CLINICAL RESEARCH PROTOCOL

PROTOCOL TITLE:	A Phase 2 Study of the Safety of Repeat Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Adult Subjects with Retinitis Pigmentosa (RP)
PROTOCOL NUMBER:	JC02-2
SPONSOR:	jCyte, Inc.
IND NUMBER:	016299

ORIGINAL PROTOCOL DATE:	25 January 2019
Amendment 1:	19 July 2019
Amendment 2:	28 September 2020
Amendment 3:	22 January 2021
Amendment 4:	12 April 2021

Investigator Protocol Agreement

The signature below constitutes that I agree to the following:

- I have reviewed the protocol and the attachments.
- This trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States federal regulations and International Conference on Harmonization (ICH) guidelines.
- I agree to periodic site monitoring of case report forms and source documents by the Sponsor or designee and by appropriate regulatory authorities.
- I agree to supply the jCyte, Inc. or designee with any information regarding ownership interest and financial ties with the Sponsor for the purpose of complying with regulatory requirements.

Investigator Name (Print)	Investigator Signature	Date

Study Synopsis

NAME OF COMPANY:jCyte, Inc **NAME OF FINISHED PRODUCT:** jCell **NAME OF ACTIVE INGREDIENT:** human retinal progenitor cells	**SUMMARY TABLE** **Volume:** **Page:** **Reference:**	*(For national Authority Use Only)*

Title of study:

JC02-2: A Phase 2 Study of the Safety of Repeat Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Adult Subjects with Retinitis Pigmentosa (RP)

Investigators/Study Centers: Dr. Mitul Mehta, University of California, Irvine/Gavin Herbert Eye Institute; Dr. David Liao, Retina-Vitreous Associates Medical Group, Los Angeles CA, Dr. Anthony Joseph, Ophthalmic Consultants of Boston

Study Period: Q4, 2020 – Q3, 2022	**Phase of development: Phase 2**

Objectives:

Primary Objective:

The primary objective of the study is to assess the safety of repeat injection of jCell

Secondary Objectives:

To assess the impact of repeat injection of jCell on measures of visual function and functional vision over a 12 month period, including BCVA, mobility (maze), CS, and VF

Methodology:

This is a prospective, multicenter, single arm, Phase 2 study of human retinal progenitor cells (jCell) for the treatment of retinitis pigmentosa (RP). Eligible subjects include those previously treated with jCell.

A group of 25-30 subjects who have participated in a prior jCell study will be eligible. A minimum of 18 months must have elapsed between the prior jCell treatment and treatment in this study and the subject must have completed the 12 month follow up visit from the prior study with a reasonable record of study compliance.

Study subjects will be screened for eligibility, informed consent obtained, and eligible subjects will receive a jCell injection in a previously treated eye of 6 x 10^6 jCell. Subjects who have previously had both eyes treated will only have one eye retreated, preferably the eye with best visual acuity. Exceptions to this can be made by the study investigator taking into consideration medical conditions or other circumstances that may impact the choice of eyes for treatment. Subjects will be monitored closely following injection for 60 minutes prior to being released home on the day of treatment, based on intraocular pressure <30mm Hg and vital signs returned to pre-injection. Following treatment, all subjects will be treated with ophthalmic corticosteroid eye drops to minimize any inflammation from injection for a minimum of 7 days (including tapering schedule), or longer as if determined by the study investigator. Blood samples for antibody testing (PRA and DRA) will be collected at baseline and at months 1 and 6. Subjects will be followed at specified intervals for 12 months for evidence of safety and efficacy.

Subjects may be asked to undergo additional, optional testing at baseline and specified timepoints to explore retinal sensitivity and the characteristics of the injected jCells during follow-up.

Number of patients:

25-30 (depending upon availability) previously treated jCell subjects will be retreated in one previously treated eye to assess safety of reinjection. If a subject has been previously treated with jCell in both eyes, the better seeing eye will be selected for re-treatment unless there are specific circumstances that make this not advisable, as judged by the study investigator. This is considered to be an adequate number of subjects to be able to judge whether the safety profile is consistent with that which has been seen previously with an initial treatment (JC-01 and JC-02) or a fellow eye treatment (JC-01E). This number assumes that there will be at least 25 previously treated subjects who desire a repeat treatment in a previously treated eye.

Diagnosis and main criteria for inclusion:

Inclusion Criteria

NAME OF COMPANY:jCyte, Inc **NAME OF FINISHED PRODUCT:** jCell **NAME OF ACTIVE INGREDIENT:** human retinal progenitor cells	**SUMMARY TABLE** **Volume:** **Page:** **Reference:**	*(For national Authority Use Only)*

The following conditions must be met before a previously treated subject may be enrolled.

1. Willing to give written informed consent, able to make the required study visits and follow study protocol instructions.
2. Completed the 12 months of follow up in the subject's most recent jCell study and did not withdraw from the study for any reason.
3. Adequate organ function:
   - blood counts (hematocrit, Hgb, WBC, platelets and differential) within normal range, or if outside of normal range, not clinically significant as judged by the investigator
   - liver function: alanine transaminase [ALT] and aspartate transaminase [AST] ≤2 times the upper limit of the normal range
   - total bilirubin ≤1.5 times the upper limit of the normal range
   - renal function: serum creatinine ≤1.25 times the upper limit of the normal range
4. A female patient of childbearing potential (not surgically sterilized and less than one year postmenopausal) must have a negative pregnancy test (urine human chorionic gonadotropin) at entry (prior to injection) and must have used medically accepted contraception for at least one month prior to treatment. Women of childbearing potential and men must be advised to use a medically accepted method of contraception for at least 12 months following treatment.

Exclusion Criteria

Patients previously treated with jCell will be excluded from this study if they meet any of the following criteria:

1. Malignancy, end-stage major organ disease (heart failure, significant arrhythmias, stroke or transient ischemic attacks, diabetes, immunosuppressive or autoimmune state, major psychiatric disorder, epilepsy, thyroid disease, COPD, renal failure, or any chronic systemic disease requiring continuous treatment with systemic steroids, anticoagulants or immunosuppressive agents.
2. History of eye disease other than RP that impairs visual function, including retinal vascular disease, elevated intraocular pressure/glaucoma, severe posterior uveitis, clinically significant macular edema, media opacity precluding visual exam, amblyopia and/or longstanding constant strabismus, as well as patients who require other intravitreal therapies
3. Allergy to penicillin or streptomycin.
4. Adverse reaction to DMSO.
5. Unable or unwilling to undergo pupil dilation, topical anesthesia or any protocol-required procedure.
6. Women who are nursing or who are planning to nurse during the 12 months that would follow study treatment.
7. Any circumstance that in the opinion of the investigator, would interfere with participation in, or compliance with the study protocol
8. Treatment with corticosteroids (systemic, periocular or intravitreal) or any other non-approved, experimental, investigational or neuroprotectant therapy (systemic, topical, intravitreal) in either eye within 90 days of planned second injection.
9. Cataract surgery within three months prior to treatment or anticipated to need cataract surgery within a year of treatment

Test product, dose and mode of administration:

The investigational product (jCell) is a live suspension of human retinal progenitor cells (hRPC) suspended in clinical grade medium. The hRPC are of allogeneic human fetal origin. Study subjects will receive a single dose of 6.0×10^6 jCell as an intravitreal injection into one eye.

Reference product, dose and mode of administration:

There is no reference product in this study.

