Statistical Analysis Plan

jCyte, Inc.

Protocol No. JC02-2

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

Protocol Version: Amendment 4 (12 April 2021)

Sponsor: jCyte, Inc.
23 Corporate Plaza Drive, Suite 23
Newport Beach, CA 92660

Prepared by: Shamima Bibi, Syneos Health
Langdon House, Unit 6,
Langdon Road,
Swansea,
SA1 8QY

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Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature
 *Electronically signed by: Shamima Bibi Reason: I am the author Date: Nov 10, 2022 11:13 GMT* Nov 10, 2022 _____ Shamima Bibi Biostatistician II Synteract
 *Electronically signed by: Adrian Morris Reason: I am the approver Date: Nov 11, 2022 11:40 GMT* Nov 11, 2022 _____ Adrian H. Morris Chief Development Officer jCyte, Inc.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BP	blood pressure
CIL	critical illumination level
CME	cystoid macular edema
CS	clinically significant
CSR	clinical study report
CST	Contrast Sensitivity Test
DRA	donor reactive antibodies
eCRF	electronic case report form
E-ETDRS	electronic visual acuity testing algorithm
EZ	ellipsoid zone
FST	full-field stimulus threshold test
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IOP	intraocular pressure
ITT	intent-to-treat
IVT	intravitreal
jCell	Human Retinal Progenitor Cells
KVF	Kinetic Visual Fields
LED	light emitting diode
LLMT	Low Luminance Mobility Test
LOD	limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
MSS	maximum step speed
NCS	not clinically significant
OCT	optical coherence tomography
OD	oculus dexter (right eye)
OS	oculus sinister (left eye)
PRA	panel reactive antibodies
PT	preferred term
PVD	posterior vitreous detachment
QC	quality control
RP	Retinitis Pigmentosa

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
SF	spatial frequency
SOC	system organ class
TEAE	treatment-emergent adverse event
TLs	tables and listings
UBM	ultrasound biomicroscopy
VF	visual field
WHO	World Health Organization

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of jCyte Inc. JC02-2 [A Phase 2 Study of the Safety of Repeat Intravitreal Injection of Human Retinal Progenitor Cells (jCell) in Adult Subjects with Retinitis Pigmentosa (RP)]. The purpose of this statistical analysis plan (SAP) is to provide specific guidelines for the statistical analyses. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the SAP:

- Protocol, version 4.0, dated 12 April 2021
- Annotated electronic case report form (eCRF), version 2.1, dated 14 Jul 2021
- Data management plan, version 1, dated 20 Jan 2021

3. STUDY OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objective

The secondary objective of the study is to assess the impact of repeat injection of jCell on measures of visual function and functional vision over a 12 month period, including Best Corrected Visual Acuity (BCVA), Low Luminance Mobility Test (LLMT), Contrast Sensitivity Test (CST), and Kinetic Visual Fields (KVF).

The study protocol lists mobility (maze) as a secondary objective. The name of this test has since changed to Low Luminance Mobility Test and this name is used throughout this analysis plan.

4. STUDY DESIGN AND PLAN

This is a prospective, multicenter, single arm, Phase 2 study of jCell for the treatment of RP. Eligible subjects include those previously treated with jCell.

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

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

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

5. DETERMINATION OF SAMPLE SIZE

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

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables and listings (TLs). The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) numbering convention will be used for all TLs.

Continuous variables will be summarized by presenting the number of observations, means, standard deviations (SDs), medians, minimums, and maximums.

Categorical variables will be summarized by presenting counts and percentages of subjects in corresponding categories. Percentages for missing values are omitted and do not account for the percent calculation of other categories. Percentages are based on the total category count excluding the missing category if not otherwise mentioned. In certain tables (e.g. adverse events [AEs]), the total number of subjects is used as the denominator. Footnotes will specify the percent basis in those cases.

All summary tables will be presented using the single jCell treatment group.

Treatment will be analyzed as actually performed rather than as planned. Any subjects who do not receive the full dose of study drug will be analyzed with those who do receive the full dose of study drug.

Individual subject data obtained from the eCRFs and any derived data will be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock.

Any analyses performed after database lock will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® statistical software, version 9.4 or higher (SAS Institute Inc). Tables and listings will be presented in RTF format.

