

## CLINICAL RESEARCH PROTOCOL

**PROTOCOL TITLE:** A Prospective, Multicenter, Open-Label, Single-Arm Study of the Safety and Tolerability of a Single, Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Adult Subjects with Retinitis Pigmentosa (RP)

**PROTOCOL NUMBER:** JC-01

**SPONSOR:** jCyte, Inc.

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## 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 University of California, Irvine or designee with any information regarding ownership interest and financial ties with the Sponsor for the purpose of complying with regulatory requirements.

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Investigator Name (Print)

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Investigator Signature

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Date

**Study Synopsis**

<p><b>NAME OF COMPANY:</b> jCyte, Inc <b>NAME OF FINISHED PRODUCT:</b> jCell <b>NAME OF ACTIVE INGREDIENT:</b> human retinal progenitor cells</p>	<p><b>SUMMARY TABLE</b> <b>Volume:</b> <b>Page:</b> <b>Reference:</b></p>	<p><i>(For national Authority Use Only)</i></p>
<p><b>Title of study:</b> JC-01: A Prospective, Multicenter, Open-Label, Single-Arm Study of the Safety and Tolerability of a Single, Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Adult Subjects with Retinitis Pigmentosa (RP)</p>		
<p><b>Investigators/Study Centers:</b> Dr. Baruch Kuppermann, University of California, Irvine/Gavin Herbert Eye Institute; Dr. David Boyer, Retina-Vitreous Associates Medical Group, Los Angeles CA</p>		
<p><b>Study Period:</b> 2015 -2016</p>	<p><b>Phase of development:</b> Phase 1/2a</p>	
<p><b>Objectives:</b> <u>Primary Objective</u> To assess the safety and tolerability of jCell injection at multiple dose levels in subjects with non-syndromic RP <u>Secondary Objective</u> To monitor ocular function over a 12 month period following a single injection of hRPC (jCell) to evaluate the potential therapeutic response in subjects with RP.</p>		
<p><b>Methodology:</b> This is a prospective, multicenter, open-label, single-arm, Phase I/II trial of human retinal progenitor cells (jCell) for the treatment of retinitis pigmentosa (RP). Study subjects will be screened for eligibility, informed consent obtained, baseline studies of primary and exploratory endpoints performed. Then the subjects will be treated with one of two doses of jCell, with initially enrolled patients receiving the lower dose. <u>Cohort 1: BCVA no better than 20/200 and no worse than Hand Motions</u> The first four subjects in Cohort 1 will receive an intravitreal injection of 0.5 x 10<sup>6</sup> hRPC (50 µL volume) into the eye with the worst visual acuity; only one eye will be injected. Subjects will be monitored closely following injection for 60 minutes prior to being released home on the day of treatment, based on intraocular pressure &lt;30mm Hg and vital signs returned to pre-injection. Patients will be treated with ophthalmic corticosteroid eye drops to minimize any inflammation from injection for up to 14 days (including tapering schedule). There will be a minimum four week interval between the treatment of the first and second subjects in this cohort to confirm no serious injection related AEs have occurred for subject #1 prior to treatment of subject #2. Subsequent cohort 1 subjects at the same dose level will be spaced at least one week apart (subjects 2, 3 and 4). All subjects will receive injection of cells into the eye with the poorest visual acuity. Following at least one week of safety observations for the last study subject at the lower dose level, safety and tolerability data will be reviewed by the DSMB. Assuming no unexpected safety issues, an additional 4 subjects will be enrolled in Cohort 1 and treated at the second dose level, 1.0 x 10<sup>6</sup> hRPC. Treatment will be similar to the first four subjects, i.e. intravitreal injection under topical anesthesia with treatment of the first two subjects separated by at least 4 weeks and subsequent subjects in this cohort (subject 6, 7 and 8) spaced at least one week apart. Following at least one week of safety observation for the last Cohort 1 subject, safety and tolerability data will be reviewed by the DSMB prior to initiation of Cohort 2. Following completion of DSMB review of the first 8 subjects in Cohort 1 (dose levels 0.5 x 10<sup>6</sup> and 1x 10<sup>6</sup> hRPC), an additional three subjects may be enrolled into Cohort 1 and treated at the third dose level, 2 x 10<sup>6</sup> hRPC (50µL volume). Treatment will be administered as described above for the first two dose levels, with all subjects spaced at least a week apart. Following at least one week of safety observations for the last study subject at the 2 x 10<sup>6</sup> hRPC dose level, safety and tolerability data will be reviewed by the DSMB. Assuming no unexpected safety issues and with DSMB recommendation, an additional 3 subjects may be enrolled into Cohort 1 for treatment at the highest dose level, 3.0 x 10<sup>6</sup> hRPC (50 µL volume). Treatment will be administered as described above for the first two dose levels, with all subjects spaced at least a week apart.</p>		