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Duration of treatment:

Treatment with jCell consists of a single intravitreal injection . The injection procedure itself takes approximately 2 minutes. Patients will be released to home on the day of injection. All study subjects will be followed for one year from injection.

Criteria for Evaluation:

Safety:

Safety will be assessed on an ongoing basis by adverse events, physical examinations and vital signs, clinical laboratory values, and anti-drug antibodies (DRA, PRA). In addition, specific ophthalmalogic tests to monitor safety will be performed, including slit lamp and fundus examiniation, and intraocular pressure (IOP). Clinical safety data will be reviewed on an ongoing basis.

Efficacy:

Efficacy will be assessed based on a series of ophthmalogic assessments performed at specified intervals, including best corrected visual acuity, mobility (maze), contrast sensitivity, and visual field testing.

Statistical methods:

Background and demograhic data will be summarized for all subjects using descriptive statistics.

Efficacy: Secondary efficacy endpoints include mean change at six and 12 months in the following assessments: best corrected visual acuity (BCVA), to be measured with the electronic visual acuity testing algorithm (E-ETDRS); mobility score (maze navigation scored by critical illumination level, CIL); visual fields assessed by kinetic visual field testing, and contrast sensitivity.

Descriptive statistics will be used to tabulate and summarize study outcomes. The baseline results of clinical examinations of the injected eye serve as controls for the injected eye. Results of testing of the non-treated eye will also be described. Continuous variables will be summarized descriptively (sample size, mean standard deviation and error, minimum and maximum). Discrete variables will be summarized by frequency or percentage, and analyzed with non-parametric statistics.

Safety: The primary endpoint of this study is to obtain safety profiles for reinjection of jCell. The safety analyses of AEs and laboratory parameters will include descriptive statistics. Summaries of AEs will be generated by type (AE or SAE), body system and preferred term, severity, and relationship to study product.

Exploratory: Descriptive statistics will used to tabulate and summarize exploratory assessments.

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1.0 INTRODUCTION

1.1 Background

1.1.1 Retinitis Pigmentosa

Retinitis pigmentosa (RP) refers to a group of inherited diseases causing retinal degeneration. The cell-rich retina lines the back inside wall of the eye. It is responsible for capturing images from the environment. People with RP experience a gradual decline in their vision because photoreceptor cells (rods and cones) die. Forms of RP and related diseases include Usher syndrome, Leber's congenital amaurosis, rod-cone degeneration, Bardet-Biedl syndrome, and Refsum disease, among others.

In most forms of RP, rods are affected first. Because rods are concentrated in the outer portions of the retina and are triggered by dim light, their degeneration affects peripheral and night vision. When the more centrally located cones - responsible for color and sharp central vision - become involved, the loss is in color perception and central vision. Night blindness is one of the earliest and most frequent symptoms of RP.

RP is typically diagnosed in adolescents and young adults. The classic clinical sign of the disease is the presence of dark deposits in the retina. The main risk factor is a family history of retinitis pigmentosa. It is an uncommon condition affecting about 1 in 4,000 people or roughly 100,000 individuals in the US[1]. Cases of RP are associated with a wide variety of known gene mutations, with new mutations still being discovered. The mutations can be inherited from one or both parents or occur spontaneously; the pattern of inheritance can be autosomal recessive, autosomal dominant, X-linked or mitochondrial.

There is no effective treatment for RP; once photoreceptors are lost, they do not regenerate. The rate of deterioration of vision varies from person to person, with most people with RP legally blind by age 40. People with RP also often develop cataracts at an early age or swelling of the retina (retinal edema). Numerous breakthroughs in the treatment of cataract and corneal disease have greatly decreased the incidence of blindness from these causes. In contrast, treatment of retinal and optic nerve disease is more limited, with these conditions now representing major causes of incurable visual loss and a significant unmet medical need.

1.1.2 Stem /Progenitor Cells

No restorative treatments for retinal cell loss currently exist, but stem cell treatment has emerged as a particularly promising strategy. In addition, the concept of delaying retinal cell death through the use of neuroprotective agents has considerable merit and committed progenitor cells are useful platforms for delivery of neuroprotective cytokines. Also, the possibility of reinvigorating non-functional yet viable cones is an underappreciated yet attractive potential clinical target.

Cells and tissues of many types survive injection to the subretinal space, in part because this location exhibits characteristics often referred to as those of an "immune privileged" site[2]. Both photoreceptors[3] and RPE cells[4,5] survive beneath the retina, however, failure of donor photoreceptors to integrate with surviving host circuitry and failure of donor RPE cells to adhere to Bruch's membrane have thus far frustrated attempts to achieve functional repair using these methods. For photoreceptors, there is a fundamental problem that must be overcome, namely the physical barrier to neurite outgrowth posed by the outer limiting membrane (OLM). In photoreceptor degeneration, the OLM undergoes hypertrophy and regenerating neurites are impeded by this barrier[6]. Glial hypertrophy has been often been implicated in the failure of endogenous regenerative mechanisms to bridge a lesion[7], e.g., after spinal cord injury[8].

1.1.3 CNS and Retinal Progenitor Cells

It has been demonstrated that transplanted CNS progenitor cells are not impeded by the hypertrophied OLM and cross in large numbers[9,10]. The ability to migrate into the mature retina is characteristic of CNS progenitor cells, which do not simply migrate, but exhibit widespread integration into the local cytoarchitecture, with pronounced tropism for areas of disease.

Hippocampal progenitors transplanted to the vitreous of neonatal rats integrated into the retina and developed morphologies appropriate to their layer of residence[11]. In the dystrophic Royal College of Surgeons (RCS) rat, it has been shown that grafted hippocampal progenitors developed rod photoreceptor-like morphologies and extended neurites into the optic nerve[9]; however, brain-derived progenitors did not express retina-specific markers. This lineage restriction has been overcome using progenitor cells derived from the retina. Retinal progenitor cells can be derived from the developing neural retina of rats, mice, pigs, cats and humans.

The first simultaneous sourcing of retinal- and brain-derived neural progenitors from the same premature infant occurred in 1999 and both progenitor cell types were found to express MHC I antigens, but not MHC II[12]. Cultured hRPCs expressed a range of markers consistent with CNS progenitor cells. hRPCs could be distinguished from human brain progenitor cells by the expression of retinal specification genes, particularly recoverin. More recently, age 18 weeks gestation was found to be a suitable age developmental stage for isolation of hRPCs.

Although rejection is the norm for grafts between individuals of disparate genetic background, this tendency is markedly less problematic when placed in an "immune privileged" site such as the eye. This does not mean that allogeneic grafts to these sites cannot be rejected, but that they benefit from a decreased likelihood of rejection. It has also been shown that CNS progenitor cells themselves exhibit properties of cell-specific immune privilege. Rat hippocampal progenitor cells were not recognized by human mononuclear cells in vitro[13] and murine brain progenitor cells survived transplantation to the allogeneic kidney

capsule, a non-privileged site[14]. The mechanisms underlying cell-specific immune privilege may relate in part to the major histocompatibility (MHC) antigens.

Studies have indicated that MHC class I expression is consistent for progenitors from different individuals or strains within a given species. This is the case for multiple examples of CNS progenitors from the brain and retina of mouse and human. Another trend, of considerable importance to clinical transplantation studies, is an absence of detectible MHC class II expression for all CNS progenitor cells examined from mouse, rat, and human. The classical mechanism of graft rejection involves the nonspecific recognition of foreign MHC class II molecules by CD4+ host lymphocytes. Hence, an absence of class II molecules would allow grafted progenitor cells to evade immune rejection mediated by this important mechanism. CNS progenitor cells therefore differ from solid tissue grafts of either brain or retina, both of which contain class II-expressing cells.