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction "SAS Programming Quality Control".

7. NOTATION OF TREATMENT GROUPS AND VISITS

7.1 Notation of Treatment Groups

The following notation of the treatment group will be used throughout the report:

Notation Used Throughout all Tables and Listings
6.0×10^6 jCell

7.2 Visit Terminology

The following notation of the visit terminology will be used throughout the report:

Visit	**Notation Used Throughout all Tables and Listings**
SCREENING	Screening
BASELINE	Baseline
DAY 0	Day 0
DAY 1	Day 1
DAY 7	Day 7
DAY 28	Day 28
MONTH 3	Month 3
MONTH 6	Month 6
MONTH 9	Month 9

MONTH 12	Month 12
EARLY TERMINATION	Early Termination

8. ANALYSIS POPULATIONS

- The intent-to-treat (ITT) population comprises all subjects who enroll in the study and who provide any post screening data.
- The safety population comprises all subjects who receive any study treatment.

For the purposes of this study the safety population will be used for efficacy and safety analyses.

9. DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND STUDY MEDICATIONS

9.1 Subject Disposition

Subject disposition information will be summarized for all subjects. Summaries will include the number of subjects enrolled, in each analysis population, the number and percentage of subjects completing the study and the primary reason for discontinuation.

9.2 Protocol Deviations

Protocol deviations that could potentially affect the safety or efficacy conclusions of the study are captured during the study and periodically reviewed. The final determination of major protocol deviations will be done prior to database hard lock during the data review meeting.

A listing of all protocol deviations including the category (major or minor) will be presented.

9.3 Demographic and Baseline Characteristics

Demographic variables include: age of subject at time of informed consent (years), sex, ethnicity, race, and childbearing potential. Other baseline characteristics include treatment eye, medical history, ocular medical history, height and weight.

Descriptive statistics will be presented for age, height and weight. Frequency counts and percentages will be presented for sex, ethnicity, race and treatment eye. Demographic and baseline characteristics will be summarized for the safety population. Data on childbearing potential will be included in a data listing only.

9.4 Medical History

The verbatim term of the ocular medical history or medical history condition/event will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1.

Summary tables will be prepared, summarizing the incidence and percentages within each system organ class (SOC) and preferred term (PT), ordered by descending subject incidence for each SOC and PT. Subjects reporting more than incidence at each level of summarization will be

included only once for the subject count.

Data on ocular medical history and medical history will also be presented in data listings.

9.5 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification and preferred names using the WHODrug Global B3 format, Sep.1.2020 release.

Partial dates will be imputed. For details on imputation rules, refer to Appendix A: Presentation of Data and Programming Specifications. Imputed dates are only used for classification of a medication as a prior or concomitant medication; no other calculation, such as durations, will be performed.

Prior medications are defined as any medication with an (imputed) start date and (imputed) stop date before the date of study drug administration.

Concomitant medications are defined as any medication that was started before the date of study drug administration and with an (imputed) stop date on or after the date of study drug administration, or that are ongoing from Screening/Baseline, or that are taken on or after the date of study drug administration.

If the medication cannot be classified as a prior or concomitant medication, the medication will be considered concomitant.

Concomitant medications will be summarized by ATC class and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if they reported one or more medications at that level. Each summary will be ordered by descending subject count in the total column by ATC level and preferred name.

Separate tables will be prepared to summarize concomitant medications. A listing will be created containing all prior and concomitant medications and will contain a flag identifying whether a medication is prior or concomitant.

10. EFFICACY ANALYSES

The efficacy endpoints for this study are secondary analyses and will be based on the safety population.

10.1 Efficacy Variables

Efficacy will be assessed based on a series of ophthalmologic assessments performed at specified intervals, including BCVA, LLMT, CST, and KVF testing.

10.1.1 Secondary Efficacy Assessments

Secondary efficacy endpoints include mean change at Month 6 and Month 12 in the following assessments: BCVA, to be measured with the electronic visual acuity testing algorithm (E-ETDRS); LLMT scored by critical illumination level [CIL]); KVF assessed by Octopus 900 kinetic visual field testing, and peak CS measured with gratings in the Beethoven system.

