Amendment 6 to the JC-02 Clinical Research Protocol

October 26, 2017

A Prospective, Multicenter, Randomized, Study of the Safety and Efficacy of Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Adult Subjects with Retinitis Pigmentosa (RP)

NCT03073733

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PROTOCOL TITLE:	A Prospective, Multicenter, Randomized, Study of the Safety and Efficacy of Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Adult Subjects with Retinitis Pigmentosa (RP)
PROTOCOL NUMBER:	JC-02
SPONSOR:	jCyte, Inc
IND NUMBER:	IND 016299
ORIGINAL PROTOCOL DATE:	August 31, 2016
Amendment 1 Date:	January 6, 2017
Amendment 2 Date:	March 22, 2017
Amendment 2.1 Date:	April 13, 2017
Amendment 3 Date:	June 24, 2017
Amendment 4 Date:	August 14, 2017
Amendment 5 Date:	September 6, 2017
Amendment 6 Date:	October 26, 2017

1. Purpose of Amendment

The main purpose of this amendment is to modify the second dose level for subjects randomized to one of the Test cohorts. The second dose level (4 x 10^6 jCell) was added as part of amendment 4 due to the suggestion of dose response effect in the phase 1/2a study, a good safety profile, and based on a discussion with the FDA that if technically feasible, a second higher dose group would be advantageous to the phase 2b study. It was emphasized at that time that jCyte should try to limit dosing to volumes less than 100µL; the 4 x 10^6 dose was therefore incorporated as it was considered feasible to provide that dose with a minimal increase in volume (change from 50 to 65µL). Further investigation has revealed that that as many as 6 x 10^6 cells can be administered in this 65µL dose volume, and at the recommendation of expert advisors and study investigators, it is considered that this larger difference between the two dose levels provides more opportunity for the potential observation of a dose response effect. Furthermore there is still approximately a three-fold safety margin between the highest equivalent dose in the animal toxicity study and the 6 x 10^6 human dose.

In addition:

- The PIs are being changed at the two study sites; the synopsis has been updated to reflect this.
- The use of FrACT for assessment of VA in eyes worse than 20/800 has been added back, since there may be non-study eyes and/or deteriorated study eyes that will not be measurable with E-EDTRS.
- The requirement for B-scan assessments has been reduced to three time points post-injection (Day 7, Month 6 and Month 12) from six time points, as it was not considered particularly valuable for monitoring of safety and fewer assessments are adequate for assessment of duration/persistence of injected cells in the vitreous cavity.
- Errors or minor edits that were missed in previous versions were addressed.

2. Changes to the Protocol

Synopsis	
Changes:	The synopsis has been updated to reflect the changes to the protocol and to note the change in site PIs
Universal change:	
Original: Change:	All subjects randomized to the Test group will receive an intravitreal injection of either 3 x 10^6 hRPC or 4 x 10^6 hRPC. All subjects randomized to the Test group will receive an intravitreal injection of either 3 x 10^6 hRPC or 6 x 10^6 hRPC

Reason for change:	Rationale is described above. This change has been made throughout the protocol and is not listed.
Section 1.3 Rationale for the Proposed Study	
Deleted: Reason for change:	~~If both eyes fall within the visual acuity range required for treatment, the non-dominant eye should be designated as the study eye.~~ This was intended to be deleted with a prior amendment that no longer required the study eye to be the eye with the worst vision; this change has been made throughout the protocol.
Section 3.2 Study Population	
Original: Change: Reason for change:	The phase 2b study design is focused on subjects with visual acuity of 20/40 or worse in both eyes, without macular edema, and whose quality of life is already negatively impacted by the disease to a large degree. The phase 2b study design is focused on subjects with visual acuity of 20/80 or worse in ~~both eyes~~the study eye, without macular edema, and whose quality of life is already negatively impacted by the disease to a large degree. Correct omission from prior amendment.
Section 6.1 Dose and Schedule	
Table 2 Schedule of Assessment	Assessment of BCVA has been changed to note that for eyes worse than 20/800, FrACT should be used. B-scan assessments have been removed at Day 28 and at Months 3 and 9. Section 7.0 (Study Evaluations) has been updated to reflect this change.
Section 8.2.1 BCVA (E-ETDRS or FrACT)	
Original:	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). 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