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<p><u>Cohort 2: BCVA no better than 20/40 and no worse than 20/200</u></p> <p>The first four subjects in Cohort 2 will receive an intravitreal injection of <math>0.5 \times 10^6</math> hRPC into the eye with the worst visual acuity; only one eye will be injected. Subjects will be monitored closely following injection for 60 minutes prior to being released home on the day of treatment, based on intraocular pressure &lt;30mm Hg and vital signs returned to pre-injection. Patients will be treated with with ophthalmic corticosteroid eye drops to minimize any inflammation from injection for up to 14 days (including tapering schedule). Assuming no unexpected safety issues in the low dose group, an additional 4 subjects will be enrolled in Cohort 2 and treated at the second dose level, <math>1.0 \times 10^6</math> hRPC.</p> <p>Once the first two dose levels are completed in Cohort 2, and following the review of safety data from Cohort 1 subjects who were treated at the third dose level (<math>2.0 \times 10^6</math> hRPC), three additional subjects may be enrolled into Cohort 2 and treated at the <math>2 \times 10^6</math> hRPC dose level. Following this and assuming no unexpected safety issues in the Cohort 1 subjects at the <math>3 \times 10^6</math> dose level, three additional subjects may be enrolled into Cohort 2 and treated at this highest dose level.</p> <p>Assuming safety and tolerability data from both dose levels in cohort 1 are acceptable, there will be no minimum interval between treatment of subjects in Cohort 2.</p> <p>If <math>\geq 2</math> patients develop the same CTCAE grade 3 adverse event or 1 patient develops a CTCAE grade 4 adverse event, the study will be suspended until the DSMB reviews the events and makes a determination whether to continue. If a Grade 3 or worse event is clearly attributable to a non-treatment event and therefore not a suspected adverse reaction: [21CFR312.32(a)] the event will not be considered for the purposes of stopping.</p>		
<p><b>Number of patients:</b> up to 28 patients are planned for inclusion, 14 in each vision cohort</p>		
<p><b>Diagnosis and main criteria for inclusion:</b> <b>Inclusion Criteria</b></p> <p>The following conditions must be met before a subject may be enrolled in the study.</p> <ol style="list-style-type: none"> <li>1. Willing to give written informed consent, able to make the required study visits and follow study protocol instructions.</li> <li>2. Willing to consent to gene mutation typing. Mutation typing will be restricted to typing for eye disease-related genes known to be involved in inherited retinal degenerations and related disorders. If typing results are already available for the subject, the previous results can be recorded and this requirement is waived.</li> <li>3. Clinical diagnosis of RP confirmed by ERG.</li> <li>4. BCVA 20/200 or worse and no worse than HM in cohort 1; and BCVA 20/40 or worse and no worse than 20/200 for the second cohort.</li> <li>5. Male or female, age <math>\geq 18</math> yr.</li> <li>6. Adequate organ function:             <ul style="list-style-type: none"> <li>o 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</li> <li>o liver function: alanine transaminase [ALT] and aspartate transaminase [AST] <math>\leq 2</math> times the upper limit of the normal range</li> <li>o total bilirubin <math>\leq 1.5</math> times the upper limit of the normal range</li> <li>o renal function: serum creatinine <math>\leq 1.25</math> times the upper limit of the normal range</li> </ul> </li> <li>7. Negative infectious disease screen (hepatitis B, C or HIV); and drugs of abuse (negative urine screen).</li> <li>8. 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</li> </ol>		

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<p>least 12 months following treatment.</p> <p>9. Willing to provide a blood sample for HLA typing, if not done previously with available results</p> <p><b>Exclusion Criteria</b> Patients will be excluded from this study if they meet any of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Eye disease other than RP that impairs visual function (including retinal vascular disease, elevated intraocular pressure/glaucoma, severe posterior uveitis, clinically significant macular edema), or media opacity precluding visual exam, as well as patients who require other intravitreal therapies</li> <li>2. Pseudo-RP, cancer-associated retinopathies (CAR, MAR) excluded as part of differential diagnosis</li> <li>3. History of 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.</li> <li>4. Known allergy to penicillin or streptomycin.</li> <li>5. Known allergy to or history of adverse reaction to fluorescein.</li> <li>6. History of adverse reaction to DMSO.</li> <li>7. Unable or unwilling to undergo genetic testing, pupil dilation, topical anesthesia or any protocol-required procedure.</li> <li>8. Women who are nursing or who are planning to nurse during the 12 months that would follow study treatment.</li> <li>9. Any circumstance that in the opinion of the investigator, would interfere with participation in, or compliance with the study protocol</li> <li>10. 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 study enrollment</li> <li>11. Cataract surgery within three months prior to enrollment or anticipated to need cataract surgery within a year of treatment</li> <li>12. Participation in a clinical trial for eye disease within 6 months.</li> </ol>		
<p><b>Test product, dose and mode of administration:</b> The investigational product (jCell) is a live suspension of 0.5-3.0 x 10<sup>6</sup> 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 either 0.5, 1.0, 2.0, 3.0 x 10<sup>6</sup> jCell as an intravitreal injection under topical anesthesia into the eye with the worst visual acuity.</p>		
<p><b>Duration of treatment:</b> 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. Study subjects will be followed for one year post-injection under this protocol with a separate protocol planned for two additional years of long term follow up.</p>		
<p><b>Criteria for Evaluation:</b> <u>Efficacy:</u> Efficacy will be assessed based on a series of ophthalmologic assessments at specified timepoints, including best corrected visual acuity (BCVA), spectral domain optical coherence tomography (OCT), electroretinogram (ECG), visual field testing (where appropriate), fluorescein angiography, autofluorescence and a visual quality of life</p>		

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<p>questionnaire (VFQ-25). In addition, several low vision assessment tools may be explored in subsets of subjects in order to better understand which assessments may be most useful for this type of treatment approach. None of these assessments are invasive.</p> <p><u>Safety:</u>                  Safety will be assessed on an ongoing basis by adverse events, identification of dose-limiting toxicities (if any), physical examinations and vital signs, clinical laboratory values, and anti-drug antibodies. In addition, specific ophthalmologic tests to monitor safety will be performed, including slit lamp and fundus examination, B-scans and intraocular pressure (IOP). Additional ophthalmologic tests described above will also contribute to safety monitoring. Clinical safety data will be reviewed on an ongoing basis. Safety data will undergo formal review by a DSMB following completion of each dose level 1 in Cohort 1 before initiation of the next dose level in Cohort 1, and before the initiation of the same dose level in Cohort 2.</p>		
<p><b>Statistical methods:</b>                  Background and demograhic data will be summarized for all subjects using descriptive statistics.</p> <p><u>Efficacy:</u>                  Since this is an exploratory study, no formal hypothesis testing will be done. 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-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.</p> <p><u>Safety:</u>                  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.</p>		

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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<sup>1</sup>. 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 nonfunctional 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<sup>2</sup>. Both photoreceptors<sup>3</sup> and RPE cells<sup>4,5</sup> 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<sup>6</sup>. Glial hypertrophy has been often been implicated in the failure of endogenous regenerative mechanisms to bridge a lesion<sup>7</sup>, e.g., after spinal cord injury<sup>8</sup>.