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

- **LLMT (performed at jCyte Central Testing Facility):** In general, the LLMT will consist of differing but structurally similar configurations of a relatively short courses (e.g. arrows on a printed floor mat) with ten obstacles, of various sizes. Subject testing consists of walking through several configurations each at a different illumination level as a test of mesopic visual function. Each test is videotaped and scored for speed and accuracy (number of errors) by masked independent trained graders and a score, the Critical Illumination level (CIL), is derived from the illumination level at which a significant drop in functional performance is observed (slow walking speed and increase in errors).

  For subjects assessed during the baseline testing who have an estimated monocular CIL of 1 lux or lower (near normal vision), they will be tested with that eye on both a high contrast (black and white) and a low contrast version (either 25% or 10% light grey arrows) at Baseline. At follow-up visits, the same low contrast version will be used for that eye at each later visit. A larger range of testing improvement should occur in the low contrast version, allowing for greater test sensitivity (i.e., preventing a ceiling effect) if the subject's vision improves with treatment. If a subject can only perform the high contrast version, then each eye and both eyes together will be assessed.

- **Kinetic Visual Field Testing (performed at jCyte Central Testing Facility):** The Octopus 900 will be used for KVF testing using a specified target of V4e for subjects with a more severely impaired visual field ($<10{,}000 deg^2$) and a target of III4e and I4e for better seeing subjects ($>10{,}000 deg^2$). Target size will be selected based on Baseline visit for each eye separately. Whatever target size(s) is/are selected, the same size will be used throughout the study on that particular eye.

- **Contrast Sensitivity Test (performed at jCyte Central Testing Facility):** A CST 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. CST 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 [SF]) provide an in-depth view of functional vision. Using the Beethoven System, multiple thresholds and varying spatial frequencies creating a curve will be measured monocularly and the peak of the curve will be compared over time. Each spatial frequency is tested up to seven times (thresholds) so the mean threshold at the peak CST for each eye will be compared over time.

For each eye, threshold CST values will be recorded for spatial frequencies from the following range: 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 (not all frequencies will be tested for each eye for each subject). If a subject can test at more than one target size (or SF), then at least three SFs will be tested with multiple trials at each to determine the mean thresholds for each SF.

10.1.2 Exploratory Assessments

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

- **B-Scan (performed at jCyte Central Testing Facility):** B-scan ultrasound uses high-frequency sound waves to obtain measurements and produce detailed images of the eye. In the area of the typical intravitreal (IVT) injection site, two or more probe directions (perpendicular to the corneal surface and inferotemporal) will be used to locate jCells. This test may provide information regarding the location of the injected cells and the general size of the cell clusters at different time points post-treatment.

- **Ultrasound Biomicroscopy (UBM) (performed at jCyte Central Testing Facility):** With the same ultrasound instrument as for B-scans, but using a different probe for UBM, high-frequency high-resolution images of the cross-sectional anterior chamber can be acquired. UBM will be used to explore a more thorough volume estimation by ultrasound imaging of the jCell aggregate over time.

- **Slit lamp biomicroscopy with gonioscopy lens & photography (performed at jCyte Central Testing Facility):** Binocular slit lamp biomicroscopy provides a stereoscopic magnified view of eye structures, enabling general anatomical exploration of the jCell aggregate over time. When combined with a gonioscopy contact lens (three-mirror lens with gel between the lens and cornea), a greater viewing angle into the anterior vitreous behind the iris to view and photograph/videograph jCells may be achieved. Photography and/or video recording with or without the gonioscopy lens will be used as a means to explore the physical description of the jCell aggregate over time.

- **SD-Optical Coherence Topography (performed at jCyte Central Testing Facility):** Standard spectral domain optical coherence tomography (SD-OCT) imaging is primarily used for image segmentation of the posterior segment and often specifically the macular

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

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

The study protocol also lists A-scan ultrasound as an exploratory assessment. However, this assessment was not included in the final list of study assessments and was not performed on any patients.

10.2 Baseline Values

For the efficacy variables, apart from BCVA, the baseline value of an assessment will be the value collected at the Baseline visit. For BCVA, the value collected at the Day 0 visit will be used as the baseline value for analysis. If for any reason a subject does not have a BCVA assessment at Day 0, then the value collected at the Baseline visit will be used as the baseline value for analysis.