1.2 jCell (human Retinal Progenitor Cells, hRPC)

The investigational product (jCell) to be tested is a live suspension of human retinal progenitor cells (hRPC) suspended in clinical grade medium. The hRPC are of allogeneic human fetal origin. Following manufacture, the hRPC intended for therapeutic use are cryopreserved using 90% complete growth medium and 10% DMSO in a controlled-rate freezer. The characteristics and functional properties of the investigational product are summarized in the following table (Table 1). Most functional assays are performed after the cryopreserved cells are thawed and cultured for approximately 48 hours.

Table 1 Characterization and Functional Properties of jCell hRPCs

Test	Results
Cell count and viability	1.0 – 1.6 x 10^6/mL with at least 85% viability post-thaw
Protein expression by immunocytochemistry	jCell is positive for the expression of Nestin (a marker of neural stem cells), Sox2 (a transcription factor essential for self-renewal) and Ki67, a marker of proliferation
Gene expression by qPCR	jCell is positive for the expression of Nestin and Sox2; jCell is negative for the expression of RHO (rhodopsin gene) and the pluripotency marker, Nanog
MHC markers profile by flow cytometry (FACS)	MHC Class I antigens are expressed on >75% of cells and MHC Class II antigens on <2% of cells in the product
Neurogenesis	Cells in product differentiate into retinal neuronal or glial cell types in culture based on expression of genes

Test	Results
	associated with different retinal neuronal/glial cell types as assessed by qPCR.
OPN gene and protein expression by qPCR and ELISA, respectively	Cells are positive for gene and protein expression of OPN with >40 ng per million cells over a 24 hour period
Karyotype	Cells have a normal human karyotype
In vitro tumorigenicity	jCell is unable to form colonies in a standard soft agar colony formation assay.
Human telomerase reverse transcriptase (hTERT)gene expression by qPCR	Cells are negative for expression of the hTERT gene.

A range of non-clinical studies has been performed to assess the functionality and distribution of injected hRPC. Collectively the nonclinical data demonstrated that allogeneic grafts show prolonged survival in the vitreous, retina, and subretinal space in all mammalian species tested, despite the absence of immunosuppressive agents, with evidence of graft-associated benefits at the behavioral level, specifically with respect to neuroprotection of host photoreceptors. Prolonged survival is possible except in cases of xenotransplantation to non-immunosuppressed animals, and differentiation with expression of relevant markers together with functional rescue has been demonstrated in animal models. The scope, duration, and exposure achieved in these studies are considered to be fully supportive of the planned human clinical trials.

1.3 Rationale for the Proposed Study

RP is an incurable blinding disease caused by death of first rod, then cone, photoreceptors in the retina. Photoreceptors are specialized nerve cells essential for vision. Once photoreceptors are lost, they do not regenerate. Therefore, when all rods and cones have died, the patient is left completely blind. Preclinical studies demonstrated that transplantation of retinal progenitor cells into the eye can result in both photoreceptor replacement and significant slowing of host photoreceptor loss[10]. Thus, the primary goal of jCell therapy is to preserve, and potentially improve, vision by intervening in the disease at a time when dystrophic host photoreceptors can be protected and reactivated.

Three clinical trials of jCell have completed enrollment and treatment. A phase 1/2a clinical trial of jCell of 28 subjects included four Data Monitoring Committee reviews of safety data over the course of the study, with no important safety concerns noted at any time point.

One SAE was reported in the Phase 1/2a study. The event, which was reported as Grade 2 migratory pain, occurred in the 17th patient enrolled in the study. He was noted to have severe migratory arthralgias starting six months after a single intravitreal injection of jCell

(human retinal progenitor cells). The subject's relevant medical history was remarkable for nonspecific musculoskeletal abnormalities, myocardial bridge, hypercholesterolemia, clavicle fracture, ruptured disc, hypertension, colon polyps, esophageal reflux, fracture reduction, coronary artery disease, vitiligo, diabetes (Type II), vitamin D deficiency, actinic keratosis, obstructive sleep apnea and anemia. The study investigator reported the event as possibly related to study treatment initially but after further testing indicated that the event was unlikely to be related.

Subjects who completed the phase 1/2a study were allowed to enroll in an extension study with an option to be followed longer term for safety and, if desired, to receive an injection of jCell in the fellow eye (eye that was not treated in the main study). Twenty four of 28 subjects from JC-01 study enrolled in the extension study, including 22 subjects who received a second injection (1 x 10^6 jCell). All subjects have been followed for at least a year beyond the second injection, with the safety profile continuing to be very acceptable.

One SAE was reported in the extension study. "Atrial fibrillation or worsening of atrial fibrillation" has been reported as a Grade 1 AE on two occasions for one study subject. This subject was noted as having atrial fibrillation since 2015 on entry to study JC-01. It appears that the first instance in the extension study required a cardioversion procedure and the second an ablation procedure. The events were not considered to be related to study treatment.

Based on the demonstration of acceptable safety and tolerability in the phase 1/2a study at doses up to 3 x 10^6 hRPC, a phase 2b study was performed to compare the changes in visual function and functional vision in subjects who receive a single jCell injection in comparison to a comparable mock-treated control group of subjects with RP, with a requirement for BCVA between 20/80 and 20/800 in the study eye, to provide a sufficient "margin" for assessment of improvement after treatment. The study included jCell doses of 3.0 x 10^6 and 6 x 10^6 based on the results of BCVA testing in the phase 1/2a study, which were suggestive of a dose response relationship, with best results at the highest dose (3 x 10^6 jCell). Subjects enrolled in the phase 2b study (JC-02) were randomized 1:1:1 to receive an intravitreal injection of either 3 x 10^6 hRPC or 6 x 10^6 hRPC, or a mock injection.

The mean change in BCVA in the test eye groups compared to the control eyes is the primary visual function parameter in the phase 2b study. Other efficacy outcome measures that were assessed in these subjects at periodic intervals throughout the study include mobility testing, VA LV-VFQ 48, VF, and contrast sensitivity. Visual acuity is a standard and expected endpoint in vision studies, although perhaps not the most relevant endpoint in the poor vision subjects in these studies. The other methods were selected based on preliminary assessment of a battery of visual assessment tools in the phase 1/2a study subjects by low vision experts who have indicated that these are likely to be effective methods in subsets of study subjects, depending upon their visual acuity range and/or because they have been shown to be

endpoints of value in other studies of low vision subjects. The enrollment, treatment and follow-up of subjects in the main JC_02 study has been completed, and the crossover portion of the study is still ongoing. A masked review of the safety data from all subjects in this study continue to support the very acceptable safety profile of jCell with mostly mild to moderate and transient treatment emergent adverse events that are largely related to the injection itself.

There have been two SAEs reported in the JC-02 study. The first event, which was reported as Grade 3 medically significant ocular hypertension of the right eye, six days following study treatment with 3 x 10^6 hRPC. Treatment for this event included medications and two "taps" to relieve intraocular pressure during the week following study treatment. At a follow up visit, the IOP was reported to have returned to normal levels. Although the study investigator was apparently unaware of it at the time of subject enrollment, the medical records (received subsequent to the event) indicate the subject had a history of glaucoma, an exclusion criterion for the study. It is considered possible that this may have increased the subject's risk for IOP following the intravitreal injection procedure.

