operations Manual for full details.

7.5.1.2 GS030-MD

GS030-MD is composed of a head unit (head unit board, camera, micro-mirror array, light source, and projector), a pocket unit (battery, controller, and pocket unit board), a connector (high-speed link and power cable) and a charger unit. The device is controlled by functional and safety software applications.

GS030-MD is manufactured by GenSight Biologics.

GS030-MD will only be dispensed with the written authorization of the investigator or a specifically designated delegate of the investigator. Please refer to the Clinical Operations Manual for full details.

7.5.2 Device Complaints and Malfunctions and Complaint Reporting

Subjects will be instructed to contact the study investigator as soon as possible if there is a problem, deficiency, or malfunction with the GS030-MD, so that the situation can be assessed and a complaint issued.

7.5.3 Packaging and Labeling

The labels on the primary container (vial) and secondary container is in the country-specific language for each site. The labels are compliant with local regulatory requirements. The primary and secondary packaging together comply with the labelling requirements. Packaging of GS030-DP will be compliant with the International Air Transport Association (IATA) regulation for genetically modified organisms.

The GS030-MD is individually packaged. The package labelling is in the country-specific language for each site. The labels are compliant with local regulatory requirements. Packaging of GS030-MD will be compliant with the International Air Transport Association (IATA).

7.5.4 Method of Assigning Subjects to Treatment Groups

After the successful completion of the screening visit and all 3 inclusion phase visits, eligible subjects will receive GS030-DP IVT according to the cohort dose assignment (see Section 8.2 for a description of dose escalation).

7.5.5 Selection of Doses in the Study

The doses of GS030-DP to be studied are:

- Cohort 1: Low dose ~5.0×10^{10} vg in treated eye
- Cohort 2: Medium dose ~1.5×10^{11} vg in treated eye
- Cohort 3: High dose ~ 5.0×10^{11} vg in treated eye

7.5.6 Selection and Timing of Dose for Each Subject

Doses are administered via a single IVT in a volume of 100 µL. Subjects will be dosed according to their assigned dose cohort (see Section 7.2 for a description of dose escalation).

7.5.7 Masking

Not applicable, as this is an open-label study.

7.5.8 Prior and Concomitant Therapy

All prior medications and procedures received by the subject within 90 days before Visit 1 will be recorded. Concomitant medication use will be recorded throughout the study. Information to be recorded includes name of medication, daily dose, route of administration, frequency, and reason for use. Any procedures or non-pharmacologic interventions should also be recorded.

A systemic immune modulation regimen will be utilized to prevent or reduce the extent of ocular inflammation from the GS030-DP. Subjects will be given a 5-week course of oral corticosteroid at a daily dose of 0.5 mg/kg of body weight for 1 week before administration of the gene therapy, 1 mg/kg for the first week after administration, 0.5 mg/kg for the second week, 0.25 mg/kg for the third week, and 0.125 mg/kg for the fourth week. The daily dose for the patient of oral corticosteroid should be ≤60 mg per day, to prevent over-dosing with the corticosteroid regimen. All medications or procedures utilized to prevent or reduce the extent of ocular inflammation will be recorded.

Topical (ocular) immune modulating agents (e.g. anti-inflammatory or steroid eye drops) may be used at the discretion of the investigator based on the clinical status of each subject.

7.5.8.1 Prohibited Medication/Therapy

Prohibited medications include any IMP received within 90 days before Visit 1, as well as photosensitizing drugs like psoralen plus ultraviolet light therapy for psoriasis, eczema, vitiligo, and other similar diseases, or photosensitizing drugs used for photodynamic therapy in the treatment of cancer or eye diseases. These may include psoralens (also known as psoralene or methoxsalen), porfimer sodium (Photofrin®), aminolevulinic acid (Levulan®), or the methyl ester of aminolevulinic acid (Metvixia® cream), and other similar photosensitizing drugs/agents. These medications must be discontinued or switched to an allowable alternative medication 90 days before the screening visit (Visit 1).

It should be noted that this list is not exhaustive. Investigators should contact the sponsor's medical monitor to discuss any medications not on this list.

Subject with known allergy or who will be unable to tolerate the corticosteroid regimen (see Section 7.5.8) should not be selected for this study.

Prior receipt of any gene therapy is prohibited.

7.5.9 Treatment Compliance

GS030-DP will be administered as a single IVT at the study site. Compliance will be confirmed by study personnel.

GS030-MD use will be monitored via subject interview and documented beginning at Week 8 (Visit 9), with documentation of use continuing for the remaining study visits.

8 TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent via a signed ICF before any study-related procedures are performed.

The planned study assessments are detailed in Table 1.

8.1 Screening Visit (Visit 1)

Screening visit assessments will include:

- Obtaining ICF
- Assessment for eligibility using selection and non-selection criteria
- General Assessment
  - Diagnosis and disease history
  - Prior medications
  - Demographic data
  - Medical/surgical history
  - Physical examination
  - 12-lead electrocardiogram (ECG)
  - Vital signs assessment
  - Hematology/clinical chemistry panels
  - Serum HIV test
  - Serum pregnancy test
- Vision and Ocular Assessments
  - Best Corrected Visual Acuity (BCVA)
  - Iris Color measurement
  - Freiburg visual Acuity and Contrast Test (FrACT)
  - Full field electro retinogram (ERG)
  - Slit-lamp examination (pre- and post-pupil dilation)
  - Tonometry for IOP
  - Color fundus photography
  - Fundus autofluorescence (FAF)
  - SD-OCT
- Measurement of physical attributes (including Distance between centre of selected eye and middle of nose bridge, and optical aberrations of the study eye) for the ability to wear GS030-MD.
  - If the GS030-MD does not fit adequately resulting in the subject's inability to wear GS030-MD, the subject will be considered a screen failure.
- Determination of the study eye
- Photophobia assessment (Photophobia questionnaire).

After confirming that all selection and non-selection criteria have been met and that GS030-MD fits adequately, subjects will proceed to the inclusion phase.
See Section 7.4.1 for rescreening guidelines.

8.2 Inclusion Phase (Visit 2, Visit 3, and Visit 4)

During the 3 inclusion phase visits, continued compliance with all selection and non-selection criteria will be confirmed. Inclusion and exclusion criteria will be assessed during the inclusion phase. The 3 inclusion phase visits must be completed over an 8week period; timing of visits over this time period will be at the discretion of the subject and the investigator. Each visit can be performed over 1 or 2 days.

One assessment to establish baseline vision values and one assessment to assess photophobia and tolerance to GS030-MD stimulating light may be performed on the same day, allowing for all 3 assessments for each to be completed within 3 visits. The baseline value for comparison to post-GS030-DP treatment outcomes will be the mean value of the 3 baseline vision tests performed during the inclusion phase.

The inclusion phase visits will:

- Establish baseline vision values (evaluated in 3 separate assessments) using:
  - BCVA
  - Iris Color measurement if it is not assessed at the screening visit
  - FrACT
  - GAT
  - Humphrey visual field 10-2
  - Full field threshold stimulus test
  - Square localization
  - Direction of motion
- Assess photophobia and tolerance to repeated light stimulation with the GS030-MD stimulating light (evaluated over 3 separate assessments). A standard procedure for photophobia assessment will be provided in a separate Clinical Operations Manual.
- Test predefined stimulation parameters with specific psychophysical vision tests before GS030-DP administration
  - A standard procedure for detecting visual acuity and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
  - The pulse length is set by default and cannot be changed or modified by the clinical site personnel.