Subjects who cannot perform CS or KVF at Baseline will not be compared at later visits for that assessment. For the two secondary endpoints of BCVA and LLMT, 0 letters will be used for BCVA and -1 for the scale score for LLMT if the subject attempts but is unable to meet the minimum score for the assessment. This will be done during the programming of the analysis datasets and will not be done by the site/testing facility.

10.3 Handling of Dropouts or Missing Data

Subjects with missing data (no assessment) at Baseline will be considered non-evaluable for analysis of that assessment, except for the two secondary endpoints of BCVA and LLMT. If a subject attempts but is unable to meet the minimum score for the assessment at any visit, a value of 0 letters will be used for BCVA and -1 for the scale score for LLMT. This will be done during the programming of the analysis datasets and will not be done by the site/testing facility.

Other than what is noted above, any other data that is not obtained due to lack of assessment or missed visits will not be imputed.

10.4 Interim Analysis and Data Monitoring

No interim analysis is planned for this study.

10.5 Examination of Subgroups

There are no planned subgroup analyses for this study.

10.6 Multiple Comparison/Multiplicity

No adjustments for multiplicity will be made in this study.

10.7 Multicenter Studies

No analyses are planned to compare differences in the response by center.

11. METHODS OF EFFICACY ANALYSIS

No formal efficacy evaluation will be performed as the study is primarily a safety study. However, secondary endpoints will be observed over time and summarized in tables. These assessments include BCVA as assessed at the clinical site at all visits, as well as LLMT, CST, and KVF at Baseline and at Month 6 and Month 12 as assessed at the jCyte central testing facility.

All efficacy analyses will be based on the safety population.

11.1 Efficacy Analyses

11.1.1 Best Corrected Visual Acuity (BCVA)

BCVA will be analyzed using summary statistics of the average number of letters correct at each time point. Separate tables will be created for the Study Eye and the Non-Study Eye. Change from baseline will also be summarized using summary statistics for each post-baseline time point. Subjects who cannot see any letters on the chart at Baseline will be considered to have a 0 letter score. The assignment of a 0 letter score will be done during the programming of the analysis datasets and will not be done by the site/testing facility.

11.1.2 Low Luminance Mobility Test (LLMT)

Low luminance mobility will be assessed by comparison of mean change in CIL scale scores from baseline. CIL scale scores will be summarized in Study Eye and Both Eyes at Baseline, Month 6 and Month 12. In addition, change from baseline will also be summarized using summary statistics for each post-baseline time point.

CIL scores will be converted to a scale score of -1 (cannot pass at the brightest light level) to 13 (does not slow even with room lights off). Conversion of CIL lux values to scale scores are included in the following table:

CIL (Lux)	Lights off	0.12	0.25	0.5	1.0	2.0	4.0	8.0	16	32	63	125	250	500	No Pass
Scale Score	13	12	11	10	9	8	7	6	5	4	3	2	1	0	-1

Subjects who cannot perform mobility testing at Baseline will be considered to have a scale score of -1 for CIL. The assignment of a -1 CIL scale score will be done during the programming of the analysis datasets.

11.1.3 Contrast Sensitivity Test (CST)

Contrast Sensitivity will be summarized for both Study Eye and Non-Study Eye at Baseline, Month 6 and Month 12 using descriptive statistics.

For any spatial frequency with more than one threshold value (or trial), the values will be averaged (mean), and a single mean value for that spatial frequency will be calculated. A single value trial at a spatial frequency indicates exploratory testing only and does not represent repeatable trials and will not be analyzed. Each of the mean threshold values is plotted per spatial frequency by the Beethoven instrument to create a curve. The highest mean threshold value for any of the spatial frequencies will be used to represent the nearest peak of the curve and will be called Peak Contrast Sensitivity and will be used for summary statistics. The spatial frequency at which the peak of the curve corresponds may vary from visit to visit or patient to patient. The threshold Peak Contrast Sensitivity value will be compared for the Safety population.

Change from baseline will also be summarized using summary statistics for each post-baseline time point.

Values for subjects who do not have a visit record at all post-baseline are considered to be close to missing at random (visit missed or assessment not attempted) and these missing values will not be imputed. Subjects with completely missing baseline values (e.g. no visit or assessment attempted) will be considered unevaluable for this analysis.