### 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<sup>9,10</sup>. 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<sup>11</sup>. 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<sup>9</sup>; 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<sup>12</sup>. 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*<sup>13</sup> and murine brain progenitor cells survived transplantation to the allogeneic kidney

capsule, a non-privileged site<sup>14</sup>. 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 0.5-1.0 x 10<sup>6</sup> 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 24-48 hours, as is planned for the initial clinical study.

**Table 1 Characterization and Functional Properties of jCell hRPCs**

Test	Results
Cell count and viability	1.0 – 1.6 x 10 <sup>6</sup> /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 associated with different retinal neuronal/glial cell types

Test	Results
	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 have 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<sup>10</sup>. 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.

There are only extremely limited human data available for hRPC that may not be entirely representative of the current jCell investigational product but are considered supportive. In an extremely limited non-US pilot group of 3 legally blind patients that received a single hRPC injection of 500,000 cells each in one eye, there were no surgical complications other than 1 transient sterile anterior chamber reaction that resolved with standard steroid drops. There were no signs of immune rejection, without immunosuppression, and despite the transient anterior inflammation in one patient, there was no clinically evident cell

proliferation in vivo based on all examinations (slit-lamp, 30D lens, B scan, fundus photos, etc.) and no tumor formation was detected during follow up to 8 months.

All three patients experienced some improvement in visual acuity and one patient also showed evidence of improvement in visual field area and ERG. These limited results of hRPC administration reported in these three patients are encouraging but are interpreted with caution due to the extremely small number of subjects.

The study population proposed herein is limited to adults since the severe stage of the degeneration of the type described typically occurs in adulthood. In non-syndromic RP, the retina is the isolated disease focus, without involvement of other organs or systems that might contribute to adverse events. The criterion for baseline visual acuity in the range of 20/200 to “hand motions” (HM) in the initial cohort is chosen because in this range, the disease is advanced and visually disabling, yet some residual photoreceptors are still present to be acted upon therapeutically. In the second cohort, patients will have best corrected visual acuity (BCVA) of 20/40 or worse and visual fields of 10 degrees or less. This level of vision is significantly impaired, yet better than the initial cohort, thereby allowing greater potential for macular cone rescue.

## **2.0 OBJECTIVES**

### **2.1 Primary Objective**

The primary objective is to evaluate the safety and tolerability of jCell injection in adult subjects with non-syndromic RP.

### **2.2 Secondary Objectives**

The secondary objectives of the study are to monitor ocular function over a 12 month period following a single injection of hRPC (jCell) to evaluate the potential therapeutic response in subjects with RP.

## **3.0 STUDY DESIGN**

This is a prospective, multicenter, open-label, single-arm, Phase I/II trial of hRPC (jCell) for the treatment of retinitis pigmentosa (RP). Study subjects will be screened for eligibility, informed consent obtained, baseline studies of primary and exploratory endpoints performed. Then the subjects will be enrolled into one of two cohorts. Cohorts will be treated consecutively for each dose level, with review of safety data at scheduled intervals. That is, once a dose level is completed in Cohort 1, the enrollment of Cohort 2 subjects into that dose level can be initiated assuming no safety issues in Cohort 1 subjects at that dose level. Subjects will be entered into a treatment cohort based upon the order of enrollment at each of the study sites. Subjects in both cohorts will be followed for one year under this protocol and will be encouraged to participate in a follow-on study of long term safety and tolerability for an additional two years at study completion.

### 3.1 Study Population

#### 3.1.1 Cohort One

Up to 14 subjects will be enrolled into Cohort 1. Subjects in Cohort 1 must have BCVA no better than 20/200 and no worse than Hand Motions (HM, i.e. the patient can distinguish horizontal from vertical hand motions at 1 foot). The first four subjects in Cohort 1 will receive an intravitreal injection of  $0.5 \times 10^6$  hRPC (50  $\mu$ L volume) into the eye with the worst visual acuity; only one eye will be injected. The procedure does not require in-patient hospitalization and can be done under topical anesthesia. 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. Patients will be treated with ophthalmic corticosteroid eye drops to minimize any inflammation from injection for up to 14 days (including tapering schedule). There will be a minimum four week interval between the treatment of the first and second subjects in this cohort, with follow up at 1, 2, 3, 7, 14 and 21 days post-injection by the study investigator to confirm no serious injection related AEs have occurred for subject #1 prior to treatment of subject #2. Subsequent cohort 1 subjects at the same dose level will be spaced at least one week apart (subjects 2, 3 and 4), with follow up at 1, 2 and 3 days post-injection for each subject prior to treatment of the next subject at that dose level. All subjects will receive injection of cells into the eye with the poorest visual acuity. Following at least one week of safety observations for the last study subject at the lower dose level, safety and tolerability data will be reviewed by the DSMB. Assuming no unexpected safety issues and with DSMB recommendation, an additional 4 subjects will be enrolled in Cohort 1 and treated at the second dose level,  $1.0 \times 10^6$  hRPC. Treatment will be similar to the first four subjects, i.e. intravitreal injection under topical anesthesia with treatment of the first two subjects separated by at least 4 weeks and subsequent subjects in this cohort (subject 6, 7 and 8) spaced at least one week apart. Following at least one week of safety observation for the last Cohort 1 subject, safety and tolerability data will be reviewed by the DSMB prior to initiation of Cohort 2.