Change:	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. 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) for eyes with vision better than 20/800, including all study eyes at baseline. The Freiburg Visual Acuity & Contrast Test (FrACT) using Landolt C's has a broader range for testing and should be used for eyes worse than 20/800. For any individual eye, the same method must be used throughout the study for consistency unless the eye has deteriorated to the point where E-ETDRS can no longer be administered. 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 assess an individual's visual acuity in a greater range than traditional ETDRS testing.
Reason for change:	Since the non-study eye at baseline or the study eye later in the study may not have vision at or better than 20/800, FrACT has been added back to the protocol for assessment of these eyes that cannot be measured with E-EDTRS. No study eye should require FrACT at baseline.
Section 11.7.2 hRPC Reconstitution (Thaw and Culture) and Administration	
Original	When a study subjects has been scheduled for treatment, the qualified dose preparati 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 1 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.
Changes:	When a study subjects has been scheduled for treatment, the qualified dose preparation site will prepare the patient dose according to a standard procedure. For subjects randomized to a Test arm, ~~Briefly,~~ frozen cells are thawed and cultured 40-48 hours prior to injection.

Reason for change:	Following successful culture and testing, ~~50~~65 µl of cell suspension containing ~~1~~3 million or 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. Should have been changed in a prior version; oversight.

CLINICAL RESEARCH PROTOCOL

PROTOCOL TITLE:	A Prospective, Multicenter, Randomized, Study of the Safety and Efficacy of Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Adult Subjects with Retinitis Pigmentosa (RP)
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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.

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:

JC-02: A Prospective, Multicenter, Randomized, Study of the Safety and Efficacy of 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, others TBD

Study Period: 2017-2020	**Phase of development: Phase 2b**

Objectives:

Primary Objective

To assess the changes in visual function as measured by best corrected visual acuity (BCVA) at 12 months following a single injection of jCell (Test) compared to sham-treated controls in a cohort of adult subjects with RP with baseline BCVA in tstudy eye equal to or worse than 20/80.

Secondary Objectives

- To assess the impact of jCell injection based on visual function (VF, CS) and functional vision (mobility, VA LV-VFQ-48), at specified time points over a 12 month observation period
- To evaluate the safety and tolerability of jCell injection in subjects with RP

Methodology:

This is a prospective, multicenter, randomized, three-arm, single-masked, Phase 2b trial of human retinal progenitor cells (jCell) for the treatment of retinitis pigmentosa (RP). Study subjects will be screened for eligibility, informed consent obtained, and eligible subjects will be randomized 1:1:1 to either treatment with 3 x 10^6 jCell, 6 x 10^6 jCell or to sham treatment (mock injection). Randomization will be stratified by study site. Blood samples for HLA typing and antibody testing will be collected at baseline. Blood samples for gene mutation typing may be collected anytime during the study.

Test subjects will receive an intravitreal injection of either 3.0 or 6.0 x 10^6 hRPC (65 µL volume), depending upon randomization assignment, into the study eye; only one eye will be injected. Control subjects will receive a mock injection (sham treatment). They will undergo the same screening and baseline testing. Control subjects will undergo essentially the same treatment procedure as Test subjects, except that instead of an intravitreal injection, they will receive a mock injection, that is, after topical anesthesia, the surface of the study eye will be pressed with the hub of an empty syringe to mimic the injection of cells, but no actual injection will be performed.

Subjects will be monitored closely following injection or mock 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 up to 7 days (including tapering schedule). All subjects will receive treatment (jCell or mock injection) into the eye designated as the "study eye". Subjects will be followed for 12 months for safety and evidence of effect.