8.2.1 Inclusion Visit 2

The following procedures will be performed at Visit 2:

- Assess compliance with inclusion and exclusion criteria

- Record any AEs/Adverse Device Effects (ADEs) that have occurred since the previous visit and any changes in concomitant medication
- Assess tolerance of the GS030-MD stimulating light and photophobia (Photophobia questionnaire)
- Establish baseline vision values per the Schedule of Assessments
- Perform SD-OCT
- Iris Color measurement if it is not assessed at previous visit

8.2.2 Inclusion Visit 3

The following procedures will be performed at Visit 3:

- Assess compliance with inclusion and exclusion criteria
- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess tolerance of the GS030-MD stimulating light and photophobia (photophobia questionnaire)
- Establish baseline vision values per the Schedule of Assessments
- Perform SD-OCT
- Assess orientation and mobility
- Iris Color measurement if it is not assessed at previous visit

8.2.3 Inclusion Visit 4

The following procedures will be performed at Visit 4:

- Assess compliance with inclusion and exclusion criteria
- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess QoL (Note: QoL assessments must be performed prior to any vision and ocular assessments [including visual acuity, visual function, orientation and mobility])
- Assess tolerance of the GS030-MD stimulating light and photophobia (Photophobia questionnaire)
- Establish baseline vision values per the Schedule of Assessments
- Perform urine pregnancy test
- Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Collect sample for bio-dissemination (blood, urine, tears)
- Collect sample for genotyping (having an identified mutation is not a requirement for inclusion)
- Iris Color measurement if it is not assessed at previous visit

- Assess final outcome for tolerance of the GS030-MD; if tolerated, subjects will then proceed to the treatment visit for administration of GS030-DP
- Confirm full eligibility

8.3 GS030-DP IVT Visit (Visit 5)

After confirming that all selection and non-selection criteria and inclusion and exclusion criteria continue to be met, subjects will be considered fully qualified to receive GS030-DP IVT.

Each subject will receive a single administration of GS030-DP in the study eye, following standard IVT preparation and administration procedures according to the cohort dose assignment (see Section 7.2).

The following procedures will be performed at Visit 5, prior to the GS030-DP IVT:

- Assess compliance with inclusion and exclusion criteria
- Record vital signs
- Perform slit-lamp examination pre- and post-pupil dilation
- Iris Color measurement if it is not assessed at previous visit

The following procedures will be performed at Visit 5, pre- and post-IVT:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Perform tonometry for IOP (the schedule for IOP measurement is provided in the Clinical Operations Manual)

The following procedure will be performed at Visit 5 post-IVT:

- Collect sample for bio-dissemination (blood, urine, tears) 4 hours post-IVT

8.4 Post-GS030-DP Treatment Phase (Visit 6 through Visit 14/Year 1)

In this phase, subjects will continue to be assessed for safety at each post-GS030-DP treatment visit. Safety and tolerability assessments, vision and ocular assessments (including visual acuity, visual function, orientation and mobility), as well as evaluation of QoL will occur per the Schedule of Assessments (see Table 1). GS030-MD use will begin at Week 8, and a minimum of 6 visual training sessions will occur from Week 12 to Week 24 (See Section 7.1.4.1). During this phase, the visit can be done over one or two separate days depending on the availability of the site staff and the patient, especially when there is orientation and mobility assessment.

8.4.1 Week 1 (Visit 6) (± 2 days)

The Week 1 visit (Visit 6) will take place 1 week ± 2 days after the GS030-DP IVT visit. The following procedures will be performed at Visit 6:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess ocular inflammation (treated eye)
- Record vital signs
- Perform ocular and vision assessments per the Schedule of Assessments
- Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Collect samples for bio-dissemination (blood, urine, tears)
- Iris Color measurement if it is not assessed at previous visit

Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur without GS030-MD.

8.4.2 Week 2 (Visit 7) (± 2 days)

The Week 2 visit (Visit 7) will take place 1 week ± 2 days after the previous visit. The following procedures will be performed at Visit 7:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess ocular inflammation (treated eye)
- Record vital signs
- Perform ocular and vision assessments per the Schedule of Assessments
- Collect samples for hematology and clinical chemistry tests
- Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Collect samples for bio-dissemination (blood, urine, tears)
- Iris Color measurement if it is not assessed at previous visit

Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur without GS030-MD.

8.4.3 Week 4 (Visit 8) (± 2 days)

The Week 4 visit (Visit 8) will take place 2 weeks ± 2 days after the previous visit. The following procedures will be performed at Visit 8:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication

- Assess ocular inflammation (treated eye)
- Record vital signs
- Perform vision and ocular assessments per the Schedule of Assessments
- Collect samples for hematology and clinical chemistry tests
- Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Collect samples for bio-dissemination (blood, urine, tears)
- Iris Color measurement if it is not assessed at previous visit

Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur without GS030-MD.

8.4.4 Week 8 (Visit 9) (± 1 week)

The Week 8 visit (Visit 9) will take place 4 weeks ± 1 week after the previous visit. The following procedures will be performed at Visit 9:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess ocular inflammation (treated eye)
- Record vital signs
- Perform vision and ocular assessments per the Schedule of Assessments
- Collect samples for hematology and clinical chemistry tests
- Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Collect samples for bio-dissemination (blood, urine, tears)
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Iris Color measurement if it is not assessed at previous visit

At Week 8, subjects will begin using GS030-MD. Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur with GS030-MD and without GS030-MD.

8.4.5 Week 12 (Visit 10) (± 1 week)

The Week 12 visit (Visit 10) will take place 4 weeks ± 1 week after the previous visit. The following procedures will be performed at Visit 10:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess ocular inflammation (treated eye)
- Record vital signs
- Perform vision and ocular assessments per the Schedule of Assessments
- Assess orientation and mobility
  Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Collect samples for bio-dissemination (blood, urine, tears)
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Iris Color measurement if it is not assessed at previous visit

Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur with GS030-MD and without GS030-MD.

At Week 12, subjects should initiate at least 6 training sessions (performed separately from study visits according to procedures described in the Clinical Operations Manual) and undergo the door and line tasks to assess orientation and mobility. These sessions will occur between Week 12 and Week 24.

8.4.6 Week 16 (Visit 11) (± 1 week)

The Week 16 visit (Visit 11) will take place 4 weeks ± 1 week after the previous visit. The following procedures will be performed at Visit 11:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess ocular inflammation (treated eye)
- Record vital signs
- Perform vision and ocular assessments per the Schedule of Assessments
- Assess orientation and mobility
  Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Iris Color measurement if it is not assessed at previous visit

Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur with GS030-MD and without GS030-MD.

At Week 16, subjects should continue training sessions (performed as separate visits from study visits according to a procedure described in the separate Clinical Operations Manual) and undergo the door and line tasks to assess orientation and mobility. These sessions will occur between Week 12 and Week 24.

8.4.7 Week 24 (Visit 12) (± 2 weeks)

The Week 24 visit (Visit 12) will take place 8 weeks ± 2 weeks after the previous visit. The following procedures will be performed at Visit 12:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess ocular inflammation (treated eye)
- Record vital signs
- Assess QoL (Note: QoL assessments must be performed prior to any vision and ocular assessments [including visual acuity, visual function, orientation and mobility])
- Perform vision and ocular assessments per the Schedule of Assessments
- Assess orientation and mobility
- Collect samples for hematology and clinical chemistry tests
- Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Complete medical device survey regarding usability of the GS030-MD
- Collect samples for bio-dissemination (blood, urine, tears)
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Iris Color measurement if it is not assessed at previous visit

Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur with GS030-MD and without GS030-MD.

At Week 24, subjects should complete training sessions (performed separately from study visits according to a procedure described in the separate Clinical Operations Manual) and undergo the door and line tasks to assess orientation and mobility. These sessions will occur between Week 12 and Week 24.

From this starting point and after, at least 2 training sessions performed with GS030-MD optimized for the home-use, the patient may perform a qualification test to see if the

patient can use the device at home (via a qualification questionnaire, see Clinical Operation Manual).

8.4.8 Week 36 (Visit 13) (± 2 weeks)

The Week 36 visit (Visit 13) will take place 12 weeks ± 2 weeks after the previous visit. The following procedures will be performed at Visit 13:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess ocular inflammation (treated eye)
- Record vital signs
- Perform vision and ocular assessments per the Schedule of Assessments
- Collect samples for hematology and clinical chemistry tests
- Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
  Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Iris Color measurement if it is not assessed at previous visit

Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur with GS030-MD and without GS030-MD.