Following completion of DSMB review of the first 8 subjects in Cohort 1 (dose levels  $0.5 \times 10^6$  and  $1 \times 10^6$  hRPC), an additional three subjects may be enrolled into Cohort 1 and treated at the third dose level,  $2 \times 10^6$  hRPC (50 $\mu$ L volume). Treatment will be administered as described above for the first two dose levels, with all subjects spaced at least a week apart. Following at least one week of safety observations for the last study subject at the  $2 \times 10^6$  hRPC dose level, safety and tolerability data will be reviewed by the DSMB. Assuming no unexpected safety issues and with DSMB recommendation, an additional 3 subjects may be enrolled into Cohort 1 for treatment at the highest dose level,  $3.0 \times 10^6$  hRPC (50  $\mu$ L volume). Treatment will be administered as described above for the first two dose levels, with all subjects spaced at least a week apart.

### 3.1.2 Cohort Two

Up to 14 subjects will be enrolled into Cohort 2, following completion of Cohort 1 and review of Cohort 1 safety and tolerability data by the DSMB at the relevant dose level. Subjects in Cohort 2 must have BCVA no better than 20/40 and no worse than 20/200. The first four subjects in Cohort 2 will receive an intravitreal injection of  $0.5 \times 10^6$  hRPC into the eye with the worst visual acuity; only one eye will be injected. As noted above, the procedure can be done under topical anesthesia. Subjects will be monitored closely following injection for 60 minutes prior to being released home on the day of treatment, based on intraocular pressure  $<30$ mm Hg and vital signs returned to pre-injection. Patients will be treated with ophthalmic corticosteroid eye drops to minimize any inflammation from injection for up to 14 days (including tapering schedule). Assuming no unexpected safety issues in the low dose group, an additional 4 subjects will be enrolled in Cohort 2 and treated at the second dose level,  $1.0 \times 10^6$  hRPC.

Once the first two dose levels are completed in Cohort 2, and following the review of safety data from Cohort 1 subjects who were treated at the third dose level ( $2.0 \times 10^6$  hRPC), three additional subjects may be enrolled into Cohort 2 and treated at the  $2 \times 10^6$  hRPC dose level. Following this and assuming no unexpected safety issues in the Cohort 1 subjects at the  $3 \times 10^6$  dose level, three additional subjects may be enrolled into Cohort 2 and treated at this highest dose level. Assuming safety and tolerability data from the relevant dose levels in Cohort 1 are acceptable, there will be no minimum interval between treatment of subjects in Cohort 2.

## 3.2 Endpoints

### 3.2.1 Efficacy Endpoints

The response to jCell injection will be assessed based on the following:

- Change in BCVA at scheduled time points compared to baseline as well as contralateral eye. Acuity testing will be standardized using E-ETDRS.
- Changes in ellipsoid zone (EZ) band width at specified time points based on Spectral Domain Optical Coherence Tomography (OCT) compared to baseline as well as contralateral eye.
- Changes in electroretinogram (ERG) physiologic analysis compared to baseline as well as contralateral eye.
- Visual field sensitivity at scheduled time points post-treatment, using Goldmann visual field area and Humphrey 10-2, in subjects with adequate fixation to allow reliable testing.

In addition to the assessments listed above, a number of visual assessments that may be more appropriate for low vision subjects have been recommended by low vision experts. While BCVA is the gold standard for vision assessment, it is clear that this test is not particularly



relevant or accurate for subjects with very poor vision (legally blind). As there is little experience with our treatment approach, and subjects with very advanced vision loss are included in Cohort 1, it is planned to try some non-invasive assessments in subgroups of subjects, dependent upon the subjects' visual range and capabilities. These assessments include but are not limited to trial frame refraction, testing for contrast sensitivity (examples include Pelli-Robson Contrast Sensitivity Chart, Mars Letter Contrast Sensitivity Test, low luminance testing and mixed contrast eye charts); testing for color vision changes (e.g. D15 large caps, pseudoisochromatic plates), FrACT, California Central Visual Field Test, Tangent Screen Perimetry, ADL questionnaire (e.g. VFQ25, activity inventory, Low Vision Visual Functional Questionnaire [LF-VFQ], Function Independence Measures [FIM], Prosthetic Low Vision Rehabilitation [PVoVR]) and testing for changes in reading ability (e.g. Continuous Text Reading, MN Read). The goal of exploring some or all of these assessments is to develop a qualified, quantitative tool or set of tools for assessing post-treatment changes.

### **3.2.2 Safety Endpoints**

The primary goal of the study is to evaluate the safety and tolerability of jCell injection: The criteria that will be used to establish safety include:

- Slit-lamp findings, i.e., anterior chamber cell or flare; acute cataract development or progression in phakic patients, vitreous haze.
- Absence of tumor formation, overt immune rejection, decrease in BCVA attributable to treatment
- Absence of clinically significant, persistent increase in intraocular pressure (>10 mm Hg above baseline or IOP > 25 mm Hg), clinically significant epiretinal membrane, retinal detachment, neovascularization, or endophthalmitis
- No clinically significant adverse events attributable to investigational product (jCell) injection
- Patient comfort (no intolerable pain related to procedure)

### **3.3 Study Duration**

The overall duration of the study is anticipated to be approximately 2 years. The study will be considered to have started when the first site is initiated. The study will be considered to have finished after the last subject has completed the last follow-up visit in the study (12 months following treatment).