11.1.4 Kinetic Visual Fields (KVF)

Results from the KVF examination will be summarized for both Study Eye and Non-Study Eye at specified time points. The total VF area will be summarized at Baseline, Month 6 and Month 12. The mean change from baseline in the total VF area at Month 6 and Month 12 will also be summarized.

Total VF area is calculated by taking the sum of the adjusted calculated size for all individual field areas (i.e., islands) for a subject with the same visit, same eye, same date and same time. If a subject only has one stimulus size populated at a particular visit/date/time, that stimulus size

should be used to calculate the total VF area. If a subject has multiple stimulus sizes populated at a particular visit/date/time, then the size used at baseline should be used for comparison. If at baseline, a subject has a near normal visual field for the V4e target size (>10,000 deg^2), then the next smaller size target should be used (e.g. III4e) to calculate the total VF area for that visit/date/time and that target sized used for all visit comparisons.

Subjects with completely missing baseline values (e.g. no visit or assessment attempted) or who are unable to perform the kinetic field testing at Baseline, will be considered not evaluable for this analysis.

11.2 Exploratory Analyses

Exploratory endpoints include UBM, B-Scan, Slit lamp biomicroscopy and photography, SD-OCT of jCell, and FST.

Exploratory testing may occur at Baseline, Day 7, Day 28, Month 3, Month 6, Month 9 and Month 12 or Early Termination depending on what equipment is available.

Data on exploratory assessments will be provided in data listings only.

12. PHARMACOKINETIC ANALYSES

No pharmacokinetic analyses are planned for this study.

13. SAFETY ANALYSES

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

All safety analyses will be based on the safety population.

13.1 Study Drug Administration

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

Study drug administration responses will be tabulated according to questions asked in the eCRF, including whether the total dose was administered, whether there were any dose interruptions, whether there were any AEs observed, whether the subject's vital signs are comparable to pre-treatment of study drug injection, the subject's IOP measurement post-treatment of study drug injection and whether the subject was prescribed topical treatment after treatment of study drug injection.

13.2 Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), which are defined as those AEs that occurred after dosing and those existing AEs that worsened during the study. In the case of worsening in severity, a new entry is created in the database with start date equal to start of worsening. If it cannot be determined whether the AE is treatment-emergent due to a partial onset date, then it will be counted as such. Verbatim terms in the eCRFs will be mapped to SOCs and PTs using MedDRA, version 23.1.

AE summaries that are displayed by SOC and PTs will be ordered by descending subject count by SOC and PT within SOC. Summaries of the following types will be presented:

- Overall summary of TEAEs that contains a summary of the following:
    - Subject and event count of any TEAE
    - Subject and event count of TEAEs related to study drug
    - Subject and event count of serious TEAEs
    - Subject and event count of any serious TEAE related to study drug
    - Subject and event count of severe TEAEs related to study drug

Separate TEAE summary tables will be provided as follows:

- Subject incidence and event count of TEAEs by MedDRA SOC and PT.
- Subject incidence and event count of TEAEs by MedDRA SOC, PT, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported more than one of the same event. Categories of severity will be “Mild”, “Moderate”, “Severe” and “Life threatening”. Adverse events with missing severity will be assigned to “Severe” for this summary.
- Subject incidence and event count of TEAEs related to study drug by MedDRA SOC and PT. Related AEs are those reported as “Related” and “Possibly Related”. At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported more than one of the same event. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence and event count of serious TEAEs by MedDRA SOC and PT.

Separate listings of related TEAEs and SAEs will be provided.

13.3 Ophthalmic Safety Assessments

Procedures will be performed at scheduled intervals to specifically assess eye AEs that may not be detected by usual AE reporting and to try and visualize the injected cells.

13.3.1 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. Fundus exam allows for inspection of the retina, the cellular graft, and detection of retinal detachment.

13.3.1.1 Slit Lamp

For eye structures of eyelids, eyelashes, conjunctiva, sclera, cornea, and iris, subjects will be tabulated by the categories of Normal, Abnormal not clinically significant (NCS), and Abnormal clinically significant (CS) at each time point, and percentages will be displayed. For anterior chamber flare, subjects will be tabulated by the flare grade and the categories of Abnormal NCS and Abnormal CS.