8.4.9 Week 52/Year 1 (Visit 14) (± 2 weeks)

The Week 52/Year 1 visit (Visit 14) will take place 16 weeks ± 2 weeks after the previous visit. The following procedures will be performed at Visit 14:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Assess ocular inflammation (treated eye)
- Record vital signs
- Perform a physical examination
- Perform a 12-lead ECG
- Assess QoL (Note: QoL assessments must be performed prior to any vision and ocular assessments [including visual acuity, visual function, orientation and mobility])
- Perform vision and ocular assessments per the Schedule of Assessments
- Assess orientation and mobility
- Collect samples for hematology and clinical chemistry tests

- Collect samples for humoral and cellular immune response against rAAV2.7m8 and expressed ChR-tdT protein
- Complete medical device survey regarding usability of the GS030-MD
- Assess photophobia and tolerance of the GS030-MD stimulating light (Photophobia questionnaire)
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Iris Color measurement if it is not assessed at previous visit

Vision and ocular assessments (including visual acuity, visual function, orientation and mobility) will occur with GS030-MD and without GS030-MD.

8.5 Long-Term Follow-up Phase (Visit 15 through Visit 19)

8.5.1 Year 1.5 (Visit 15) (± 4weeks)

The Year 1.5 visit (Visit 15) will take place 26 weeks ± 4 weeks after the previous visit. The following procedures will be performed at Visit 15:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Record vital signs
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Perform vision and ocular assessments per the Schedule of Assessments with GS030-MD and without GS030-MD
- Collect samples for hematology and clinical chemistry tests
- Iris Color measurement if it is not assessed at previous visit

8.5.2 Year 2 (Visit 16) (± 4weeks)

The Year 2 visit (Visit 16) will take place 1 year ± 4 weeks after the previous visit. The following procedures will be performed at Visit 16:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Record vital signs

- Assess QoL (Note: QoL assessments must be performed prior to any vision and ocular assessments [including visual acuity, visual function, orientation and mobility])
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Perform vision and ocular assessments per the Schedule of Assessments with GS030-MD and without GS030-MD
- Assess orientation and mobility
- Collect samples for hematology and clinical chemistry tests
- Iris Color measurement if it is not assessed at previous visit

8.5.3 Year 3 (Visit 17) (± 4 weeks)

The Year 3 visit (Visit 17) will take place 26 weeks ± 4 weeks after the previous visit. The following procedures will be performed at Visit 17:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Record vital signs
- Assess QoL (Note: QoL assessments must be performed prior to any vision and ocular assessments [including visual acuity, visual function, orientation and mobility])
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Perform vision and ocular assessments per the Schedule of Assessments with GS030-MD and without GS030-MD
- Assess orientation and mobility
- Collect samples for hematology and clinical chemistry tests
- Iris Color measurement if it is not assessed at previous visit

8.5.4 Year 4 (Visit 18) (± 4 weeks)

The Year 4 visit (Visit 18) will take place 1 year ± 4 weeks after the previous visit. The following procedures will be performed at Visit 18:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Record vital signs

- Assess QoL (Note: QoL assessments must be performed prior to any vision and ocular assessments [including visual acuity, visual function, orientation and mobility])
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Perform vision and ocular assessments per the Schedule of Assessments with GS030-MD and without GS030-MD
- Assess orientation and mobility
- Collect samples for hematology and clinical chemistry tests
- Iris Color measurement if it is not assessed at previous visit

8.5.5 Year 5 (Visit 19) (± 4 weeks) (End of Study)

The Year 5 visit (Visit 19) will take place 1 year ± 4 weeks after the previous visit. The following procedures will be performed at Visit 19:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Record vital signs
- Perform a physical examination
- Perform a 12-lead ECG
- Assess QoL (Note: QoL assessments must be performed prior to any vision and ocular assessments [including visual acuity, visual function, orientation and mobility])
- Test predefined stimulation parameters of the device with specific psychophysical vision tests. It is a standard procedure for detecting perceived resolution and setting automatically the range of parameters of the GS030-MD (irradiance level, pixel size, maximum percentage of active pixels) is provided in the User Manual.
- Perform vision and ocular assessments per the Schedule of Assessments with GS030-MD and without GS030-MD
- Assess orientation and mobility
- Collect samples for hematology and clinical chemistry tests
- Iris Color measurement if it is not assessed at previous visit

8.6 Home-Use Monitoring Phase from start of GS030-MD use at home: T1 through 24 Weeks post T1

Please refer to Table 2.

The Home-Use Monitoring Phase will complement the initial schedule of assessment and follow-up (see Table 1) once the patient is qualified to use the device at home (see Section 7.1.4.2). A monitoring phase will be organized over 6 months once the subject starts using the GS030-MD at home. We note T1 as the first day the subject uses the device at home. The safety and tolerability of the device use at home will be assessed by the following seven scheduled visits post T1: Day 4; Week 1; Week 2; Week 4; Week 8; Week 16 and Week 24 (see Table 2).

After Week 24 Visit post T1, the subject will get into the long-term follow-up phase with visit time points calculated post D0, D0 corresponding to the GS030-DP IVT.

For example, a subject starting using GS030-MD at home after completion of Week 24 visit, will be monitored for 24 Weeks post T1 as previously described (7 scheduled visits post T1; see Table 2) and will enter into the long term follow-up period at 1.5 Years Visit (calculated post D0, D0 corresponding to the GS030-DP IVT).

User manuals for GS030-MD home use will be provided as separate documents:

- A User Manual for clinical sites
- A Patient Manual for the patient in paper and audio formats

The home-use monitoring visits over 24 Weeks might be combined with scheduled study visits of the post-treatment phase or of the long-term follow-up phase if the timing corresponds. The study coordinator will make phone calls to the subject to check the use of the device at home, in terms of observance, technical aspects, practicality and comfort for the patient. The phone calls are scheduled post T1 at Week 3, Week 6 and Week 12. A home use questionnaire will be provided to run the phone calls and the visits in a consistent way over all sites. Phone calls are added in the long-term follow-up phase at Year 2.5, Year 3.5 and Year 4.5 (see Table 1 and Figure 3).

The home use questionnaire will be provided in the Clinical Operation Manual.

8.6.1 T1

After the subject is qualified for use of GS030-MD at home, the subject will be provided with the GS030-MD.

T1 corresponds to the first of GS030-MD use at home for each subject.

8.6.2 Post-T1 Monitoring Phase for Home Use (Post T1 Day 4 Visit through Week 24 Visit)

8.6.2.1 Post T1 Day 4 Visit

Day 4 Visit will take place 4 days ± 1 day after the start of GS030-MD use at home. The following procedures will be performed at Day 4:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Perform Home use Questionnaire
- Perform ocular and vision assessments per the Schedule of Assessments (see Table 2); BCVA will be performed on both eyes; other ocular and vision assessments will be performed on the treated eye
- Ocular and vision assessments of the treated eye will be performed with and without the GS030-MD when applicable

8.6.2.2 Post T1 Week 1 Visit

Week 1 Visit will take place 1 week ± 2 days after the start of GS030-MD use at home. The following procedures will be performed at Week 1:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Perform Home use Questionnaire
- Perform ocular and vision assessments per the Schedule of Assessments (see Table 2); BCVA will be performed on both eyes; other ocular and vision assessments will be performed on the treated eye
- Ocular and vision assessments of the treated eye will be performed with and without the GS030-MD when applicable

8.6.2.3 Post T1 Week 2 Visit

Week 2 Visit will take place 2 weeks ± 2 days after the start of GS030-MD use at home. The following procedures will be performed at Week 2:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Perform Home use Questionnaire
- Perform ocular and vision assessments per the Schedule of Assessments (see Table 2); BCVA will be performed on both eyes; other ocular and vision assessments will be performed on the treated eye
- Ocular and vision assessments of the treated eye will be performed with and without the GS030-MD when applicable

8.6.2.4 Post T1 Week 3 Phone Call

Week 3 Phone Call will take place 3 weeks ± 2 days after the start of GS030-MD use at home. The study coordinator, or a delegated trained member of the study team, will call the subject to address the home use Questionnaire.

8.6.2.5 Post T1 Week 4 Visit

Week 4 Visit will take place 4 weeks ± 2 days after the start of GS030-MD use at home. The following procedures will be performed at Week 4:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Perform Home use Questionnaire
- Perform ocular and vision assessments per the Schedule of Assessments (see Table 2); BCVA will be performed on both eyes; other ocular and vision assessments will be performed on the treated eye
- Ocular and vision assessments of the treated eye will be performed with and without the GS030-MD when applicable

8.6.2.6 Post T1 Week 6 Phone Call

Week 6 Phone Call will take place 6 weeks ± 2 days after the start of GS030-MD use at home. The study coordinator, or a delegated trained member of the study team, will call the subject to address the home use Questionnaire.