The second event, which was reported as Grade 2 medically significant ocular hypertension of the left eye on the day following treatment in a crossover patient, with decreased visual acuity secondary to this, occurred in a study subject that had been assigned to the control group initially and elected to "cross-over" to a test group after completing 12 months of follow-up. Study treatment in the cross over part of the study is still masked, with subjects assigned to intravitreal injection of 3 x 10^6 hRPC or 6 x 10^6 hRPC. Treatment for this event included medications and an anterior chamber tap to relieve intraocular pressure on the day following study treatment. The following morning the intraocular pressure was assessed at 6 mm Hg, visual acuity had improved, and the event was considered to have resolved.

The results from the main portion of the phase 2b study further indicate a potential benefit of treatment with jCell at the highest dose (6 x 10^6 hRPC), and especially in a subset of subjects who are defined by the ability to fixate centrally, with visual fields of at least 12 degrees, and with the study eye being at least equally functional to the non-study eye at study start (e.g., not significantly worse). In addition, preliminary data are also suggestive that the thickness of the remaining EZ layer as assessed by OCT at baseline may be a predictor of the subjects most likely to benefit from jCell treatment. The rationale for the proposed study is to answer a key safety question about jCell reinjection into a previously treated eye.

While retreatment of a patient in the fellow eye at least 12 months after the initial treatment has been shown to be safe to date, no subject has received a second injection in a previously treated eye. This is an important consideration, since data suggest that the effects of the injected cells are likely to decrease over time as the injected cells gradually disappear from the vitreous. Current estimates based on data to date suggest that an adequate dose is likely to be effective for at least 12 months (primary endpoint in the phase 2b study) and perhaps

longer in some subjects, but because the most important mechanism of action depends on the presence of the cells, which are not immortal, the effect will eventually diminish. Thus, it becomes important to establish the safety of retreatment.

In addition to safety, all subjects will be followed for efficacy for 12 months using the following methods: best corrected visual acuity (BCVA), mobility (maze), contrast sensitivity, and visual field testing.

Subjects may be asked to undergo additional testing to assess the characteristics of the jCell aggregate inside the eye (size and structure) and retinal sensitivity following treatment. Participation in these additional assessments at the jCyte low vision facility is optional and is not required for study participation.

2.0 OBJECTIVES

2.1 Primary Objectives:

The primary objective of the study is to assess the safety of repeat injection of jCell at a dose of 6×10^6 hRPC.

2.2 Secondary Objectives:

The secondary objectives of the study are to assess the impact of repeat injection of jCell on measures of visual function and functional vision over a 12 month period.

3.0 STUDY DESIGN

This is a prospective, multi-center, single arm, Phase 2 study of human retinal progenitor cells (jCell) for the treatment of retinitis pigmentosa (RP). The study will include only subjects previously treated with jCell.

To assess reinjection of a previously treated eye, subjects who have previously been treated with jCell and desire a second treatment in the same eye will be enrolled. Subjects must have completed at least 12 months of follow up since the prior injection of jCell. Subjects who have had both eyes previously treated with jCell will only have one eye retreated; the eye to be retreated will preferably be the better seeing eye, but exceptions may be made by the study investigator, taking into consideration BCVA, prior response to treatment, and any other medical conditions that may indicate which eye is the best candidate for retreatment. Subjects will be followed for 12 months for safety and efficacy.

As noted above, subjects may be asked to undergo additional testing at the jCyte low vision facility to assess the characteristics of the jCell aggregate inside the eye (size and structure) and retinal sensitivity following treatment. These are exploratory assessments, and any/all may be discontinued if they are determined to be difficult to conduct or the results appear to be of little value in understanding the course of the injected cells and/or changes in retinal

sensitivity over time. Participation in these exploratory assessments is not required for study participation.

3.1 Study Population

Subject treatment with jCell is primarily to assess safety of retreatment and is focused solely on subjects who have previously received jCell and desire to be retreated in the same eye. Study subjects will be screened for eligibility and informed consent obtained. Eligible subjects will receive a single injection of 6 x 10^6 jCell into one previously treated eye. If both eyes were previously treated, the preference is to treat the better eye. However, the study Investigator may select the poorer seeing eye taking into consideration BCVA, prior response to treatment, and any other medical conditions that may indicate which eye is the best candidate for retreatment. Strong rationale must be provided if the decision is made not to treat the better seeing eye. The study investigator must determine that there are no unforeseen or unusual safety issues that would preclude the retreatment. Following treatment, subjects will be followed for at least 12 months to assess safety and efficacy.

3.2 Endpoints

3.2.1 Efficacy Endpoints

Efficacy will be assessed as secondary endpoints in this study and will include for all subjects vision parameters of Best Corrected Visual Acuity (BCVA) as assessed at the clinical site at all visits, as well as mobility (maze navigation), contrast sensitivity (CS), and visual fields (VF) at baseline and at six and 12 months after treatment as assessed at the jCyte low vision facility.

3.2.2 Safety Endpoints

The main criteria that will be used to assess safety include:

- Incidence and severity of treatment-emergent adverse events (TEAE)
- Safety visual assessments: slit lamp and fundus exam, IOP

Blood samples will be collected from subjects at baseline and at designated times post-treatment to assess immunogenicity of the injected cells (PRA, DRA).

3.3 Study Duration

The overall duration of the study is anticipated to be approximately two years. This assumes subjects will be enrolled and treated within one year or less and a follow up of 12 months for each subject. The study will be considered to have started when the first site is initiated.

3.4 Early Study Termination

The Sponsor may terminate this study at any time. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of AEs in this or other studies point to a potential health hazard for study subjects.
- Insufficient subject enrollment.
- Any information becoming available during the study that substantially changes the expected benefit-risk profile of the investigational drug.

4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

The following conditions must be met before a previously treated subject may be enrolled.

1. Willing to give written informed consent, able to make the required study visits and follow study protocol instructions.
2. Completed the 12 months of follow up in the subject's most recent jCell study and did not withdraw from the study for any reason.
3. Adequate organ function:
    - blood counts (hematocrit, Hgb, WBC, platelets and differential) within normal range, or if outside of normal range, not clinically significant as judged by the investigator
    - liver function: alanine transaminase [ALT] and aspartate transaminase [AST] ≤2 times the upper limit of the normal range
    - total bilirubin ≤1.5 times the upper limit of the normal range
    - renal function: serum creatinine ≤1.25 times the upper limit of the normal range
4. A female patient of childbearing potential (not surgically sterilized and less than one year postmenopausal) must have a negative pregnancy test (urine human chorionic gonadotropin) at entry (prior to injection) and must have used medically accepted contraception for at least one month prior to treatment. Women of childbearing potential and men must be advised to use a medically accepted method of contraception for at least 12 months following treatment.

4.2 Exclusion Criteria

Patients previously treated with jCell will be excluded from this study if they meet any of the following criteria:

1. Malignancy, end-stage major organ disease (heart failure, significant arrhythmias, stroke or transient ischemic attacks, diabetes, immunosuppressive or autoimmune state, major psychiatric disorder, epilepsy, thyroid disease, COPD, renal failure, or any chronic systemic disease requiring continuous treatment with systemic steroids, anticoagulants or immunosuppressive agents.