All subjects who receive jCell treatment will be closely monitored throughout the observation period. All subjects who receive treatment with jCell will be encouraged to participate in a follow-on study to assess potential long term effects (safety and efficacy) of jCell treatment. The follow-on study is planned to include an at least two years of additional subject monitoring; additional follow up visits will be scheduled at least every 6 months with

monitoring to include medical history and physical exam, vital signs, safety lab tests (as at other visits), urinalysis, adverse events, BCVA and slit lamp/fundus exam at each visit; and additional ophthalmic exams at specified visits. More frequent visits will be scheduled during the initial or follow-on study as appropriate should this be indicated by safety concerns.

### **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 subject may be enrolled in the study.

1. Willing to give written informed consent, able to make the required study visits and follow study protocol instructions.
2. Willing to consent to gene mutation typing. Mutation typing will be restricted to typing for eye disease-related genes known to be involved in inherited retinal degenerations and related disorders. If typing results are already available for the subject, the previous results can be recorded and this requirement is waived.
3. Clinical diagnosis of RP confirmed by ERG.
4. BCVA 20/200 or worse and no worse than HM in cohort 1; and BCVA 20/40 or worse and no worse than 20/200 for the second cohort.
5. Male or female, age  $\geq 18$  yr.
6. Adequate organ function:
  - a. 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
  - b. liver function: alanine transaminase [ALT] and aspartate transaminase [AST]  $\leq 2$  times the upper limit of the normal range
  - c. total bilirubin  $\leq 1.5$  times the upper limit of the normal range

- d. renal function: serum creatinine  $\leq 1.25$  times the upper limit of the normal range
7. Negative infectious disease screen (hepatitis B, C or HIV); and drugs of abuse (negative urine screen).
8. 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. Note: Women of childbearing potential and men must be advised to use a medically accepted method of contraception for at least 12 months following treatment.
9. Willing to provide a blood sample for HLA typing, if not done previously with available results

#### 4.2 Exclusion Criteria

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

1. Eye disease other than RP that impairs visual function (including retinal vascular disease, elevated intraocular pressure/glaucoma, severe posterior uveitis, clinically significant macular edema), or media opacity precluding visual exam, as well as patients who require other intravitreal therapies
2. Pseudo-RP, cancer-associated retinopathies (CAR, MAR) excluded as part of differential diagnosis
3. History of 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.
4. Known allergy to penicillin or streptomycin.
5. Known allergy to or history of adverse reaction to fluorescein.
6. History of adverse reaction to DMSO.
7. Unable or unwilling to undergo genetic testing, pupil dilation, topical anesthesia or any protocol-required procedure.
8. Women who are nursing or who are planning to nurse during the 12 months that would follow study treatment.
9. Any circumstance that in the opinion of the investigator, would interfere with participation in, or compliance with the study protocol

10. 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 study enrollment
11. Cataract surgery within three months prior to enrollment or anticipated to need cataract surgery within a year of treatment
12. Participation in a clinical trial for eye disease within 6 months.

### **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
- Development of intolerable AEs during the study
- Major protocol violation
- Lost to follow-up
- Any event that prevents the subject from meeting the study requirements

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 SUBJECT REGISTRATION**

At the time informed consent is obtained, qualified subjects will be assigned a study number. At the time a study number is assigned by the Sponsor or designee, the interval between the

last subject treated and the planned treatment of the new subject will be assessed to assure that it meets study requirements for separation of patient treatments.

## **6.0 TREATMENT PLAN**

### **6.1 Dose and Schedule**

All subjects will receive a single intravitreal injection of hRPC at the assigned dose into the eye with the poorest visual acuity or, if vision is comparable in both eyes, the non-dominant eye. After topical anesthesia, a single 50 microliter suspension of cells (0.5, 1, 2 or 3 million) will be delivered under direct visualization 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 are summarized in Table 2.

**Table 2 Schedule of Assessments (JC -01)**

Timepoint	Scr	BL*	Day 0	Day 1	Day 2	Day 7 <sup>7</sup>	Day 14 <sup>7</sup>	Day 21 <sup>7</sup>	Day 28 <sup>7</sup>	M <sub>2</sub> <sup>8</sup>	M3 <sup>8</sup>	M4 <sup>8</sup>	M5 <sup>8</sup>	M6 <sup>8</sup>	M9 <sup>8</sup>	M12 or Early Term
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		
HLA typing	x															
Weight	x	x*	x			x										x
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test	x	x*														x
Safety laboratory tests <sup>1</sup>	x	x*				x			x		x			x		x
Infectious disease tests <sup>2</sup>	x	x*														
Urinalysis <sup>3</sup>	x	x*									x			x		x
Electrocardiogram	x	x*	x	x												
Slit lamp and fundus exam	x	x <sup>4</sup>		x	x	x	x	x	x	x	x	x	x	x	x	x
BCVA (ETDRS)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ERG	x <sup>9</sup>	x <sup>9</sup>												x		x
IOP		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT		x							x		x			x	x	x
FA		x												x <sup>6</sup>		x
AF		x												x		x
VF (if applicable)		x												x		x
B-scan		x				x					x			x		x
Exploratory non-invasive visual assessments (optional)		x									x			x	x	x
Study Drug Injection			x													
Con Meds			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood sample for Ab testing <sup>5</sup>		x					x		x							x
Written consent for FU study																x

<sup>1</sup>Hematology (minimally Hct, Hgb, CBC with diff, plt), coagulation panel and blood chemistries (minimally AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein) <sup>2</sup>Hepatitis B and C, HIV <sup>3</sup>Drug screen included at screening visit <sup>4</sup>Fundus photographs at baseline <sup>5</sup>Testing for Panel Reactive Antibodies (PRA) and Donor Reactive Antibodies (DRA) <sup>6</sup>Only if cystoid macular edema (CME) is observed on OCT <sup>7</sup>Visit window +/- 1 day <sup>8</sup>Visit window +/- 4 days <sup>9</sup>ERG can be performed at screening to confirm eligibility; if so, does not need to be repeated at baseline. \*Day -30 to 0. Does not need to be repeated if Day 0 is within 30 days of screening.