8.6.2.7 Post T1 Week 8 Visit

Week 8 Visit will take place 8 weeks ± 2 days after the start of GS030-MD use at home. The following procedures will be performed at Week 8:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Perform Home use Questionnaire
- Perform ocular and vision assessments per the Schedule of Assessments (see Table 2); BCVA will be performed on both eyes; other ocular and vision assessments will be performed on the treated eye
- Ocular and vision assessments of the treated eye will be performed with and without the GS030-MD when applicable

8.6.2.8 Post T1 Week 12 Phone Call

Week 12 Phone Call will take place 12 weeks ± 2 days after the start of GS030-MD use at home. The study coordinator, or a delegated trained member of the study team, will call the subject to address the home use Questionnaire.

8.6.2.9 Post T1 Week 16 Visit

Week 16 Visit will take place 16 weeks ± 2 days after the start of GS030-MD use at home. The following procedures will be performed at Week 16:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Perform Home use Questionnaire
- Perform ocular and vision assessments per the Schedule of Assessments (see Table 2); BCVA will be performed on both eyes; other ocular and vision assessments will be performed on the treated eye
- Ocular and vision assessments of the treated eye will be performed with and without the GS030-MD when applicable

8.6.2.10 Post T1 Week 24 Visit

Week 24 Visit will take place 24 weeks ± 2 days after the start of GS030-MD use at home. The following procedures will be performed at Week 24:

- Record any AEs/ADEs that have occurred since the previous visit and any changes in concomitant medication
- Perform Home use Questionnaire
- Perform ocular and vision assessments per the Schedule of Assessments (see Table 2); BCVA will be performed on both eyes; other ocular and vision assessments will be performed on the treated eye
- Ocular and vision assessments of the treated eye will be performed with and without the GS030-MD when applicable.

8.7 Early Withdrawal (or Discontinuation) Visit

The following procedures will be performed at the Early Withdrawal Visit (procedures for this visit are consistent with Visit 19):

- Record any AEs/ADEs that have occurred since the last visit and any changes in concomitant medication
- Record vital signs
- Perform a physical examination and record any changes from baseline

- Perform a 12-lead ECG
- Assess QoL (Note: QoL assessments must be performed prior to any vision and ocular assessments [including visual acuity, visual function, orientation and mobility])
- Perform vision and ocular assessments per the Schedule of Assessments with GS030-MD and without GS030-MD
- Assess orientation and mobility
- Collect samples for hematology and clinical chemistry

9 VARIABLES TO ASSESS TREATMENT EFFECT AND SAFETY VARIABLES

Table 1 presents the planned Schedule of Assessments.

9.1 Population Characteristics

9.1.1 Demographics

Subject demographic data will be collected at screening (Visit1) and will include age, date of birth, and sex.

9.1.2 Medical/Surgical History

Medical/surgical history and diagnosis and disease history will be collected at screening (Visit 1) and will include medical and surgical, psychiatric, and medication histories, as well as non-pharmacologic interventions. Medication history should include concomitant medications as well as medications taken within the last 3 months prior to enrollment.

9.2 Variables to Assess Treatment Effect and Safety Measurements Assessed

9.2.1 Variables to Assess Treatment Effect

9.2.1.1 Perceptual Threshold Assessment

9.2.1.1.1 Full-Field Threshold Stimulus Test

The full-field threshold stimulus test (FST) measures the illuminance necessary to comfortably stimulate the most sensitive parts of the retina, and thus determines a quantifiable stimulation threshold that can be assessed before and after intervention.
This test is used to configure the GS030-MD on a per-visit basis.
The FST will be performed from Visit 2 through Visit 4, and from Visit 9 through Visit 19, and during the home-use monitoring phase per the Schedule of Assessments (see Table 2).

9.2.1.2 Visual Field Assessments

9.2.1.2.1 Humphrey Visual Field 10-2

Standardized, automated perimetry with Humphrey visual fields will be obtained, with central 10-2 strategy. This may be performed by a trained certified ophthalmic assistant (COA), certified ophthalmic technician (COT), nurse, or research coordinator.

The Humphrey visual field 10-2 will be performed **in both eyes** from Visit 2 through Visit 4, at Visit 12, Visit 14/Year 1, and Visit 19; and **only in the treated eye** at Visit 8, Visit 10, and from Visit 16 through Visit 18. This test is performed with and without GS030 MD.

9.2.1.3 Visual Acuity Assessments

9.2.1.3.1 BCVA

BCVA will be performed on both eyes per the Schedule of Assessments (see Table 1 and Table 2).

9.2.1.3.2 Iris Color assessment

The iris color will be assessed at one timepoint at the screening visit by using the scale provided on the Clinical Operation Manual. If the patient at the time of the protocol amendment approval is already included, the iris measurement will be done at his/her next visit.

9.2.1.3.3 Freiburg Visual Acuity & Contrast Test

The Freiburg Visual Acuity & Contrast Test (FrACT) assesses visual acuity and contrast sensitivity. It is a free computer program that uses graphics capabilities and psychometric methods to provide automated, self-paced measurement of visual acuity and contrast sensitivity.

The FrACT will be performed at all visits with the exception of Visit 5 (GS030-DP IVT Visit). This test is performed with and without GS030-MD, except from Visit 5 to Visit 7 included, where this test is performed without GS030-MD only. The FrACT will also be performed during the home-use monitoring phase per the Schedule of Assessments (see Table 2).

9.2.1.3.4 Grating Visual Acuity Test

The GAT is designed to determine a subject's visual discrimination power for different spatial frequencies, using the principles of acuity charts such as the Early Treatment Diabetic Retinopathy Study, modified for extremely low vision subjects. It measures the ability of subjects to determine the orientation of black and white bars and uses this information to calculate the highest spatial frequency the subject can correctly discriminate. The GAT is a 4-alternative forced-choice test, where black and white bars of different sizes are presented in 1 of 4 orientations (horizontal, vertical, diagonal to the left, or diagonal to the right). The bars are presented for 5 seconds; after 5 seconds, subjects are required to provide a response to each trial, even if they are just guessing (4AFC task). The bar width varies to evaluate the discrimination power at different spatial frequencies. The test will be used to configure the GS030-MD to the patient's visual abilities.

The GAT will be performed from Visit 2 through Visit 4, and from Visit 9 through Visit 19, and during the home use monitoring phase per the Schedule of Assessments (see Table 2).

9.2.1.4 Visual Function Assessments

9.2.1.4.1 Square Localization and Direction of Motion

Two additional spatial vision assessments will be performed. Square localization and direction of motion are designed to provide an objective measure of spatial vision in

subjects who cannot reach the lowest level of the visual acuity scale. These tests are inspired by 2 of the procedures included in the Basic Assessment of Light and Motion, developed by Bach et al. in 2010 (the Location Module and the Motion Module).

In square localization, subjects are placed 16 inches (40 cm) from a touch-screen monitor. On each trial, a white square is displayed at a random location on a black background, and the subject is instructed to try to touch the square. Subjects are allowed to scan their head to locate the square. A test consists of a total of 40 trials involving 3 different levels of contrasts between the target and the background, randomly presented. For each trial, the difference between the center of the target square and the subject's response is calculated; smaller values indicate more accurate results. The test is repeated with and without GS030-MD at baseline and the designated visits.

The direction of motion test is intended to objectively measure the ability of subjects to determine the direction of an object moving in the visual field. Subjects are placed 16 inches (40 cm) from a touch-screen monitor and are instructed to maintain head (camera) fixation on the center of the screen during the test. On each trial, after an audio prompt, a white line of fixed width sweeps across the touch-screen monitor in 4 different directions randomly selected (up/down, down/up, left/right and right/left). After the stimulus presentation, subjects are asked to confirm the direction of motion they perceived. A test consists of 40 trials involving 3 different levels of contrasts between the target and the background, randomly presented. The test is repeated with GS030-MD and without GS030-MD, except from Visit 5 to Visit 8 included, when this test is performed without GS030-MD only.

Square localization and direction of motion will be performed at all visits, with the exception of screening and Visit 5 (GS030-DP IVT Visit).