2. History of eye disease other than RP that impairs visual function, including retinal vascular disease, elevated intraocular pressure/glaucoma, severe posterior uveitis, clinically significant macular edema, media opacity precluding visual exam, amblyopia and/or longstanding constant strabismus, as well as patients who require other intravitreal therapies
3. Allergy to penicillin or streptomycin.
4. Adverse reaction to DMSO.
5. Unable or unwilling to undergo pupil dilation, topical anesthesia or any protocol-required procedure.
6. Women who are nursing or who are planning to nurse during the 12 months that would follow study treatment.
7. Any circumstance that in the opinion of the investigator, would interfere with participation in, or compliance with the study protocol
8. Treatment with corticosteroids (systemic, periocular or intravitreal) or any other non-approved, experimental, investigational or neuroprotectant therapy (systemic, topical, intravitreal) in either eye within 90 days of planned second injection.
9. Cataract surgery within three months prior to treatment or anticipated to need cataract surgery within a year of treatment

4.3 Subject Withdrawal Criteria

Subjects may withdraw from the study at any time. Subjects may be discontinued from the study for any of the following reasons:

- Withdrawal of consent by the subject
- Lost to follow-up

The investigator may also withdraw a subject at any time at his/her discretion. The sponsor reserves the right to terminate the study or withdraw any subject from the study for any reason at any time.

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time and for any reason. If such action is taken, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB promptly and provide the reason for suspension or termination.

4.4 Discontinuation/Withdrawal Procedures

If a subject is withdrawn from the study (i.e., ceases participation in the study prior to completion of the assessments planned in the protocol), the primary reason should be recorded in the case report form (CRF). Investigators should make every effort to capture withdrawal assessments, which will be recorded in the CRF.

The investigator will provide or arrange for appropriate follow-up (if required) for subjects withdrawing from the study and will document the course of the subject's condition.

5.0 TREATMENT PLAN

5.1 Dose and Schedule

At the time informed consent is obtained, qualified subjects will be assigned a study number. All subjects will receive a single intravitreal injection of 6.0×10^6 hRPC into one previously treated eye. After topical anesthesia, a single 65 microliter suspension of cells will be delivered into the vitreous cavity using a 30 g needle. This treatment does not require surgical detachment or manipulation of the retina. The injection procedure itself takes approximately 2 minutes. Following 60 minutes of observation with no serious clinical symptoms or manifestations (IOP < 30 mm Hg and vital signs comparable to pre-treatment), subjects will be released to home on the day of injection. Please refer to the study procedure manual for details of patient preparation and monitoring.

The schedule of observations and assessments during the study is summarized in Table 2.

Table 2 Schedule of Assessments

Timepoint	Scr	BL*	Day 0	Day 1	Day 7 [3]	Day 28[3]	M3[4]	M6[4]	M9[4]	M12 or Early Term[5]
Written informed consent	x									
Medical history (MH)	x	x*								x
Physical examination (PE)	x	x*								x
Brief MH and PE				x	x	x	x	x	x	
Vital signs	x	x	x	x	x	x	x	x	x	x
Pregnancy test	x	x*								x
Safety laboratory tests [1]	x	x*				x	x	x		x
Urinalysis	x	x*					x	x		x
Slit lamp and fundus exam	x	x		x		x	x	x	x	x
Optos photography		x		x		x	x	x	x	x
BCVA (E-ETDRS)	x	x	x	x	x	x	x	x	x	x
IOP		x	x	x	x	x	x	x	x	x
OCT		x								x
VF		x						x		x
Exploratory Testing (optional)[6]		x			x	x	x	x	x	x
Contrast sensitivity		x						x		x
Mobility test		x						x		x
Study Drug Injection			x							
Con Meds			x	x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x	x	x
Blood sample for Ab testing[2]		x				x		x		

[1] Hematology (minimally Hct, Hgb, CBC with diff, plt), coagulation panel (screening only) and blood chemistries (minimally AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin, total protein and HbA1c)
[2] Testing for Panel Reactive Antibodies (PRA) and Donor Reactive Antibodies (DRA)
[3] visit window +/- 1 day
[4] visit window +/- 4 days
[5] visit window +/- 10 days
[6] subjects may have some or all of the following assessments at the jCyte Low Vision Facility at the indicated timepoints: ultrasound imaging [ultrasound biomicroscopy (UBM), A-scan, and/or B-scan], slit lamp biomicroscopy with photography/videography using gonioscopy lens, OCT imaging of jCells, retinal sensitivity with FST of both eyes separately (monocular testing, FST only performed at Baseline, M3, M6, and M12)
*Day -30 to 0. Does not need to be repeated if Day 0 is within 30 days of screening.

5.2 Treatment Compliance

Treatment compliance will be assessed via direct observation by the Study Investigator who is responsible for study drug administration. The exact time of injection will be recorded in the CRF.

5.3 Supportive Care/Prohibited Treatments

Subjects will receive supportive measures as determined by their needs and according to the accepted standards of care. All subjects will be treated with ophthalmic corticosteroid eye drops (prednisolone acetate ophthalmic suspension) to minimize any inflammation for 7 days starting on the day of injection, with a decision by the Study Investigator at the Day 7 visit regarding whether/when to taper the Predforte or to switch to a different medication. If extended beyond 7 days, the reason for longer treatment should be documented. CycIogyl, one drop twice daily, may also be given to the treated eye for 7 days. Upon day 7 examination, the Investigator will determine whether the drop can be discontinued depending on the exam findings. The CycIogyl will cause dilation of the affected eye. This may result in light sensitivity or a brief burning sensation after instillation of the drop, but should not be a significant burden for subjects. The prohibited treatments are any immunosuppressant other than topical steroids as noted above.

6.0 STUDY EVALUATIONS

Where indicated below, some study assessments will be performed at the jCyte Low Vision facility at baseline, and at 6 and 12 months post-treatment.

6.1 Screening

a. informed consent
b. prior participation in jCell study; subject must have completed the prior study through the 12 month follow up visit.
c. updated medical history and physical exam, including vital signs, height, weight and detailed ocular medical history including any previously undocumented history of eye diseases or disorders other than RP
d. pregnancy test, if female
e. CBC, platelet, differential, hemoglobin, hematocrit
f. blood chemistries, not limited to, but must include AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein
g. urinalysis
h. slit lamp and fundus exam
i. BCVA

6.2 Baseline

The assessments (indicated by an asterisk*) do not need to be repeated if Day 0 (treatment day) is within 30 days of screening. Subjects should be advised to discontinue daily aspirin or clopidogrel regimens for 5 days prior to study treatment.

Performed at clinical study site at baseline

a. Updated medical history and physical exam*, including height, weight, and detailed ocular medical history including any previously undocumented history of eye diseases or disorders other than RP
b. vital signs
c. pregnancy test, if female*
d. hematology [CBC, platelet, differential, hemoglobin, hematocrit]*
e. blood chemistries*, not limited to, but must include AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein
f. urinalysis*
g. slit lamp, fundus exam
h. Optos photography
i. BCVA
j. IOP
k. OCT (performed at site and sent to central reading lab for analysis)
l. blood sample for Ab testing

Performed at jCyte low vision facility at baseline

m. VF
n. Contrast Sensitivity
o. Mobility test
p. Optional exploratory ophthalmic imaging: ultrasound imaging (ultrasound biomicroscopy, ultrasound A- and B-scan), additional variants of slit lamp biomicroscopy with photography/videography using gonioscopy lens, optical coherence tomography (OCT) of jCells and/or retinal sensitivity with full-field sensitivity threshold testing (FST)