Once a study subject has completed 12 months of follow up, that subject may request to have his/her treatment assignment revealed. If the subjects was assigned to the Control group, the subject will be offered the opportunity to cross over to the Test group, assuming no safety or other issues that preclude this, and will be randomized to one of the two dose levels.

Blood samples for antibody testing (PRA and DRA) will be collected at baseline and at months 1 and 12.

Number of patients: Subjects will be randomized 1:1:1 to the 3.0 x 10^6 dose level, the 6.0 x 10^6 dose level or the sham treatment control group. A sample size of 25 subjects per treatment arm is needed to achieve the targeted level of statistical power; the trial could enroll up to 85 subjects if needed to address irregularities in trial conduct.

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Diagnosis and main criteria for inclusion:

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. Clinical diagnosis of RP with visual acuity no better than 20/80 and no worse than 20/800 in the eye to be treated (study eye); if both eyes fall within this range, the non-dominant eye should be designated as the study eye.
3. Absence of macular edema
4. Subject must consent to testing for RP gene mutation typing
5. Male or female, age 18 yr or older
6. 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
7. Negative infectious disease screen (hepatitis B, C or HIV).
8. Willing to provide a blood sample for HLA typing, if not done previously with available results
9. A female patient of childbearing potential must have a negative pregnancy test (urine human chorionic gonadotropin) at entry (prior to the first infusion). Note: Women of childbearing potential and men must be advised to use a medically accepted method of contraception for at least 4 months following the last injection.

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, 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. History of adverse reaction to [redacted]
6. Unable or unwilling to undergo genetic testing, pupil dilation, topical anesthesia or any protocol-required procedure.
7. Women who are nursing or who are planning to nurse during the 12 months that would follow study treatment.
8. Any circumstance that in the opinion of the investigator, would interfere with participation in, or compliance with the study protocol

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9. 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
10. Cataract surgery within three months prior to enrollment or anticipated to need cataract surgery within a year of treatment
11. Participation in a clinical trial for eye disease within 6 months.
12. Previous participation in a jCyte clinical trial.

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 randomized to one of the test groups will receive a single dose of either 3.0×10^6 jCell or 6.0×10^6 jCell as an intravitreal injection under topical anesthesia into the study.

Reference product, dose and mode of administration:

There is no reference product, however subjects randomized to the Control group will undergo sham treatment, e.g., a mock injection administered as an empty hub without a needle in the study eye.

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. Subjects randomized to the control group will receive a mock injection. All study subjects will be followed for one year from injection (Test) or baseline (Control).

Criteria for Evaluation:

Efficacy:
Best corrected visual acuity (BCVA) will be used as the primary visual function parameter in this study. Other efficacy outcome measures that will be followed in test and control subjects include mobility testing, VA LV-VFQ 48, VF, and contrast sensitivity.

Safety:
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 ophthalmalogic tests to monitor safety will be performed, including slit lamp and fundus examiniation, B-scans and intraocular pressure (IOP). Additional ophthalmalogic tests (IOP, B-scan, OCT) will also contribute to safety monitoring.

Clinical safety data will be reviewed on an ongoing basis.

Statistical methods:

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

Efficacy:
Primary endpoint and analysis:

The primary efficacy endpoint will be the 12-month mean change in the study eye of the best corrected visual acuity (BCVA), to be measured with the electronic visual acuity testing algorithm (E-ETDRS). The eligible study subjects will be randomized 1:1:1 to either treatment with 3×10^6 jCell, 6×10^6 jCell or to sham treatment (mock injection). The primary analyses of the primary endpoint will be based on two pairwise comparisons of the mean change at 12 months in BCVA for the study eyes between each experimental j-Cell group and the Control group. Assume the standard deviation for the 12-month change in BCVA is 5 letters. Then, for each pairwise comparison with the control group, a randomized trial with 25 patients per arm will have 90% power to detect a true treatment effect of a mean of 5

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letters, when using a t-test having (one-sided) 0.0125 false positive error rate.