9.2.1.5 Orientation and Mobility Assessments

9.2.1.5.1 Door Task

The door task involves walking toward a high-contrast door on the wall. A simulated door made of black cloth on a white wall is placed across a room and the subject is asked to locate it, walk toward it, and touch it while wearing or not the GS030-MD. This task is repeated 12 times (6 times without the GS030-MD and 6 times with GS030-MD). Trials where the subject's hand is touching the door are considered successful. Subjects are tested with the non-treated eye patched during all runs.

The door task will be performed at Visit 3, from Visit 10 through Visit 12, Visit 14/Year 1 and from Visit 16 through Visit 19.

9.2.1.5.2 Line Task

The line task involves following a line on the floor. A white line is placed on the black floor and the subject is instructed to follow the line to the end. This task is repeated 12 times (6 times without the GS030-MD and 6 times with the GS030-MD). Trials where the subject stops within a predefined 75 cm² zone at the end of the line are considered successful. Repeating the tests with the GS030-MD and without GS030-MD within each test session provides an important control for variability in the room lighting and configuration conditions. No other visual aids are used without the GS030-MD. Subjects are tested with the non-treated eye patched during all runs.

The line task will be performed at Visit 3, from Visit 10 through Visit 12, Visit 14/Year 1, and from Visit 16 through Visit 19.

9.2.1.5.3 Visual perception tests, eye-hand coordination

This test is designed to provide a quantitative assessment of eye-hand coordination for the patient.
For the test, the patient sits at a distance of around 20 cm in front of a white table (at least 80cm wide) with two type of objects and at different contrast levels. The patient has to find the object on the table and then he has to touch it. This task is repeated in different conditions (changing the object size/color and the place), with the GS030-MD and without GS030-MD. Within each test session an important control is provided to follow the room lighting and configuration conditions. No other visual aids are used without the GS030-MD. Subjects are tested with the non-treated eye patched during all repetitions.

This test will be performed at Visit 3, from Visit 10 through Visit 12, Visit 14/Year 1, and from Visit 16 through Visit 19.

9.2.1.5.4 Visual Exploration and relative position

This test is designed to provide a quantitative assessment of visual exploration and relative positioning capabilities of the subject.
For the test, the patient sits at a distance of around 20 cm in front of a white table (at least 80cm wide) where up to 3 cups with different levels of contrast are placed on 6 different positions. The patient reports the number of objects perceived and information about their location on the table. This task is repeated in different conditions (changing the position, the number of cups and their contrast), with the GS030-MD and without GS030-MD. Within each test session an important control is provided to follow the room lighting and configuration conditions. No other visual aids are used without the GS030-MD. Subjects are tested with the non-treated eye patched during all runs.

This test will be performed at Visit 3, from Visit 10 through Visit 12, Visit 14/Year 1, and from Visit 16 through Visit 19.

9.2.1.6 Quality of Life Assessments

Vision-related QoL will be assessed using the Visual Function Questionnaire-25 (VFQ-25) and the SF 36v2 questionnaire. Both questionnaires will be presented in the local language and should be administered in a quiet room by a person certified to administer these types of questionnaires, before all other visit procedures are performed. As the subject will be unable to read due to vision impairment, a family member, other legal representative of the subject, or study physician will assist the subject in completing the questionnaire.

All QoL assessments will be performed at Visit 4, Visit 12, Visit 14/Year 1, and from Visit 16 through Visit 19.

9.2.1.6.1 Visual Functioning Questionnaire-25

The VFQ-25 is a 25-item questionnaire with 47 questions. Composite scale and subscales include: general health, general vision, ocular pain, near activities, distance activities, vision specific (social functioning, mental health, role difficulties, dependency), driving, color vision, and peripheral vision. Each question has several responses scored on a scale from 0 to 5, 0 to 6, or 0 to 10. Values are calculated in percentages.

9.2.1.6.2 Short Form Survey 36 Version 2

The SF-36v2 is a subject-rated 36-item questionnaire assessing subject health. There are 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-to-100 scale on the assumption that each question carries equal weight. A lower score indicates more disability, and a higher score indicates less disability (a score of 0 is equivalent to maximum disability, and a score of 100 is

equivalent to no disability). The 8 assessment sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.

9.2.1.7 Medical device survey

The medical device survey consists of verifying and validating all GS030-MD primary operating functions (involving user interaction) and collecting feedback on usability of the V1b device prototype to improve future versions.

The usability goals will be evaluated by user survey during the clinical trial. There will 2 questionnaires: one for the clinical site personnel and one for the subject. The questionnaires will be presented in the local language.
Clinical site personnel will be prompted to fill out their questionnaire.
Taking into account patient's condition, the clinical site personnel will also interview the subjects in order to get their feedback based on the subject's questionnaire that will be provided.

This survey will be completed by the patient at Visit 12 and Visit 14/Year 1.

For the Site Staff who handles the medical device, the survey will be completed V12 of the third patient from the extension cohort.

9.2.1.8 Home use Questionnaire

The home use Questionnaire will be used during the home use monitoring phase to observe:
-the use of the device at home, in terms of observance, technical aspects and practicality
-the patient comfort and tolerance with the device (eg. photophobia)
-the patient perception of changes in vision

This questionnaire will be provided to run the phone calls and visits in a consistent way over all sites. The study coordinator, or a delegated trained member of the study team, will address the questionnaire to the subject.

The questionnaire is addressed to the subject in the local language. Clinical site personnel will be prompted to fill out the questionnaire with the subject's answers.

9.2.1.9 Photophobia assessment and tolerance of the GS030-MD stimulating light (Photophobia questionnaire)

Photophobia will be assessed in a questionnaire presented in the local language, with the objective to assess any abnormal sensitivity or intolerance to light, to rate it and provide feedback on tolerability.
As the subject will be unable to read due to vision impairment, a family member, other legal representative of the subject, or study physician will assist the subject in completing the questionnaire.
This test will be completed from screening visit (Visit 1) through Visit 4, and at Visit 14/Year 1.

9.2.2 Safety Assessments

9.2.2.1 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence (unintended disease or injury or untoward clinical signs) in a clinical study subject administered an IMP/device which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product/device, whether it is related to the medicinal (investigational) product/device. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a non-leading question (e.g. “Have you experienced any new or changed symptoms since we last asked/since your last visit?”). AEs should be reported on the appropriate page of the eCRF.

Adverse Device Effect Definition

An ADE is defined as an Adverse Event related to the use of an investigational medical device. This includes:

- Any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device

- Any event that is a result of a use error or intentional misuse

Assessment of Severity

Common Terminology Criteria for Adverse Events Version 4.03 will be used.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, not bedridden).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE to the study drug/device, if any. Causality should be assessed using the categories presented in the following table:

Unrelated: Clinical event with an incompatible time relationship to study drug administration or use of the device, and that could be explained by underlying disease or other drugs or chemicals, or is incontrovertibly not related to study drug/device.

Unlikely: Clinical event or laboratory abnormality whose time relationship to study drug administration or use of the device makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.

Possibly: Clinical event or laboratory abnormality with a reasonable time relationship to study drug administration or use of the device, but that could also be explained by concurrent disease or other drugs or chemicals.

Probably: Clinical event or laboratory abnormality with a reasonable time relationship to study drug administration or use of the device, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Definitively: Clinical event or laboratory abnormality with plausible time relationship to study drug administration or use of the device, and that cannot be explained by concurrent disease or other drugs or chemicals.

Action Taken

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- GS030-MD use permanently stopped
- GS030-MD use temporarily interrupted
- Concomitant medication
- Other, specify

Follow-up of Adverse Events

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

Subjects should be followed up after receiving the dose of study drug according to the scheduled of assessment. Any AEs that occur should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event

- Classification as “serious” or “not serious”
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

9.2.2.2 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose:

- Results in death.
- Is life-threatening. An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that might have caused death if it had occurred in a more serious form.
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF.)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject’s ability to carry out normal life functions.)
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious, and that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Serious Adverse Device Effect Definition

A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. This includes device deficiencies that might have led to an SAE if (a) suitable action had not been taken or (b) intervention had not been made or (c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

A planned hospitalization for pre-existing condition or a procedure required by the protocol, without a serious deterioration in health, is not considered to be an SAE.