## 6.2 Treatment Compliance

Treatment compliance will be assessed via direct observation by the study investigator who is responsible for study drug administration. The cell dose and exact time of injection will be recorded.

## 6.3 Supportive Care/Prohibited Treatments

Subjects will receive supportive measures as determined by their needs and according to the accepted standards of care. Subjects will be treated with ophthalmic corticosteroid eye drops to minimize any inflammation for up to 14 days starting on the day of injection, including tapering schedule. The prohibited treatments are any immunosuppressant other than topical steroids as noted above.

## 7.0 STUDY EVALUATIONS

### 7.1 Screening

- a. informed consent
- b. documentation of initial diagnosis confirmed by ERG (ERG can be performed at screening to confirm eligibility)
- c. consent to mutation typing (if not already done – can be done at baseline or screening)
- d. complete medical history and physical exam, including vital signs, height, weight
- e. pregnancy test, if female
- f. blood sample for HLA typing
- g. CBC, platelet, differential, hemoglobin, hematocrit
- h. blood chemistries, not limited to, but must include AP, ALT, AST, BUN, Cr, total bilirubin, serum electrolytes, glucose, calcium, phosphate, albumin and total protein
- i. coagulation function, including PT/INR, PTT
- j. infectious disease screen (Hepatitis B and C, HIV)
- k. urinalysis, including drug screen
- l. ECG
- m. slit lamp and fundus exam
- n. BCVA

### 7.2 Baseline (should be within 30 days of treatment)

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.

- a. medical history and physical exam\*, including height, weight
- 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. coagulation function, including PT/INR, PTT (if abnormal at baseline, this test should be repeated each time standard safety labs, e.g. hematology and blood chemistries, are performed)\*
- g. infectious disease screen\* (Hepatitis B and C, HIV)
- h. urinalysis\*
- i. ECG\*
- j. slit lamp and fundus exam, including fundus photographs
- k. BCVA
- l. ERG (does not need to be repeated if performed at screening to confirm eligibility)
- m. IOP
- n. OCT
- o. FA
- p. B-scan
- q. AF
- r. VF
- s. blood sample for Ab testing
- t. exploratory visual assessments, dependent upon subject's abilities

### **7.3 Before administration of jCell (Day 0)**

- a. weight
- b. vital signs, within 15 minutes prior to injection
- c. ECG – does not need to be repeated if within one week of baseline or screening ECG
- d. BCVA

### **7.4 After administration of a single intravitreal dose of jCell (Day 0)**

- a. exact dose and time of injection; any dose interruption must be documented
- b. vital signs at 15 and 60 minutes after injection or until returned to pre-treatment levels
- c. intraocular pressure by tonometry post-treatment must be  $\leq 30$  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

## **7.5 Follow up Visits**

### **7.5.1 Day 1 (24 hours)**

- a. brief medical history and physical exam, including any changes 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. ECG (24 hours post-injection)
- d. slit lamp and fundus exam
- e. BCVA
- f. IOP
- g. con meds
- h. adverse events

### **7.5.2 Day 2 (48 hours)**

- a. vital signs
- b. slit lamp and fundus exam
- c. BCVA
- d. IOP
- e. con meds
- f. adverse events

### **7.5.3 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 H & PE
- b. weight
- c. vital signs
- 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. coagulation function, including PT/INR, PTT – only participants who had abnormal values (out of normal range) at baseline
- g. slit lamp and fundus exam
- h. BCVA
- i. B-scan
- j. IOP
- k. con meds

- l. adverse events

**7.5.4 Day 14 (week two) +/- 1 day**

- a. vital signs
- b. slit lamp and fundus exam
- c. BCVA
- d. IOP
- e. con meds
- f. adverse events
- g. blood sample for Ab testing

**7.5.5 Day 21 (week three) +/- 1 day**

- a. vital signs
- b. slit lamp and fundus exam
- c. BCVA
- d. IOP
- e. con meds
- f. adverse events

**7.5.6 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 H& 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. coagulation function, including PT/INR, PTT – only participants who had abnormal values (out of normal range) at baseline
- f. slit lamp and fundus exam
- g. BCVA
- h. IOP
- i. OCT
- j. con meds
- k. adverse events
- l. blood sample for Ab testing

**7.5.7 Month 2 (Day 60) +/- 4 days**

- a. vital signs
- b. slit lamp and fundus exam
- c. BCVA

- d. IOP
- e. exploratory visual assessments
- f. con meds
- g. adverse events

**7.5.8 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 H & 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. coagulation function, including PT/INR, PTT – only participants who had abnormal values (out of normal range) at baseline
- f. urinalysis
- g. slit lamp and fundus exam
- h. BCVA
- i. B-scan
- j. IOP
- k. OCT
- l. exploratory visual assessments
- m. con meds
- n. adverse events

**7.5.9 Month 4 (Day 120) +/- 4 days**

- a. vital signs
- b. slit lamp and fundus exam
- c. BCVA
- d. IOP
- e. con meds
- f. adverse events

**7.5.10 Month 5 (Day 150) +/- 4 days**

- a. vital signs
- b. BCVA
- c. IOP
- d. con meds
- e. adverse events

**7.5.11 Month 6 (Day 180) +/- 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 H & 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. coagulation function, including PT/INR, PTT – only participants who had abnormal values (out of normal range) at baseline
- f. urinalysis
- g. slit lamp and fundus exam
- h. BCVA
- i. B-scan
- j. IOP
- k. ERG
- l. OCT
- m. FA only if cystoid macular edema (CME) is observed on OCT
- n. AF
- o. VF (if applicable)
- p. con meds
- q. adverse events
- r. exploratory visual assessments

**7.5.12 Month 9 (Day 270) +/- 4 days**

- a. vital signs
- b. slit lamp and fundus exam
- c. BCVA
- d. IOP
- e. exploratory visual assessments
- f. con meds
- g. adverse events

**7.6 End of Treatment (Month 12) or Early Termination Visit**

- 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. coagulation panel, including PT/INR, PTT
- g. urinalysis
- h. slit lamp and fundus exam
- i. BCVA
- j. B-scan
- k. ERG
- l. IOP
- m. OCT
- n. FA
- o. VF (if applicable)
- p. con meds
- q. adverse events
- r. blood sample for Ab testing
- s. exploratory visual assessments
- t. informed consent for follow-up study

## **8.0 ASSESSMENTS**

### **8.1 Safety Assessments**

#### **8.1.1 Adverse Events**

Subjects will be monitored for AEs from the time the subject receives a study 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.