Secondary endpoints and analyses:

For assessment of mobility, similar methods will be used as have been reported for the RPE65 studies. Briefly, subjects who are capable of maze navigation will be evaluated for their performance in navigating a mobility course under a variety of specified light levels ranging from 0.1 lux (dimmer than a moonless summer night) to 500 lux (a brightly lit office) using bilateral testing condition. Each attempt will be recorded, and the videos will be sent to independent, centralized, masked graders to assign a score based on speed and accuracy with which the subjects navigate the course. The mean improvement in functional vision at specified lux levels, as measured by the change in mobility testing using the study eye will be calculated for the three treatment groups.

Other visual test results will be compared between the 3 treatment groups using analysis of covariance (ANCOVA) method with baseline values as covariates. Subjects who cannot perform any specific test at baseline (e.g. mobility) will not be considered evaluable for that analysis.

Similar analytical methods will be used for QOL measures. The total and individual scores from VA LV VFQ-48 will be analyzed using linear mixed model, which is designed for longitudinal study with correlated measurements. The Pearson Chi-square test with alpha levels adjusted for multiplicity issues will be applied to evaluate the proportion of subjects who show specific improvement compared to the proportion of control subjects in any secondary endpoints at the pre-specified time of primary analysis.

Safety:
The safety analyses of AEs and laboratory parameters will include descriptive statistics. Summaries of treatment-emergent AEs (TEAE) will be generated by type (AE or SAE), body system and preferred term, severity, and relationship to study product.

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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.

[redacted]

[redacted]

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.

A phase 1/2a clinical trial of jCell has completed enrollment and treatment of 28 subjects. All subjects from study JC-01 have completed one year of safety follow-up. There have been four Data Monitoring Committee reviews of safety data, 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 [redacted] patient enrolled in the study. [redacted] was noted to have severe migratory arthralgias starting six months [redacted] 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.

Based on the demonstration of acceptable safety and tolerability in the phase 1/2a study at doses up to 3 x 10^6 hRPC, this phase 2b study is designed as a controlled comparison of the changes in visual function and functional vision in subjects who receive a single jCell injection in comparison to a comparable untreated control group of subjects with RP. The 3.0 x 10^6 and 6 x 10^6 cell doses were selected for the phase 2b study based on the results of BCVA testing in the phase 1/2a study, which are suggestive of a dose response relationship, with best results at the highest dose (3 x 10^6 jCell). Because of the suggestion of a dose response in the phase 1/2a study, and because it is technically feasible to increase the dose to 6 x 10^6 cells without significantly increasing the injection volume, it was considered reasonable to add one additional dose level in the phase 2b study that would be likely to show a dose response difference to the 3 x 10^6 dose level. All subjects randomized to the Test group will receive an intravitreal injection of either 3 x 10^6 hRPC or 6 x 10^6 hRPC, depending upon randomization assignment, in the eye that meets the inclusion criterion for visual acuity range (study eye).

In the phase1/2a study, the largest improvement in BCVA was seen in subjects at the highest dose level (difference of 9 letter change between the test and control eyes). The mean change in BCVA in the test eye groups compared to the control eyes will be used as the primary visual function parameter in this study. Other efficacy outcome measures that will be followed in these subjects at periodic intervals throughout the study include mobility testing, VA LV-VFQ 48, VF, and contrast sensitivity. There are many components to vision; 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 are 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. Data for these endpoints will be compared to the subject's baseline status and changes in the treated groups will be compared to those in the control (sham-treated) group.

The phase 2b study design is focused on subjects with visual acuity of 20/80 or worse in the "study eye", without macular edema, and whose quality of life is already negatively impacted by the disease to a large degree. The cut off of 20/80 for the study eye is important to provide a sufficient "margin" for assessment of improvement after treatment.