Device Deficiency

A medical Device Deficiency (DD) is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse, or use error and inadequate labeling.

Reporting of Serious Adverse Events

Any AE/ADE as well as Device Deficiency must be reported by the investigator in the eCRF Safety report regardless of whether or not the event is considered to be related to the investigational product or not.

An eCRF Safety report consists of the AE form, ADE form, DD form, and the concomitant medication form. When the case is entered as **serious** AE/ADE and/or Device Deficiency and saved in the eCRF, the Pharmacovigilance group receives the SAE/SADE/DD notification via automatic alert from site to "ICON-Safety-CentralReceipt@iconplc.com". The Investigator needs to complete the SAE, SADE and DD forms and forward it to ICON PVSS within 24 hours, email address as above, the alert is only notifying the PVSS of the SAE, but the details and information is in the forms.

The investigator should not wait to receive additional information to document fully the event before notification of an SAE/SADE/DD, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

All SAE/SADE (expected and unexpected) will be reported by the sponsor to the EU National Competent Authorities without any delay after knowledge by sponsor of such a case.

The UADE and the SUSAR will be reported to the FDA respectively according to the 21 CFR Part 812, Section 812.150 and to the 21 CRF Part 312, section 312.32.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of IMP/device administration and linked by the investigator to this study, should be reported to the medical monitor.

The sponsor and/or the Contract Research Organization (CRO) will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the

study. In addition, the CRO, on behalf of the sponsor, will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all AEs that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided below.

Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study, in subjects or female partners of male subjects, should be confirmed and reported to the investigator. Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery.

Full details will be recorded on the withdrawal page of the eCRF, or an SAE report will be completed if the subject has completed the study.

9.2.2.3 Classification and Grading of Ocular Inflammation

Specific assessment and documentation of ocular inflammation will be required. Ocular inflammation is an expected event based on preclinical studies of GS030 and reports of preclinical and clinical studies of intravitreal administration of AVV-based vectors. Specific, standardized schemes for assessing anatomic location, severity and clinical evolution will be employed. Specific scales will be used for anterior uveitis (anterior chamber) and intermediate uveitis (vitreous).

The Standardization of Uveitis Nomenclature Working Group (Trusko et al 2013) provided standardized methods for (a) anatomic classification of uveitis; (b) grading scheme for anterior chamber cells; (c) grading scheme for anterior chamber flare; and (d) activity of uveitis terminology (for clinical evolution) (Jabs et al 2005). Investigators will grade cases of ocular inflammation according to these scales. These scales are provided in Table 3, Table 4, Table 5, Table 6 , and Table 7 below.

Table 3. Anatomic Classification of Uveitis (SUN Working Group)

Type	Primary Site of Inflammation[a]	Includes
Anterior uveitis	Anterior chamber	Iritis Iridocyclitis Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis Posterior cyclitis Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis Chorioretinitis Retinochoroiditis Retinitis Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

Abbreviation: SUN = Standardization of Uveitis Nomenclature.
[a] As determined clinically. Adapted from the International Uveitis Study group anatomic classification.

Table 4. Grading Scheme for Anterior Chamber and Anterior Vitreous Cells (SUN Working Group)

Grade	Cells in Field[a]
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Abbreviation: SUN = Standardization of Uveitis Nomenclature.
[a] Field size is a 1 mm × 1 mm slit beam.

Table 5. Grading Scheme for Anterior Chamber Flare (SUN Working Group)

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Abbreviation: SUN = Standardization of Uveitis Nomenclature.

Table 6. Activity of Uveitis Terminology (SUN Working Group)

Term	Definition
Inactive	Grade 0 cells [a]
Worsening activity	Two-step increase in level of inflammation (e.g. anterior chamber cells, vitreous haze) or increase from Grade 3+ to Grade 4+.
Improved activity	Two-step decrease in level of inflammation (e.g. anterior chamber cells, vitreous haze) or decrease to Grade 0.
Remission	Inactive disease for ≥ 3months after discontinuing treatments for eye disease

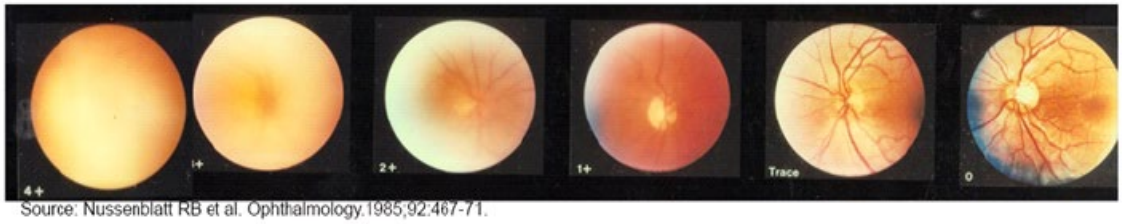
Abbreviation: SUN = Standardization of Uveitis Nomenclature.
[a] Applies to anterior chamber inflammation.

Grading of anterior vitreous cells will be performed based on the slit-lamp examination utilizing a 1 mm × 1 mm slit-lamp beam and the same grading scheme utilized for anterior chamber cells (Table 4).

Grading of vitreous haze will be performed in a standardized fashion by the central ophthalmology reading center, based on color fundus photos of the posterior pole. Baseline color fundus photos will be obtained at Visit 1 for all subjects. Color fundus photos will be obtained at Visit 12, Visit 14/Year 1 and Visit 19 for grading of vitreous inflammation. The National Institutes of Health grading system (Nussenblatt 1985) will be used to grade the vitreous haze on the fundus photo. Table 7 and photos will serve as the basis for vitreous haze grading:

Table 7. National Institutes of Health Grading System for Vitreous Haze

Grade	Amount of Vitreous Flare/Haze
0	No flare
0.5+	Trace
1+	Clear optic disc and vessels, hazy nerve fiber layer
2+	Hazy optic disk and vessels
3+	Optic disc visible
4+	Optic disc not visible
Quality unsatisfactory	Photo quality inadequate for vitreous inflammation grading
Not performed	Photograph not performed



Source: Nussenblatt RB et al. Ophthalmology.1985;92:467-71.

9.2.2.4 Unexpected Adverse Reactions/Device Effects

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the IMP at any dose that is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized IMP or summary of product characteristics for an authorized product).

All Suspected Unexpected Serious Adverse Reactions (SUSARs) will be the subject of expedited reporting. The sponsor and/or the CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB without any delay after knowledge by the sponsor of

such a case, and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB without any delay after knowledge by the sponsor of such a case. All investigators should follow SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post-study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the sponsor.

SUSAR will be reported to the FDA respectively according to the 21 CRF Part 312, section 312.32.

Unexpected Adverse Device Effect Definition

An unexpected ADE is defined as a serious ADE that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
All unexpected ADE will be reported by the sponsor to the EU National Competent Authorities without any delay after knowledge by the sponsor of such a case.
Any other reportable events as defined in MEDDEV 2.7.3 will be reported to the EU National Competent Authorities without any delay, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable, or of new information in relation with an already reported event.
The UADE will be reported to the FDA respectively according to the 21 CFR Part 812, Section 812.150.

9.2.2.5 Clinical Laboratory Evaluation

The hematology and clinical chemistry laboratory analyses will be performed at a central laboratory. All blood samples will be drawn by direct venipuncture prior to administration of the study drug. The exact date and time (24-hour clock) of each blood sample obtained will be recorded in the eCRF. Instructions for phlebotomy and sample handling can be found in the laboratory manual.

Reference ranges will be supplied by the central laboratory and used by the investigator to assess the laboratory data for clinical significance and pathological changes.

Any clinically significant findings from laboratory tests at screening should be entered as medical history. Any clinically significant finding from laboratory tests that results in a diagnosis and that occurs after the subject receives GS030-DP should be reported as an AE via eCRF.

A blood sample can be repeated at the investigator's discretion.

Hematology

Hematology analyses will include: hemoglobin, hematocrit, white blood cell count (total and differential), red blood cell count, platelet count, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration.

Hematology testing will be performed at screening (Visit 1), Visit 7 through Visit 9, and Visit 13 through Visit 19.