6.3 Day 0

Before administration of jCell (Day 0)

a. vital signs, within 15 minutes prior to injection
b. BCVA
c. IOP

After administration of a single intravitreal dose of jCell

a. exact dose and time of injection ; any dose interruption must be documented
b. vital signs at 15 and 60 minutes after treatment or until returned to pre-treatment levels
c. intraocular pressure by tonometry post-treatment must be ≤30 mm Hg prior to patient release
d. verify basic vision by lights, hand motions and fingers, depending upon individual patient's baseline prior to patient release
e. con meds
f. adverse events

6.3.1 Day 1 (24 hours)

a. brief medical history and physical exam, including any change in vision or light perception reported by patient or noted by study staff not specifically assessed (for example, patient reports that general vision is "brighter" or study staff reports that patient response to certain assessments seems more rapid)
b. vital signs
c. slit lamp and fundus exam
d. Optos photography
e. BCVA
f. IOP
g. con meds
h. adverse events

6.3.2 Day 7 (week one)

a. brief medical history and physical exam, including any changes in vision or light perception reported by patient or noted by study staff since prior MH & PE
b. vital signs
c. BCVA
d. IOP
e. con meds
f. adverse events

Performed at jCyte low vision facility one week post-treatment (optional)

g. exploratory ophthalmic imaging: ultrasound imaging (UBM, A- and B-scan), additional variants of slit lamp biomicroscopy with photography/videography using gonioscopy lens, OCT of jCells.

6.3.3 Day 28 (week four/month 1) +/- 1 day

a. brief medical history and physical exam, including any changes in vision or light perception reported by patient or noted by study staff since prior MH& PE
b. vital signs

c. CBC, platelet, differential, hemoglobin, hematocrit
d. blood chemistries, not limited to, but must include AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein
e. slit lamp and fundus exam
f. Optos photography
g. BCVA
h. IOP
i. con meds
j. adverse events
k. blood sample for Ab testing

Performed at jCyte low vision facility day 28 post-treatment (optional)

l. exploratory ophthalmic imaging: ultrasound imaging (UBM, A- and B-scan), additional variants of slit lamp biomicroscopy with photography/videography using gonioscopy lens, OCT of jCells.

6.3.4 Month 3 (Day 90) +/- 4 days

a. brief medical history and physical exam, including any changes in vision or light perception reported by patient or noted by study staff since prior MH & PE
b. vital signs
c. CBC, platelet, differential, hemoglobin, hematocrit
d. blood chemistries, not limited to, but must include AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein
e. urinalysis
f. slit lamp and fundus exam
g. Optos photography
h. BCVA
i. IOP
j. con meds
k. adverse events

Performed at jCyte low vision facility at 3 months post-treatment (optional)

h. exploratory ophthalmic imaging: ultrasound imaging (UBM, A- and B-scan), additional variants of slit lamp biomicroscopy with photography/videography using gonioscopy lens, OCT of jCells and/or retinal sensitivity with FST.

6.3.5 Month 6 (Day 180) +/- 4 days

Performed at clinical study site 6 months post-treatment

a. brief medical history and physical exam, including any changes in vision or light perception reported by patient or noted by study staff since prior MH & PE
b. vital signs
c. CBC, platelet, differential, hemoglobin, hematocrit
d. blood chemistries, not limited to, but must include AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein
e. urinalysis
f. slit lamp and fundus exam
g. Optos photography
h. BCVA
i. IOP
j. con meds
k. adverse events
l. blood sample for antibody testing

Performed at jCyte low vision facility 6 months post-treatment

m. VF
n. Contrast Sensitivity
o. Mobility test
p. optional exploratory ophthalmic imaging: ultrasound imaging (UBM, A- and B-scan), additional variants of slit lamp biomicroscopy with photography/videography using gonioscopy lens, OCT of jCells and/or retinal sensitivity with FST.

6.3.6 Month 9 (Day 270) +/- 4 days

a. brief medical history and physical exam, including any changes in vision or light perception reported by patient or noted by study staff since prior MH & PE
b. vital signs
c. slit lamp and fundus exam
d. Optos photography
e. BCVA
f. IOP
g. con meds
h. adverse events

Performed at jCyte low vision facility 9 months post-treatment (optional)

i. exploratory ophthalmic imaging: ultrasound imaging (UBM, A- and B-scan), additional variants of slit lamp biomicroscopy with photography/videography using gonioscopy lens, OCT of jCells.

6.3.7 End of Treatment (Month 12) or Early Termination Visit +/- 10 days

Performed at clinical study site 12 months post-treatment

a. MH and physical exam, including weight and height
b. vital signs
c. pregnancy test (if applicable)
d. CBC, platelet, differential, hemoglobin, hematocrit
e. blood chemistries, not limited to, but must include AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein
f. urinalysis
g. slit lamp and fundus exam
h. Optos photography
i. BCVA
j. IOP
k. OCT (performed at site and sent to central reading lab for analysis)
l. con meds
m. adverse events

Performed at jCyte low vision facility 12 months post-treatment

n. VF
o. Contrast Sensitivity
p. Mobility test
q. optional exploratory ophthalmic imaging: ultrasound imaging (UBM, A- and B-scan), additional variants of slit lamp biomicroscopy with photography/videography using gonioscopy lens, OCT of jCells and/or retinal sensitivity with FST.

7.0 ASSESSMENTS

7.1 Safety Assessments

7.1.1 Adverse Events

Subjects will be monitored for AEs from the time the subject receives a subject number until the study end or early termination. Adverse events that occur between clinic visits will be elicited by direct, non-leading questioning or will be recorded if offered voluntarily by the subject. Further details for AE reporting can be found in Section 9.

7.1.2 Vital Signs

Blood pressure and heart rate, body temperature and respiratory rate will be recorded at screening, before and after intravitreal injection and at all follow-up visits.

7.1.3 Clinical Laboratory Tests

Blood samples for clinical laboratory tests will be taken as indicated in Table 2.

Hematology – full blood count including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with differential and platelet count; neutrophils, lymphocytes, monocytes, eosinophils, basophils.

Biochemistry – alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), blood urea nitrogen (BUN), creatinine, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein

Urinalysis – pH, protein, ketones, glucose, bilirubin, blood, urobilinogen, specific gravity by dipstick and microscopy if any findings are abnormal.

Pregnancy A urine sample will be collected for a pregnancy test at screening for female subjects of childbearing potential to test for pregnancy. If this is found to be positive, it will be followed up with a serum pregnancy test.

7.1.4 Blood Samples for Antibody Testing

Blood samples will be collected for testing for Panel Reactive Antibodies (PRA) and Donor Reactive Antibodies (DRA) from subjects prior to treatment, at 4 weeks post-treatment, and at 6 months post-treatment. Details of preparation/shipping of samples will be provided separately.

7.1.5 Ophthalmic AEs

Procedures will be performed at scheduled intervals to specifically assess eye AEs that may not be detected by usual AE reporting and to try and visualize the injected cells. Please refer to the study procedure manual for details of all ophthalmologic assessment procedures.

Slit lamp and fundus exam - The binocular slit-lamp examination provides a stereoscopic magnified view of the eye structures in detail, enabling anatomical diagnoses to be made for a variety of eye conditions. This assessment will include detection of anterior chamber cell or flare; acute cataract development or progression in phakic patients, or vitreous haze. Fundus exam allows for inspection of the retina, the cellular graft, and detection of retinal detachment.

Optos photography - Optos photography includes a widefield dilated Optos photograph of the posterior segment with any cell cluster from the anterior vitreous visualized in the photo frame along with the posterior segment/fundus.