#### **8.1.2 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.

#### **8.1.3 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

**Coagulation** – PT/INR, PTT

**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.

#### **8.1.4 Blood Samples for Antibody Testing**

Blood samples will be collected for testing for Panel Reactive Antibodies (PRA) and Donor Reactive Antibodies (DRA) prior to treatment, at 2 and 4 weeks post-treatment, and at study termination. Details of preparation/shipping of samples will be provided separately.

#### **8.1.5 Ophthalmic AEs**

Procedures will be performed at scheduled intervals to specifically assess eye AEs that may not be detected by usual AE reporting. 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.

**B-scan** – B-scan is a test that uses high-frequency sound waves to get measurements and produce detailed images of the eye. This test may provide information regarding the location of the injected cells and the size of the cell clusters at different time points during the study.

**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

**Spectral Domain Optical Coherence Tomography (OCT)** - 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 tests, including assessment of the ellipsoid zone (EZ), will be analyzed to help define retinal anatomy, and will enable monitoring for ocular inflammation after treatment as manifest by cystoid macular edema or epiretinal membrane formation or progression.

## **8.2 Efficacy Assessments**

Please refer to the study procedure manual for details of all ophthalmologic assessment procedures.

### **8.2.1 BCVA**

BCVA will be tested at scheduled time points in both the treated and the contralateral eye. Visual acuity will be measured with the electronic visual acuity testing algorithm (E-ETDRS). E-ETDRS testing will be conducted using the electronic visual acuity tester (EVA). Based on estimates of 95% confidence intervals, a change in visual acuity of 0.2 logMAR (10 letters) from a baseline level is unlikely to be related to measurement variability using either the E-ETDRS or the S-ETDRS visual acuity testing protocol.

### **8.2.2 Electroretinogram (ERG)**

ERG examinations will be performed according to ISCEV standards and standardized among clinics to minimize difference between centers: briefly, patients are dark adapted for 30 min, electrodes attached under dim red illumination (dark room safe light). ERG responses will be recorded using single scotopically-balanced dim blue and red light flashes, and bright white flashes per detailed protocol. ERG at 6, 12 months are compared to pre-injection in terms of 1) a-wave amplitude, 2) b-wave amplitude, 3) time from flash onset to a wave trough and 4) time from flash onset to b-wave peak. In individual patients significantly faster deterioration of injected eye by ERG parameters and BCVA will halt further enrollment, although the latter measure is likely to be the more informative.

### **8.2.3 Visual Field Testing**

Visual field sensitivity will be assessed at scheduled time points post-treatment, using Goldmann visual field area and Humphrey 10-2, in subjects with adequate fixation to allow reliable testing.

### **8.2.4 Fluorescein Angiography**

Fluorescein angiography will to be assessed at scheduled time points to examine the circulation of the retina and choroid using a fluorescent dye and a specialized camera. The procedure involves pupil dilation and IV injection of the dye, sodium fluorescein. An angiogram is obtained by photographing the fluorescence emitted after illumination of the retina with blue light at a wavelength of 490 nanometers.

The fluorescein dye also appears in the patient urine, causing the urine to appear darker, and sometimes orange. It can also cause discoloration of the saliva and the skin will appear yellow for several hours after the angiogram.

### **8.2.5 Autofluorescence**

Fundus autofluorescence images specifically assess the health of the retinal photoreceptors (RODS and CONES) and the retinal layer which provides nutrition to the rods and cones (the retinal pigmented epithelium - RPE). FAF is effective because it can document metabolic change from the accumulation of toxic fluorophores in the retinal pigment epithelium. The test may require pupil dilation but does not require injection of any dye.

## 8.2.6 Exploratory Visual Assessments

### Best Corrected Visual Acuity

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.

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

### Contrast Sensitivity

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. Their usefulness as a measure for predicting performance on many real world tasks and their sensitivity to a range of visual disorders has led to the development of several easily-administered clinical tests of contrast sensitivity. Examples of tests for contrast sensitivity function include the Pelli Robson (P-R) Contrast Sensitivity Chart, the Mars Letter Contrast Sensitivity Test, and mixed contrast eye charts.

### Low Luminance

Low Luminance Visual Dysfunction Testing has been shown to be a predictor of subsequent visual acuity loss. Some believe that it is a better predictive factor for how much the disease has progressed than standard visual acuity. Examples of testing include using a wire-rimmed 2.0-log-unit neutral density filter or a NoIR U23 fitter (4% transmission) grey lens during visual acuity or visual field testing.

### Color Vision Testing

Quantitative measurement of color vision is an important diagnostic test used in evaluating deficient color vision. The exploratory tests of interest are designed to correctly identify all (congenital and acquired) color deficiencies, no matter how slight. They may include large cap sizes, which give more information about color vision function both in normally sighted



and low vision individuals. Examples include the D15 Large Caps Test and the use of pseudoisochromatic plates.