Clinical Chemistry

Clinical chemistry analyses will include: creatinine, urea (or blood urea nitrogen), aspartate transferase, alanine transferase, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol, triglycerides, calcium, and phosphorus.

Clinical chemistry testing will be performed at screening (Visit 1), Visit 7 through Visit 9, and Visit 13 through Visit 19.

Humoral Response

Humoral response to rAAV2.7m8 and to the expressed ChR-tdT protein will be assessed at the end of the Inclusion Phase (Visit 4) and during each visit during the post-GS030-DP treatment phase (Visit 6 through Visit 14/Year 1).

- rAAV2.7m8: Serum samples storage <-70°C and shipment on a monthly basis to a specific laboratory.
- ChR-tdT: Serum samples storage <-70°C and shipment on a monthly basis to a specific laboratory.

The assay for ChR-tdT analysis is currently under development. The dedicated sample will be stored as described in the lab manual. If it is not possible to identify and create a specific method of detection of humoral response against ChR-tdT, the aliquot will be destroyed.

Cellular Immune Response - Peripheral Blood Mononuclear Cells

Cellular immune response to rAAV2.7m8 and ChR-tdT protein will be assessed at the end of the Inclusion Phase (Visit 4) and during each visit during the post-GS030-DP treatment phase (Visit 6 through Visit 14/Year 1).

For both tests, peripheral blood mononuclear cells will be isolated from blood samples stored at ambient temperature on the collection day, and stored and shipped in liquid nitrogen to a specific laboratory on a quarterly basis.

Bio-Dissemination

Samples for bio-dissemination will be collected at the end of the Inclusion Phase (Visit 4), at Visit 5 (4 hours after GS030-DP IVT), then from Visit 6 through Visit 10, and at Visit 12.

- Blood: Whole blood stored at <-70°C, shipment on a monthly basis to a specific laboratory.
- Urine: Cryotube 1 ml stored at <-70°C, shipment on a monthly basis to a specific laboratory.
- Tears: Schirmer's test strips or equivalent, storage in cryotube at <-70°C, and shipment on monthly basis to a specific laboratory.

9.2.2.6 Other Laboratory Variables

Pregnancy testing (serum) will be performed at screening for all female subjects of child-bearing potential. A urine pregnancy test will be performed by Visit 4. Serum HIV test will be performed at screening.

9.2.2.7 Physical Examination

At Screening (Visit 1) and at the last visit of the post-GS030-DP treatment phase (Visit 14/Year 1) and the End of Study (Visit 19), a physical examination will be performed. Abnormal physical examination findings will be recorded either as medical history or AEs.

9.2.2.8 Vital Signs

Vital signs (blood pressure and heart rate) will be recorded at screening (Visit 1) and from Visit 5 through Visit 19 in a standardized manner (i.e. after the subject has rested in the sitting position for 5 minutes).

Any clinically significant finding from vital sign measurements that results in a diagnosis and that occur after the subject receives GS030-DP should be reported as an AE via eCRF.

9.2.2.9 12-Lead Electrocardiogram

For each subject, standard 12-lead ECGs will be collected at screening (Visit 1) and at the last visit of the post-GS030-DP treatment phase (Visit 14/Year 1) and the End of Study (Visit 19). ECGs should be recorded according to the study-specific recommendations.

Any clinically significant findings from laboratory tests at screening should be entered as medical history. Any clinically significant finding from laboratory tests that results in a diagnosis and that occurs after the subject receives GS030-DP should be reported as an AE via eCRF.

9.2.2.10 General Ocular Evaluation

Slit-Lamp Biomicroscopy – Pre- and Post-Pupil Dilation

Slit-lamp biomicroscopy and IOP measurement will be performed **in both eyes** at Visit 1, pre-dose and post dose at Visit 5, Visit 12, Visit 14/Year 1 and Visit 19; and **in treated eye** from Visit 6 through Visit 11, Visit 13, and from Visit 15 through Visit 18. Slit-lamp biomicroscopy and IOP measurement will be performed during the home use monitoring phase per the Schedule of Assessments (see Table 2). The schedule for slit-lamp is provided in the separate Clinical Operations Manual.

- Anterior segment assessment:
  - The examination of the anterior segment is to be performed only with the slit-lamp, without any additive drugs or lenses.
- Posterior segment assessment:
  - The posterior segment should be examined with the slit-lamp and the appropriate lens.
  - For this examination, the pupil must be dilated (mydriasis) with 2 to 3 drops of phenylephrine-tropicamide (or any other mydriatic) applied topically to the eye.

Intraocular Pressure Measurement

Measurement of IOP will be performed **in both eyes** at Visit 1, Visit 5, Visit 12, Visit 14/Year 1, Visit 19; and **in treated eye** from Visit 6 through Visit 11, Visit 13, Visit 15 through Visit 18. Measurement of IOP will be performed during the home use monitoring phase per the Schedule of Assessments (see Table 2). IOP is to be measured using tonometry. The same method of IOP measurement must be used in each subject throughout the study.

At Visit 5, when the study drug is administered, IOP will be measured in both eyes pre-

dose and again post-dose. The schedule of IOP assessment is provided in the separate Clinical Operations Manual.

Ocular Imaging Assessments

Color fundus photography will be completed **in both eyes** at screening (Visit 1), Visit 12, Visit 14/Year 1 and Visit 19. FAF will be completed **in both eyes** at screening (Visit 1), Visit 12, Visit 14/Year 1, Visit 19; and **in treated eye** from Visit 16 through Visit 18. FAF will be performed during the home use monitoring phase per the Schedule of Assessments (see Table 2).

Color fundus photography: a color image centered about the posterior pole will be obtained.

For the acquisition of FAF images, a standard procedure will be followed, which will include focusing of the retinal image in the infrared reflection mode at 820 nm, sensitivity adjustment at 488 nm, and acquisition of 9 single 30°x 30° FAF images that encompass the entire macular area, and at least part of the optic disc. In order to improve the signal-to-noise ratio of the FAF signal, the 9 single images will be aligned and a mean image will be calculated after detection and correction of eye movements, using the software provided by the manufacturer (Heidelberg Eye Explorer, Heidelberg Engineering, Dossenheim, Germany). Images will be digitized and saved on a hard disc for further analysis and processing.

Spectral Domain Optical Coherence Tomography

SD-OCT will be performed **in both eyes** from Visit 1 through Visit 3, at Visit 12, Visit 14/Year 1, Visit 19; and **in treated eye** from Visit 6 through Visit 11, Visit 13, Visit 15 through Visit 18. SD-OCT will be performed during the home use monitoring phase per the Schedule of Assessments (see Table 2).

Retinal characteristics will be evaluated by SD-OCT in both eyes at every study visit. Images of the study eye will be captured and assessed by study-site personnel.
Initially, SD-OCT images of up to 2 volunteers per site (anyone) may be sent to the central reading center to be assessed for quality control, in order to certify the training of study site personnel.
Subjects enrolled will have both anatomically recognizable ganglion cell layer and recognizable retinal nerve fiber layer as determined by spectral domain optical coherence tomography (SD-OCT). Those patients whose OCT imaging fails to demonstrate presence of either ganglion cell layer or recognizable retinal nerve fiber layer are to be excluded.
During the study, all SD-OCT images will be reviewed and assessed by readers at the central reading center. Additional details regarding the SD-OCT procedure will be provided in the Clinical Operations Manual. All SD-OCT assessments will be archived as part of the subject's source documentation.

9.2.2.11 Concomitant Medications

Information on prior and concomitant medications will be collected at each visit.

9.3 Data Safety Monitoring Board

To enhance the safety and integrity of the study data, a DSMB consisting of independent experts will be convened to periodically review the cumulated safety data for the study. The first safety review by the DSMB will occur after the first cohort of 3 subjects has received GS030-DP. The DSMB will provide a recommendation on study continuation or early termination, in case of safety concern. The specific responsibilities and composition of the DSMB are outlined in a separate document, the DSMB Charter. Also, the details of outputs provided for the meetings are referenced in the separate DSMB Charter.

9.4 Appropriateness of Measurements

The assessments of treatment effect and safety planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

10 STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP may modify the plans outlined in this protocol; any major modifications of the primary endpoint definition and/or its analysis will be described in the SAP and the final clinical study report. Additional statistical analyses other than those described in this section may be performed if deemed appropriate, and will be described in the SAP.