2.0 OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the changes in visual function as measured by BCVA at 12 months following a single injection of jCell at one of two dose levels (Test) compared to sham-treated controls in a cohort of adult subjects with RP with baseline best corrected visual acuity (BCVA) in the study eye equal to or worse than 20/80 and no worse than 20/800

2.2 Secondary Objectives

The secondary objectives of the study are

- To assess the impact of jCell injection at two dose levels based on visual function (VF, CS) and functional vision (mobility, VA LV-VFQ-48)
- To evaluate the safety and tolerability of jCell injection in subjects with RP

3.0 STUDY DESIGN

This is a prospective, multicenter, randomized, single-masked, three-arm, Phase 2b trial of hRPC (jCell) for the treatment of retinitis pigmentosa (RP). Study subjects will be screened for eligibility and informed consent will be obtained.

3.1 Randomization and Masking

Following confirmation of eligibility, up to 85 subjects will be randomized 1:1:1 to one of two Test (jCell treatment) arms (3×10^6 jCell dose or 6×10^6 jCell dose) or to the Control (sham-treated) study group. Study subjects will be masked with respect to which treatment they are receiving, although study Investigators and those involved in certain aspects of treatment and assessment (where injected cells are visualized) cannot feasibly be masked. However, site staff that perform key assessments (primary and secondary efficacy endpoints) will be masked to the treatment assignment. Assessors will be told which eye is the study eye for each subject but will not know whether that subject is assigned to a Test or Control group.

3.2 Study Population

The phase 2b study design is focused on subjects with visual acuity of 20/80 or worse in the study eye, without macular edema, and whose quality of life is already negatively impacted by the disease to a large degree. The cut-off of 20/80 for the study eye was selected to provide a sufficient "margin" for observation of potential benefit, as measured in terms of gains in BCVA.

Subjects randomized to one of the Test groups will receive a single intravitreal injection of either 3.0×10^6 or 6×10^6 jCell into the study eye. Subjects randomized to the Control group will not receive treatment, but will undergo a similar procedure that is a mock injection in the

study eye. Subjects in both cohorts will be followed for one year for safety and evidence of jCell effects.

3.3 Endpoints

3.3.1 Efficacy Endpoints

Primary efficacy endpoint:

- Mean change in BCVA in study eyes in subjects of each Test group compared to mean change in BCVA in the control group study eyes using E-ETDRS

Secondary efficacy endpoints:

- Changes in Test group in visual field area compared to the Control group, using primarily kinetic visual field testing
- Changes in mobility test scores in the Test group vs the Control group
- Changes in Test group peak grating contrast sensitivity thresholds compared to the Control group
- Changes in Test group VA LV LFQ-48 total and individual scale scores compared to the Control group

In addition to the assessments listed above, a number of additional visual assessments will be conducted including OCT, AF, and ERG.

3.3.2 Safety Endpoints

The criteria that will be used to assess safety include:

- Incidence and severity of treatment-emergent adverse events (TEAE)
- Immunogenicity (PRA, DRA)
- Safety visual assessments: slit lamp and fundus exam, IOP, AF, B-scan

3.4 Study Duration

The overall duration of the study is anticipated to be approximately 3.5 years. The study will be considered to have started when the first site is initiated.

At the end of follow up (12 months) for each study subject, the subject's treatment assignment may be revealed to the subject. If the subject was assigned to the Control group, the subject may elect at that time to cross over to the Test group and receive jCell treatment, assuming no safety issues have been noted that may preclude the treatment. The duration of the study is based on the assumption that some or all of the Control subjects will opt to cross over after they complete 12 months of follow up. When this occurs the subjects will revert to a new "Day 0" at the time of treatment and will be followed for an additional 12 months post-treatment. The initial part of the study (primary endpoint evaluation) is anticipated to take approximately 30 months, including 18 months to enroll and treat all subjects and 12

months of follow up on all subjects. The study will be considered to have finished after the last subject (including Control subjects who have crossed over) has completed the last follow-up visit in the study.