IOP - Intraocular pressure is measured with a tonometer as part of a comprehensive eye examination. Measured values of intraocular pressure are influenced by corneal thickness and rigidity

7.2 Efficacy Assessments

7.2.1 Please strictly adhere to the study procedure manual for details of all ophthalmologic assessment procedures.

7.2.2 Spectral Domain Optical Coherence Tomography (OCT) (performed locally and read centrally)

A clinical OCT machine will be used for data collection; the same machine should be used for any given patient at each time point. OCT results will be sent to a central reading lab for assessment.

7.2.3 Mobility Testing (performed at jCyte Low Vision Facility)

In general, the mobility test will consist of differing but structurally similar configurations of a relatively short maze (e.g. arrows on a printed floor mat) with ten obstacles, of various sizes. Subject testing consists of walking through several configurations each at a different illumination level as a test of mesopic visual function. Each test is videotaped and scored for speed and accuracy (number of errors) by masked independent trained graders and a score, the critical illumination level (CIL), is derived from the illumination level at which a significant drop in functional performance is observed (slow walking speed and increase in errors). For subjects assessed during the baseline testing who have an estimated monocular CIL of 1 lux or lower (near normal vision), they will be tested with that eye on both a high contrast (black and white) and a low contrast version (either 25% or 10% light grey arrows) at baseline and each low vision visit. A larger range of testing improvement should occur in the low contrast version, allowing for greater test sensitivity (i.e., preventing a ceiling effect) if the subject's vision improves with treatment.

7.2.4 BCVA (E-ETDRS) (performed at the clinical site)

BCVA will be tested at scheduled time points in both eyes in all subjects. Visual acuity will be measured with the electronic visual acuity testing algorithm (E-ETDRS) for eyes with vision better than 20/800. The measurements will be taken using a single line testing strategy with two measurements per eye at each study visit. In the event that the two measurements differ by more than seven letters, then a third measurement will be taken. For any individual eye that cannot be tested with the electronic visual acuity testing algorithm (E-ETDRS), a score of 0 letters will be used.

Trial frame refraction is the gold standard in obtaining the most accurate refractive error in low vision patients. It involves the use of a trial frame, loose lenses and specialized low vision eye charts that are different from the eye charts used in a regular eye examination. These special low vision eye charts contain different-sized letters or numbers that can help determine the sharpness or clarity of the subject's distance vision. Performed properly, the examiner obtains not only the refractive error, but additional potentially essential information, such as the level and quality of visual acuity, sensitivity to blur, effects of glare

and the quality of fixation. The optical theory involved is the same as when refracting the normal eye, but special adjustments in lens selection, presentation strategy, and "just noticeable difference", are incorporated for low vision patients. These adjustments usually include large lens increments and special techniques for exploring and refining cylinders.

7.2.5 Visual Field Testing (performed at jCyte Low Vision Facility)

Subjects enrolled in the study may have a severely restricted visual field (e.g., 4 degrees in diameter) with or without eccentric islands in the mid to far-periphery in advanced RP, or they may have full visual fields but reduced photopic sensitivity in earlier stages of RP. The Octopus 900 will be used for kinetic visual field testing using a specified target of V4e for more severe subjects and a target of III4e and V4e for better seeing subjects. Target size will be selected based on baseline visit for each eye separately. Whatever target size(s) is/are selected, the same size will be used throughout the study on that particular eye.

7.2.6 Contrast Sensitivity (performed at jCyte Low Vision Facility)

A contrast sensitivity test measures the ability of a subject to distinguish between finer and finer increments of light versus dark (contrast). Contrast provides critical information about edges, borders, and variations in luminance. Contrast sensitivity is correlated to performance on many real world tasks and tests that generate a curve or multiple sensitivity thresholds at varying grating sizes (spatial frequency) provide an in-depth view of functional vision. Using the Beethoven System, multiple thresholds and varying spatial frequencies creating a curve will be measured monocularly and the peak of the curve compared over time. Each spatial frequency is tested up to four times (thresholds) so the mean threshold at the peak contrast sensitivity for each eye will be compared over time.

7.3 Exploratory Assessments

7.3.1 Ultrasound Biomicroscopy (UBM) (performed at jCyte Low Vision Facility)

With an same ultrasound instrument as for A and B-scans, but using a different probe for UBM, high frequency high-resolution images of the cross-sectional anterior chamber can be acquired. UBM will be used to explore a more thorough volume estimation by ultrasound imaging of the jCell aggregate over time.

7.3.2 B-Scan (performed at jCyte Low Vision Facility)

B-scan ultrasound uses high-frequency sound waves to obtain measurements and produce detailed images of the eye. In the area of the typical IVT injection site, two probe directions (perpendicular to the corneal surface and inferotemporal) will be used to locate jCells.

This test may provide information regarding the location of the injected cells and the general size of the cell clusters at different time points post-treatment.

7.3.3 A-Scan (performed at jCyte Low Vision Facility)

A-scan ultrasound also uses high-frequency sound waves to obtain measurements of the length of the eye and the size of the jCell aggregate. These measurements can be used to support calculations that may be needed in exploratory analysis. With such corrections from A-scans, more precise volume estimation of the jCells may be achieved.

7.3.4 Slit lamp biomicroscopy with gonioscopy lens & photography (performed at jCyte Low Vision Facility)

Binocular slit-lamp biomicroscopy provides a stereoscopic magnified view of eye structures, enabling general anatomical exploration of the jCell aggregate over time. When combined with a gonioscopy contact lens (three-mirror lens with gel between the lens and cornea), a greater viewing angle into the anterior vitreous behind the iris to view and photograph/videograph jCells can be achieved. Photography and/or video recording through the gonioscopy lens will be used as a means to explore the shape and size of the jCell aggregate over time.

7.3.5 Hyperspectral OCT (whole eye) (performed at jCyte Low Vision Facility)

Standard SD-OCT imaging is primarily used for image segmentation of the posterior segment and often specifically the macular region. However, it may be possible to capture a cross-section of jCell using novel variants of OCT imaging in order to understand cell morphology. In order to image anterior vitreous or peripheral retinal locations where injected jCells may be located, an OCT instrument for anterior and posterior segment imaging will be used.

7.3.6 Full Field Scotopic Threshold Test (FST) (performed at jCyte Low Vision Facility)

Full-field stimulus threshold testing (FST) using LED-based ganzfeld stimulator (Colordome, Diagnosys LLC, Littleton, MA) can provide an estimation of which photoreceptor type (rod vs cone) is predominantly mediating light sensitivity. With serial FST assessments, changes in the retinal sensitivity of rods vs. cones in response to jCell therapy will be assessed. Blue and red stimuli can be used for testing monocularly under dark-adapted conditions.

8.0 SAFETY CONSIDERATIONS

8.1 Adverse Events

An AE is defined for this study as any untoward medical occurrence in a subject who is administered clinical study material. The occurrence of this event does not necessarily have a causal relationship with study product. 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 study (investigational) product or treatment (e.g. mock injection), whether or not related to the study product or treatment.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition
- Significant or unexpected worsening or exacerbation of the condition/indication under study (RP)
- A new condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study product or a concurrent medication
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures
- Antibody development

An AE does **not** include:

- Medical or surgical procedures (e.g., colonoscopy or biopsy); the medical condition that leads to the procedure is an AE
- Social or convenience hospital admissions where an untoward medical occurrence did not occur
- Day-to-day fluctuations of a pre-existing disease or conditions present or detected at the start of the study that do not worsen
- The disease/disorder being studied (RP), or expected progression, signs, or symptoms of the disease/disorder being studied unless more severe than expected for the subject's condition

All AEs that occur after informed consent is signed will be recorded in the source documents and on the appropriate CRF page. The information to be collected includes the nature, date and time of onset, intensity (mild, moderate, severe, life-threatening, death), duration, causality (relationship to investigational product), and outcome of the event. Even if the AE/SAE is assessed by the Investigator as not reasonably attributable to study product, its occurrence must be recorded in the source documents and on the appropriate page of the CRF.