10.1 Statistical and Analytical Plans

All study data will be summarized by treatment using descriptive statistics. Categorical variables will be summarized as frequencies and percentages. Continuous variables will be summarized as number of subjects, mean, standard deviation, median, minimum, and maximum. All summaries, statistical analyses, and individual subject data listings described below will be completed using SAS Version 9.3 or later (SAS Institute, Inc, Cary, NC, US).

Results in the treated eye will be compared with and without GS030-MD.

10.1.1 Datasets or Populations Analyzed

The primary analysis sample will be based on the principle of intention-to-treat. All subjects who sign the written ICF, meet the study entry criteria, and are enrolled (*i.e.* treated with GS030-DP and GS030-MD) will be included in the analysis sample.

10.1.2 Demographic and Other Baseline Characteristics

Subject demographics will be summarized using descriptive statistics for continuous variables (*e.g.* mean, standard deviation) and frequency tables or proportions for discrete variables.

10.1.3 Safety Endpoints and Endpoints to Assess Treatment Effect

10.1.3.1 Definition of Primary Safety Endpoint

Safety and tolerability of GS030 treatment at Week 52/Year 1, by assessments based on local and systemic safety issues, specifically those related to IVT of GS030-DP and the subsequent repeated use of GS030-MD, as assessed by analysis of AEs.

10.1.3.2 Definition of Endpoints to Assess Treatment Effect (Secondary Endpoints)

Endpoints to assess treatment effect for the study will include:

- Assessment of the treatment effect on visual function, functional vision, and mobility, with the change from baseline to Week 52 of parameters measured with FrACT, Humphrey visual field 10-2, FST, GAT, square localization test, direction of motion test, door task, line task, visual perception tests, eye-hand coordination, and, visual exploration and relative position
- Assessment of the treatment effect on structural changes of the posterior pole of the fundus from baseline to Week 52 with parameters measured with SD-OCT, color fundus photos, and FAF.
- Assessment of the treatment effect on quality of life changes from baseline to Week 52 with the VFQ-25 and SF-36v2.
- Humoral and cellular immune response to rAAV2.7m8 and ChR-tdT protein.

10.1.4 Methods of Analysis

10.1.4.1 Safety Variables

All subjects treated with GS030-DP will be evaluated for safety. No statistical tests will be performed; all safety assessments will be summarized in a descriptive manner.

10.1.4.2 Variables to Assess Treatment Effect

All subjects treated with GS030-DP and GS030-MD with baseline assessments of treatment effect will be evaluated at Visit 14/Year 1. Treatment effect will be summarized in a descriptive manner. If feasible, statistical tests will be performed to compare treated and non-treated eyes within subjects.

10.1.5 Interim Analyses

Interim analyses might be performed to support planning of further clinical development.

10.1.6 Handling of Missing Data

All subjects enrolled (*i.e.* those who receive treatment with GS030-DP and GS030-MD) will be eligible for evaluation, regardless of the sequence of treatment that ensues. All subjects enrolled in the study are considered eligible for follow-up, and will be required to adhere to the follow-up schedule. Management of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Adjustments for missing data will be performed only if deemed necessary, and will be described completely. Outlier values will be evaluated for their validity; all data will be included unless judged to be invalid.

10.2 Determination of Sample Size

No formal statistical hypothesis and sample size estimation were established for this study. The sample size is dictated by the 3 + 3 dose escalation design for the 3 dose levels. According to this design, it is sufficient to treat 3 additional subjects with the MTD (these are the subjects treated in the extension cohort), so that the MTD can be established on at least 6 subjects.
However, a few additional subjects may need to be treated at MTD to allow for statistical interpretations of the treatment effect (efficacy), according to the sample-size estimation based on current expectations. For instance, using a 1-sample Wilcoxon test (paired test) and assuming alpha = 5% and statistical power = 80%, a sample of 10 treated subjects will allow for determination of the statistical significance of an improvement of 1.0 LogMAR (with a standard deviation of 1.0) compared to baseline, using the Freiburg Visual Acuity test. Therefore, the decision to treat 3 to 9 additional subjects in the extension period will be made based on the outcome of the safety evaluations throughout the study.

10.3 Protocol Deviations

All violations and deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment are to be documented on the eCRF provided for that purpose.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

During the trial, study sites and study documentation may be subject to Quality Assurance audit by the Sponsor or its nominated representative. In addition, inspections may be conducted by Regulatory Authorities at their discretion.

11.2 Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF.

In accordance with current Good Clinical Practice (GCP) and International Council for Harmonisation (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the sponsor’s internal auditors, and representatives from Regulatory Authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

11.3 Data Management and Coding

The sponsor or CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of the sponsor.

Study sites will enter data directly into an electronic data capture system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study site. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the electronic data capture system will be recorded in the audit trail, and will be compliant with the US Food and Drug Administration CFR 21 Part 11.

Medical coding will use the Medical Dictionary for Regulatory Activities for concomitant diseases and AEs, and the World Health Organization Drug Dictionary for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

12 RECORDS AND SUPPLIES

12.1 Accountability

The GS030-DP and GS030-MD will be tracked during the handling process from prescription to destruction (through dispensation, reconstitution, administration, and decontamination). Accountability of the investigational product is the responsibility of the investigator (or deputy).

On receipt of the investigational product (including GS030-DP and GS030-MD), the investigator (or deputy) will conduct an inventory of the supplies, and verify that study supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study site and return the original receipt to the study monitor. The monitor may check the study supplies at each study site at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount of study supplies (drug product and medical device) received, dispensed, and returned on the dispensing log that will be provided. A full accountability log will be maintained at the study site at all times. The study monitor will arrange collection of unused study supplies returned by the subject. The study monitor will also perform an inventory of supplies at the close-out visit to the study site. All discrepancies must be accounted for and documented.

12.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the CRO and the sponsor.

13 ETHICS

13.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study site, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or the study drug and medical device is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

13.2 Regulatory Authorities

Relevant study documentation will be submitted to the Regulatory Authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the Regulatory Authorities will be notified that the study has ended.

13.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

13.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study via a signed ICF.

The investigator or designated personnel will inform the subject or their legally authorized representative of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points she/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study.

Each subject or their legally authorized representative must sign and date the ICF. Since subjects are severely visually impaired, the ICF should be read to the subject, in addition to providing them with a printed copy of the document along with an audio recorded version. An impartial witness must observe the consent process and must sign and date the ICF.

After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or his/her authorized representative.

It should be emphasized that the subjects may refuse to enter the study or withdraw from the study at any time, without consequences for their further care, or any penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included in or continue the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC/IRB (and regulatory authorities, if required). The study subjects will be informed about this new information and consent will have to be obtained again.

13.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC/IRB approving this research, and the US Food and Drug Administration, as well as any other applicable competent authorities will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and their staff with adequate precautions to ensure confidentiality of those data, and in accordance with the General Data Protection Regulation (Regulation (EU) 2016/679), the Health Insurance Portability and Accountability Act, and any applicable national and/or local laws and regulations on personal data protection.

14 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those that individually and collectively permit evaluation of the study and quality of the data produced.

After completion of the study (the end of study is defined as the date of the last visit of the last subject), all documents and data related to the study will be kept organized by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region, or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study site when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The essential documents for the medical device will be recorded and stored by Gensight Biologics in accordance with the Good Clinical Practice, standard EN ISO 14155 (Clinical investigation of medical devices for human subjects) and in accordance with the applicable Medical Device Regulation 2017/745. The essential documents shall be kept for a period ending at least ten years after the last product has been manufactured.

GenSight Biologics retains all rights for publication for any material related to this study.

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16 APPENDICES

16.1 Investigator Signature Page

Protocol Title: A Phase 1/2a, Open-Label, Non-Randomized, Dose-Escalation Study to Evaluate the Safety and Tolerability of GS030 in Subjects with Retinitis Pigmentosa

Protocol Number: GS030_CLIN_001

Confidentiality and Current GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments, if applicable), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments, if applicable), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval from GenSight Biologics and the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to GenSight Biologics and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be considered confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by GenSight Biologics to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

16.2 World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason

to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms

and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research.

Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.