If deemed necessary or desirable for the purposes of further safety and/or efficacy monitoring, an extension study will be offered to subjects treated with jCell for up to 12 additional months of monitoring.

3.5 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. Clinical diagnosis of RP confirmed by ERG with visual acuity no better than 20/80 and no worse than 20/800 in the study eye.
3. Absence of macular edema.
4. 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.
5. Male or female, age $\geq$ 18 yr.
6. 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] $\leq$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

7. Negative infectious disease screen (hepatitis B, C or HIV).
8. Willing to provide a blood sample for HLA typing, if not done previously with available results
9. A female patient of childbearing potential must have a negative pregnancy test (urine human chorionic gonadotropin) at entry (prior to the first infusion). Note: Women of childbearing potential and men must be advised to use a medically accepted method of contraception for at least 4 months following the last injection.

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, 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. History of adverse reaction to DMSO.
6. Unable or unwilling to undergo genetic testing, pupil dilation, topical anesthesia or any protocol-required procedure.
7. Women who are nursing or who are planning to nurse during the 12 months that would follow study treatment.
8. Any circumstance that in the opinion of the investigator, would interfere with participation in, or compliance with the study protocol

9. 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
10. Cataract surgery within three months prior to enrollment or anticipated to need cataract surgery within a year of treatment
11. Participation in a clinical trial for eye disease within 6 months.
12. Previous participation in a jCyte clinical trial.

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 SUBJECT REGISTRATION AND RANDOMIZATION

At the time informed consent is obtained, qualified subjects will be assigned a study number and randomized. Subjects will be randomized 1:1:1 to receive jCell at one of two dose levels (Test groups, 3.0×10^6 or 6.0×10^6 cells) or to sham-treatment, a mock injection that is

performed using essentially the same technique as jCell injection but without a needle (briefly pressing an empty syringe against the eye to simulate injection; Control group). Randomization will be performed by the sponsor and will occur once a subject is deemed eligible and agrees to study participation. Randomization lists will be maintained by the sponsor's designee and will not be provided to study sites, so that the next assignment will be unknown to site personnel at the time a subject is deemed eligible. Randomization assignment will be masked for the study subjects, for certain site personnel performing key study assessments (BCVA) as well as for personnel conducting vision testing at a central facility. Investigators and other site personnel will not be masked as they can visualize the cells while performing required post-treatment assessments and these observations must be documented. Subjects and study staff will not be masked as to the assignment of the "study eye" since only one eye will be treated. Study Investigators and other unmasked site staff will be instructed to take great care not reveal the subject's treatment assignment or any information that might suggest the treatment assignment to the subject during the course of the study (e.g. that the cells can be seen or visualized during certain assessments).

6.0 TREATMENT PLAN

6.1 Dose and Schedule

All subjects randomized to one of the two Test groups will receive a single intravitreal injection of 3.0×10^6 or 6.0×10^6 hRPC, depending upon randomization assignment, into the study 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.

Subjects randomized to the Control group will undergo a similar procedure in the designated study eye but with no injection. After topical anesthesia, a syringe that replicates the cell delivery syringe will be pressed against the subject's eye in a fashion that mimics the cell injection; no injection will actually be given. 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[5]	Day 28[5]		M3[6]	M6[6]	M9[6]	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	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
Infectious disease tests[2]	x	x*									
Urinalysis	x	x*						x	x		x
Blood sample for HLA typing	x										
Blood sample for gene mutation typing	Any visit										
Slit lamp and fundus exam	x	x[3]		x	x	x		x	x	x	x
BCVA (E-ETDRS or FrACT if worse than 20/800)	x	x	x	x	x	x		x	x	x	x
ERG	x[7]										
IOP		x	x	x	x	x		x	x	x	x
OCT		x							x		x
AF		x							x		x
VF		x							x		x
B-scan		x			x				x		x
Contrast sensitivity		x							x		x
VA LV-VFQ-48		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[4]		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] Hepatitis B and C, HIV
[3] Fundus photographs at baseline
[4] Testing for Panel Reactive Antibodies (PRA) and Donor Reactive Antibodies (DRA)
[5] Visit window +/- 1 day
[6] Visit window +/- 4 days
[7] ERG can be performed at screening to confirm eligibility.
*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 or mock injection. The cell dose and exact time of injection for the Test subjects will be recorded and the exact time of mock injection for the Control subjects 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. All subjects will be treated with ophthalmic corticosteroid eye drops to minimize any inflammation for up to 7 days starting on the day of injection, including tapering schedule. If extended beyond 7 days, the reason for longer treatment should be documented. Although Control subjects will not be injected, it is important that they also receive a short course of ophthalmic corticosteroid eye drops to maintain the masking. 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 – sample for mutation typing can be drawn at any study visit)
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
l. slit lamp and fundus exam
m. BCVA
n. ERG if needed to confirm eligibility