### Visual Field Testing

Visual Field testing is an important test in measuring a subject's peripheral vision. In patients with RP, the California Central Visual Field Test and Tangent Screen Perimetry Testing allows for a flexible head posture when fixating on targets. This flexibility may give a more accurate assessment and provide more information about steadiness of fixation and degrees of remaining constricted field of vision especially when the remaining vision or an island of vision in severely impaired subjects is eccentrically located. The Tangent Screen can assess up to 60 degrees of the visual field when used at a test distance of 1 meter, allowing for identification and mapping of peripheral islands of vision.

### Activities of Daily Living (ADL)

Assessing changes in the day-to-day functional changes/improvements is considered to be one of the most important assessments for subjects with low vision. There are several instruments that have been developed for this purpose that may be useful in the low vision patient population in this study.

The National Eye Institute (NEI) VFQ-25 survey measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning. A number of clinical studies have used either the 51 or the 25-item version of the NEI-VFQ across a number of chronic ocular conditions. The VFQ-25 takes approximately 10 minutes on average to administer in the interviewer format.

The Activity Inventory (AI) developed by Dr. Massof at Johns Hopkins organizes everyday activities into a hierarchical framework. Within this structure tasks refer to very specific cognitive and motor activities. Examples of tasks include cutting food, reading recipes, setting stove and oven dials, and measuring ingredients. Goals refer to the reasons for performing tasks. For example, cutting food, reading recipes, measuring ingredients, etc. are all tasks that are performed with the goal of cooking daily meals. Goals, in turn, are organized under objectives. The Activity Inventory has three objectives: living independently, social interactions, and recreation. Fifty goals are listed under those three objectives, and 450 tasks are under the fifty goals, so it is a rather lengthy test.

The Low Vision Visual Functional Questionnaire (LV-VFQ48 is a valid and reliable questionnaire that may be administered by telephone to capture changes in patients' self-report of their difficulty reading and performing other daily living activities affected by visual impairment before and after rehabilitation. In our case, the intervening "rehabilitation" would instead be the hRPC treatment.

The Functional Independence Measure (FIM) scale assesses physical and cognitive disability. Items are scored on the level of assistance required for an individual to perform activities of daily living. The scale includes 18 items, of which 13 items are physical domains and 5 items are cognition items. The scale can be administered by a physician, nurse, therapist or layperson. It takes 1 hour to train a rater to use the FIM scale, and 30 minutes to score the scale for each patient. The FIM scale has been used clinically to measure the patient's progress and assess rehabilitation outcomes.

The Prosthetic Low Vision Rehabilitation (PLoVR) Curriculum was developed for use in the Argus clinical trials because available standardized visual functioning questionnaires included few if any items that can be accomplished with rudimentary vision. The Functional Low Vision Observer Rated Assessments were deployed in these studies of retinal implants for RP patients and may be of value in studies of hRPC.

### Reading Assessments

As for ADL, a number of tools have been developed to assess reading skills in the low vision population.

The Minnesota Low Vision Reading Test (MNRead) consists of single simple sentences with equal numbers of characters. The test is computer-based, although a printed card version is also available. This test is aimed at low-vision readers. The format of the MN Read Test allows it to be performed rapidly and easily. It focuses attention on impairments of resolution and is useful for determining the impact of print size on reading performance. It can be used to establish the critical print size - the smallest font where maximal rate of reading can be accomplished and is useful for estimating the response to magnification.

The continuous-text MNREAD eye charts extend past the reach of traditional eye exams because of their capability to measure the impact of eye conditions on reading. The traditional letter charts are designed to measure acuity and contrast sensitivity, but do not provide direct information about reading vision. The MNREAD chart extends the capability of eye examinations by measuring the patient's reading acuity, maximum reading speed, and critical print size, which is the smallest print size that supports the maximum reading speed.

## **9.0 SAFETY CONSIDERATIONS**

### **9.1 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, whether or not related to the study product.

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 treatment with jCell.

## **9.2 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.

## **10.0 STATISTICAL CONSIDERATIONS**

### **10.1 Study Population**

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 jCell treatment.

### **10.2 Efficacy Analyses**

Since this is an exploratory study, no formal hypothesis testing will be done. 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-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.

### **10.3 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. Summaries of AEs will be generated by type (AE or SAE), body system and preferred term, severity, and relationship to study product.

### **10.4 Other Analyses**

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

Mutation Typing: Blood sampling for DNA extraction to determine the RP gene mutation will be completed at the screening (or baseline) visit. Testing will be performed by a central laboratory. If a subject has previously been typed and a report documenting the type of mutation is available or if the subject or parent/legal guardian decline, this test will not be performed.

## **11.0 ADMINISTRATIVE CONSIDERATIONS**

### **11.1 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.

### **11.2 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.

### **11.3 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.

### **11.4 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 subjects' 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.

### **11.5 Reporting and Recording of Data**

Records - 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.

Reporting of Data - 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 initialled 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.

### **11.6 Changes in Protocol**

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

## **11.7 Investigational Product and Label Codes**

### **11.7.1 Investigational Drug**

For this study, frozen vials of jCell (hRPC) 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.

### **11.7.2 hRPC Reconstitution (Thaw and Culture) and Administration**

When a study subjects has been scheduled for treatment, the qualified dose preparation site will prepare the patient dose according to a standard procedure. Briefly, frozen cells are thawed and cultured 40-48 hours prior to injection. Following successful culture and testing, 50 µl of cell suspension containing 0.5, 1, 2 or 3 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.

## **11.8 Product Security**

In accordance with Federal and other regulations governing investigational materials, the Investigator agrees to keep investigational material in a secure location and to carefully control and document its use. The Investigator agrees to document use of investigational products as instructed in the labelling and disposal of empty vials, and to return any unused investigational product to the Sponsor or its designee.

## References

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