Treatment-emergent AEs will be defined as AEs that occur after the study treatment (injection or mock injection).

8.2 Serious and Unexpected Adverse Events

A serious adverse event is one which:

- is fatal or life threatening,

- is permanently or significantly disabling, or
- requires in-patient hospitalization or prolongation of hospitalization

An unexpected adverse experience is one which:

- is not previously reported with the agents or procedures being undertaken, or
- is symptomatically and pathophysiologically related to a reported toxicity but differs because of greater severity or increased frequency.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

The Investigator must report all SAEs and all deaths to the study sponsor or designee immediately by telephone and in writing **within five (5) days**. A toll free number and an SAE reporting form to report such events will be provided. See also section 11 with respect to administrative responsibilities.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Populations

The intent-to-treat population comprises all subjects who enroll in the study and who provide any post-screening data. The safety population comprises all subjects who receive any study treatment. For the purposes of this study the safety population will be used for efficacy and safety analyses.

9.2 Efficacy Analyses (Secondary Endpoints)

Efficacy endpoints are secondary analyses and include assessment of change in BCVA, mobility, contrast sensitivity, and visual fields.

BCVA will be measured with the electronic visual acuity testing algorithm (E-ETDRS) and will be assessed by comparison of the mean change in number of letters correct from baseline.

Mobility will be assessed by comparison of mean change in CIL from baseline, unilaterally and bilaterally.

Descriptive statistics will be used to tabulate and summarize study outcomes. The baseline results of clinical examinations of the injected eye serve as controls for the injected eye for the purpose of reporting changes in visual parameters from baseline to 6 or 12 months post-treatment. Results of testing of the non-tested eye will also be described. Continuous variables will be summarized descriptively (sample size, mean standard deviation and error,

minimum and maximum). Discrete variables will be summarized by frequency or percentage, and analyzed with non-parametric statistics.

Subjects who cannot perform a specific visual test at baseline will be assigned the lower limit of detection, if applicable, for the relevant test. Subjects with missing data (no assessment) at baseline will be considered non-evaluable for analysis of that assessment.

9.3 Safety Analyses

Adverse events will be monitored by the investigator and the subject. The safety analyses of AEs and laboratory parameters will include descriptive statistics by treatment group. Summaries of AEs will be generated, type (AE or SAE), body system and preferred term, severity, and relationship to study product.

9.4 Other Analyses

Demographics: Background and demographic data will be summarized for all subjects.

Exploratory: Data from exploratory imaging and retinal sensitivity assessments will be summarized.

10.0 ADMINISTRATIVE CONSIDERATIONS

10.1 Adverse Experiences

All adverse experiences (AE) must be recorded and reported to the sponsor. Any serious and unexpected AE will be reported to the sponsor or designee immediately by telephone and subsequently in writing **within five (5) days**. The Investigator must also notify the institutional IRB/EC. A full report, including clear photocopies of hospital records, consultants' reports, autopsy findings where appropriate, and a summary of the outcome by the Investigator, including his opinion of study relationship or attribution, will be furnished to the study Sponsor or designee as soon as practicable. It is the sponsor's responsibility to notify the FDA, other regulatory agencies as appropriate, and all clinical sites in compliance with regulatory requirements.

10.2 Institutional Review

Prior to implementation of this study, the research protocol and the proposed subject consent form must be reviewed and approved by a properly constituted Institutional Review Committee operating under the Code of Federal Regulations (21CFR Part 56). A signed and dated statement that they have approved the protocol must be submitted to the sponsor prior to the start of the study. This committee must also approve all amendments to the protocol.

10.3 Informed Consent

Informed consent will be obtained via discussions with the subject, explaining the rationale and experimental nature of the system, the duration of the trial, alternate modes of treatment,

and prevalent adverse reactions that might occur. Each subject will receive a copy of the signed consent form.

At the time of the discussions relating to enrollment or at any time during participation in the protocol that new information becomes available relating to risks, adverse events, or toxicities, this information will be provided orally or in writing to all enrolled or prospective subject participants in a timely fashion. Documentation of communication will be provided to the local institutional review board.

10.4 Monitoring Procedure

At the time the study is initiated, the principal monitor and/or co-monitors will thoroughly review the protocol and case report forms with the Investigators and their staff. During the course of the study, the principal monitor, the co-monitor or their designated deputies shall be available to discuss by telephone or other means, questions regarding adverse reactions, removal of subjects from trial, conduct of the study, etc.

At the time of each monitoring visit, the monitor will review the case report forms of each subject in the trial to make certain that data is reported in a timely fashion, that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol. The subject's clinical records will be reviewed to confirm that the case report form data are consistent with the physician's clinical records. The monitor will verify the adherence to the procedures and schedule as defined in the protocol. The subject's clinical records will be reviewed to determine whether recording of adverse reactions or side effects has been omitted on the case report forms. If this is found to be so, then the case report forms will be returned to the Investigator and corrected to include this information.

At the time of the monitoring visit, it is the responsibility of the participating site to provide completed up-to-date case report forms, and to provide ready access to source documents.

10.5 Reporting and Recording of Data

In the US, federal regulations require that copies of case report forms be retained by the Investigator for a period of no less than two (2) years following either the approval of Biological License Application or the withdrawal of the Investigational New Drug Application. The Sponsor will advise the Investigator when the two-year period begins. Attention of the Investigator is drawn to the fact that he/she may be subject to a field audit by FDA or other regulatory inspectors to verify that the study is conducted in accordance with the requirements of the protocol, as well as in compliance with Good Clinical Practices.

All information required by the protocol is to be provided, or an explanation given for omissions. A monitor will verify the validity and completeness of the forms at each monitoring visit.

All data and information on the case report forms are to be neatly recorded in type or legibly printed in black ink for ease of duplication, interpretation and analysis before submission to the Sponsor designee. All corrections on the case report forms should be crossed out neatly and the new entry initialed and dated by the member of the Investigator's staff making the correction. Prior to forwarding the final case report forms, they should be reviewed for completeness, accuracy and legibility by the Investigator.

Copies of the completed case report forms will be provided by the Sponsor for retention by the Investigator.

10.6 Changes in Protocol

There will be no alterations or changes in this protocol without the written consent of the sponsor, jCyte.

10.7 Investigational Product and Label Codes

The investigational product is jCell. Frozen vials of jCell (hRPC) drug product are provided to the qualified dose preparation facility by Dr. Gerhard Bauer of the GMP Facility at UC Davis, where the cells were manufactured and are currently cryopreserved.

When a study subject has been scheduled for treatment, the qualified dose preparation site will prepare the patient dose according to a standard procedure. Frozen cells are thawed and cultured 40-48 hours prior to injection. Following successful culture and testing, 65 µl of cell suspension containing 6 million human retinal progenitor cells suspended in clinical grade medium (BSS PLUS) will be provided by the dose preparation facility to the clinical site, on ice, with targeted administration to the patient within 4 hours of cell harvest. Patients will undergo topical anesthesia prior to injection of the cells.

10.8 Product Security

The Investigator agrees to document use of investigational products as instructed.

References

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