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. infectious disease screen* (Hepatitis B and C, HIV)
g. urinalysis*
h. slit lamp and fundus exam, including fundus photographs
i. BCVA (designation of study eye)
j. IOP
k. OCT
l. AF
m. B-scan
n. VF
o. contrast sensitivity
p. VA LV-VFQ-48
q. mobility test
r. blood sample for Ab testing (Test only)

7.3 Before administration of jCell or mock injection (Day 0)

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

7.4 After administration of a single intravitreal dose of jCell or mock injection (Day 0)

a. exact dose and time of injection or mock injection (treatment); 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

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. slit lamp and fundus exam
d. BCVA
e. IOP
f. con meds
g. adverse events

7.5.2 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 H & PE
b. vital signs
c. slit lamp and fundus exam
d. BCVA
e. B-scan
f. IOP
g. con meds
h. adverse events

7.5.3 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 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. slit lamp and fundus exam
f. BCVA
g. IOP
h. con meds
i. adverse events
j. blood sample for Ab testing

7.5.4 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 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. urinalysis
f. slit lamp and fundus exam
g. BCVA
h. IOP
i. con meds
j. adverse events

7.5.5 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
a. urinalysis
b. slit lamp and fundus exam
c. BCVA
d. AF
e. B-scan
f. IOP
g. VF
h. contrast sensitivity
i. VA LV-VFQ-48
j. mobility test
k. con meds
l. adverse events

7.5.6 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 H & PE

b. vital signs
c. slit lamp and fundus exam
d. BCVA
e. IOP
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. urinalysis
g. slit lamp and fundus exam
h. BCVA
i. B-scan
j. IOP
k. OCT
l. AF
m. VF
n. contrast sensitivity
o. VA LV-VFQ-48
p. mobility test
q. con meds
r. adverse events
s. blood sample for Ab testing (Test only)

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.

Coagulation panel - PT/INR, PTT

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.

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 4 weeks post-treatment, and at study termination. Details of preparation/shipping of samples will be provided separately.

8.1.5 RP Gene Mutation Typing and HLA Typing

Mutation Typing: Blood sampling for DNA extraction to determine the RP gene mutation may be performed at any study 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.

HLA Typing: Blood sampling for HLA typing will be done at screening. Testing will be performed by a central laboratory. If a subject has previously been typed and a report documenting the subject's detailed HLA type is available, this test will not be performed.

Details of preparation/shipping of samples will be provided separately.

8.1.6 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 will be analyzed to help define retinal anatomy (AOSLO), 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 (E-ETDRS or FrACT)

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) for eyes with vision better than 20/800, including all study eyes at baseline. The Freiburg Visual Acuity & Contrast Test (FrACT) using Landolt C's has a broader range for testing and should be used for eyes worse than 20/800. For any individual eye, the same method must be used throughout the study for consistency unless the eye has deteriorated to the point where E-ETDRS can no longer be administered.

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 assess an individual's visual acuity in a greater range than traditional ETDRS testing.

8.2.2 Visual Field Testing

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. Goldmann or kinetic visual field testing is the preferred test to obtain an isopter with an area of remaining field(s) of vision from RP using a specified target of V4e for more severe subjects and a target of III4e for better seeing subjects. Target size/brightness will be selected based on baseline visit for each eye separately. Whatever target size is selected, the same size will be used throughout the study on that particular eye.

8.2.3 Autoflourescence

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.

8.2.4 Other Visual Assessments

Mobility testing

Mobility testing has been performed with different maze configurations, e.g., Spark Therapeutics Maze (Maguire et al 2008) and Graz Mobility test (Velikay-Parel et al 2007)]. A similar maze has been constructed and will be assessed for validity in a subset of subjects (dependent upon timing of availability). 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 independent trained graders and a score, the critical illumination level, is derived that represents a significant drop in functional performance (slow walking speed and increase in errors). The critical illumination level for each eye is compared over time.

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. 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. Multiple thresholds and varying spatial frequencies will be measured monocularly and compared over time. In more severely impaired subjects, only the lower spatial frequencies will be able to be tested, while in mild to moderately impaired subjects, several spatial frequencies can be assessed resulting in a contrast sensitivity curve. 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.

Activities of Daily Living (ADL)

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. Total instrument scores and separate scale scores will be compared over time.

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 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).

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 any study treatment.

10.2 Efficacy Analyses

10.2.1 Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint will be the 12-month mean change in the study eye of the best corrected visual acuity (BCVA), to be measured with the electronic visual acuity testing algorithm (E-ETDRS).

The eligible study subjects will be randomized 1:1:1 to either treatment with 3 x 10^6 jCell, 6 x 10^6 jCell or to sham treatment (mock injection). The primary analyses of the primary endpoint will be based on two pairwise comparisons of the mean change at 12 months in BCVA for the study eyes between each experimental j-Cell group and the Control group.

Assume the standard deviation for the 12-month change in BCVA is 5 letters. Then, for each pairwise comparison with the control group, a randomized trial with 25 patients per arm will have 90% power to detect a true treatment effect of a mean of 5 letters, when using a t-test having (one-sided) 0.0125 false positive error rate. It is planned to randomize 85 subjects in the trial, in order to address a low rate of irregularities in the quality of trial conduct.

10.2.2 Secondary Efficacy Endpoints and Analyses

For assessment of mobility, similar methods will be used as have been reported for the RPE65 studies. Briefly, subjects who are capable of maze navigation will be evaluated for their performance in navigating a mobility course under a variety of specified light levels ranging from 0.1 lux (dimmer than a moonless summer night) to 500 lux (a brightly lit office) using bilateral testing condition. Each attempt is videotaped and scored for speed and accuracy (number of errors) by independent trained graders and a score, the critical illumination level, is derived that represents the level at which a significant drop in functional performance is observed (slow walking speed and increase in errors). Other visual test results (peak contrast sensitivity, visual field area) will be compared between the 3 treatment groups using analysis of covariance (ANCOVA) method with baseline values as covariates. Subjects who cannot perform a specific visual test at baseline (e.g. mobility) will be considered non-evaluable for analysis of that assessment.

Similar analytical methods will be used for QOL measures. The total and individual scores from VA LV VFQ-48 will be analyzed using linear mixed model, which is designed for longitudinal study with correlated measurements.

The Pearson Chi-square test with alpha levels adjusted for multiplicity issues will be applied to evaluate the proportion of subjects who show specific improvement compared to the proportion of control subjects in any secondary endpoints at the pre-specified time of primary analysis.

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 by treatment group. Summaries of AEs will be generated by treatment group, 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 by treatment assignment.

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 [redacted], 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. For subjects randomized to a Test arm, frozen cells are thawed and cultured 40-48 hours prior to injection. Following successful culture and testing, 65 µl of cell suspension containing 3 million or 6 million human retinal progenitor cells suspended [redacted] 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.

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