For syneresis, subjects will be tabulated as Not Obvious and Obvious. For posterior vitreous detachment (PVD), subjects will be tabulated as None, Partial and Complete. For lens status, subjects will be tabulated as Aphakic, Pseudophakic, and Phakic.

For cataract type, subjects will be tabulated as Nuclear, Cortical, Posterior Subcapsular and Other. Subjects will also be tabulated by cataract grades of trace, 1+, 2+, 3+ and 4+.

Slit lamp assessments will be summarized separately for each eye.

13.3.1.2 Dilated Funduscopic Exam

The result from the optic nerve exam, vitreous exam, macula exam and peripheral retina exam will be summarized using counts and percentages of Normal, Abnormal NCS and Abnormal CS and will be presented by eye and time point.

13.3.2 Optos Photography

Optos photography includes a widefield dilated Optos photograph of the posterior segment with any cell cluster from the anterior vitreous visualized in the photo frame along with the posterior segment/fundus. Two directions of gaze are captured to best potentially visualize jCell.

For Optos photography, results will be included in data listings only.

13.3.3 Intraocular Pressure

The change in IOP from baseline will be summarized descriptively for each time point.

13.3.4 Clinical Vitreous Exam

For the clinical vitreous exam, counts and percentages will be summarized for method used (Indirect Ophthalmoscopy, Slit Lamp Exam, Other), whether jCell is visualized, the predominant

shape of the jCell (Sphere/Ellipsoid, Strand(s), Diffuse Haze no opacities >2DD, Debris or Graft Remnants and Other), the estimated location of jCell in the vitreous (e.g. anterior 1/3).

Other details collected for the clinical vitreous exam will be provided in a data listing, including date of examination, the secondary shape of the jCell aggregate, size on the horizontal axis, and size on the vertical axis.

13.3.5 Optical Coherence Tomography (OCT)

OCT results will be summarized in a table showing the counts and percentages of subjects whose eyes (both Study Eye and Non-Study Eye) show cystoid macular edema (CME) present, and of those who show CME, how many cases involve the foveal center; epiretinal membrane formation present and how many have evidence of retinal traction present. In addition, investigator observations of ellipsoid zone (EZ) presence will be summarized as Not Present; Present but Reduced; Present and Near Normal.

13.4 Clinical Laboratory Evaluation

Hematology and Chemistry laboratory parameters will be summarized using descriptive statistics at Baseline, Day 28, Month 3, Month 6, and Month 12. Change from baseline in the laboratory parameters will also be presented, with the baseline value defined as the last non-missing value recorded prior to the date and time of study drug administration.

Urinalysis assessments will be done at Screening, Baseline, Month 3, Month 6, and Month 12 or Early Termination and results will not be summarized but will be provided in a data listing.

Blood samples for testing for PRA and DRA will be taken at Baseline, Day 28 and Month 6 and results will be provided as a separate listing (not from the clinical database).

Coagulation tests will be done at Screening and results will be provided in a data listing.

Pregnancy test results will be provided in a data listing.

13.5 Vital Signs

Vital signs (including temperature, heart rate, respiration rate, systolic blood pressure (BP) and diastolic BP) will be summarized using descriptive statistics at Baseline and at each post-baseline time point. Changes from baseline will also be summarized. The baseline value is defined as the last non-missing value recorded prior to the date and time of study drug administration.

13.6 Physical Examination

Physical examination results will be included in data listings only.

14. OTHER DATA

14.1 Procedures

Details of any non-study procedures that occurred during the study will be collected on the eCRF. Details collected will include the type and date of procedure and whether the procedure was conducted due to a medical history, ocular history, adverse event or other indication.

Procedures will be provided in data listings only.

15. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The study protocol lists mobility (maze) as a secondary objective. The name of this test has since changed to Low Luminance Mobility Test and this name is used throughout this analysis plan. Additionally, the study protocol lists A-scan ultrasound as an exploratory assessment. However, this assessment was not included in the final list of study assessments and was not performed on any patients.

16. REFERENCES

Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/295050/2013. Guideline on adjustment for baseline covariates in clinical trials. 01 September 2015.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14. November 2005.

Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. Biometrika. 1976;63(3):655-60.

US Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER). Guidance document. Guidance for Industry. E9 Statistical principles for clinical trials [Internet]. September 1998, ICH [cited 2018 Aug 03]. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf

17. APPENDICES

APPENDIX A: PRESENTATION OF DATA AND PROGRAMMING SPECIFICATIONS

General

- Specialized text styles, such as bold, italics, borders, shading, and superscripted and subscripted text will not be used in tables, figures, and data listings (TFLs) unless they add significant value to the TFL.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters and printer- or font-specific characters, will not be used in a TFL.
- Hexadecimal character representations are allowed (e.g., μ, α, and ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes must be used sparingly and add value to the TFL.

Tables

- Means and medians will be presented to one decimal place more than the raw data. Standard deviations will be presented to two decimal places more than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of zero. Categories with zero counts will not have zero percentages displayed.
- Lower and upper CI values must be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25% and 75%) must be presented to one decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to four decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be:
  - "Source: xxx", where xxx indicates the source table number(s), if applicable (in case aggregated results, such as the mean or median, are plotted), source listing(s) (in case individual responses are plotted), and/or source dataset(s) (e.g., ADaM).
  - "PROGRAM SOURCE:...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Listings

- If not otherwise specified, all data listings will be sorted by center, subject number, visit, and date/time, as appropriate.
- All date values will be presented in an ISO8601 date (e.g., 2018-10-11) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be "PROGRAM SOURCE:...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Missing or Incomplete Dates (i.e., Adverse Events and Concomitant Medications)

The most conservative approach will be systematically considered. If the adverse event (AE) onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a treatment-emergent AE) except if the partial onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant medication.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of the first dose of study drug, provided the start month and year are the same as the date of the first dose of study drug and stop date is either after the date of the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of the first dose of study drug, provided the start year is the same as the date of the first dose of study drug and stop date is either after the date of the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g. ??-???-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and stop date is either after the date of the study drug administration or completely missing, then the start date will be estimated to be equal to the date of study drug dosing. Otherwise, the start date will be estimated to be the first day of the same year as the stop date.

All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing, and January 1 will be used if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day of resolution of the event will be assumed to be the last day of the month (e.g. ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the day of resolution of the event will be assumed to be the last day of the year (e.g. ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date of the event is completely missing or event is continuing, the event resolution will be assumed to be after the first dose of study drug, and the stop date will be imputed using the last known date on the study.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Days: A duration expressed in days between one date (date1) and another later date (date2) is calculated using the following formula: duration in days = date2 – date1 + 1
- Months: A duration expressed in months is calculated using the INTCK function of SAS using the following formula: months = intck('month', 'date1'd, date2'd, 'continuous')
- Years: A duration expressed in years between one date (date1) and another later date (date2) is calculated using the following formula: duration in years = intck('year', 'date1'd, 'date2'd, 'continuous')
- Height: Height entries made in inches are converted to centimeters using the following formula: height (cm) = height (in) × 2.54
- Weight: Weight entries made in pounds are converted to kilograms using the following formula: weight (kg) = weight (lb)/2.2046
- Temperature: Temperature entries in degrees Fahrenheit are converted to degrees centigrade using the following formula: temperature (°C) = 5/9 × [temperature (°F) – 32]
- Body Mass Index (BMI): BMI is calculated using height and weight using and is calculated using the following formula: BMI (kg/m^2) = weight (kg)/[[height (cm)/100]^2]
- Change from baseline: Change from baseline will be calculated using the following formula: change = post-baseline value – baseline value
- Percent change from baseline: Percent change from baseline will be calculated using the following formula: percent change from baseline = (post-baseline value – baseline value)/baseline value × 100.

APPENDIX B: LIST OF TABLES, LISTINGS, AND FIGURES

The following proposal for Sections 14 and 16.2 is completed according to ICH E3 guidelines. The heading numbers and description are in **bold**. Minor changes from this planned index do not need to be amended in the statistical analysis plan.

Index of Section 14

Table Number	Table Title	Analysis Set	Comment
14	**Tables and Figures Referred to but not Included in the Text**		
14.1	**Demographic Data**		
14.1.1	Subject Disposition	All Subjects	
14.1.2	Demographic and Baseline Characteristics	Safety Population	
14.1.3	Medical History	Safety Population	
14.1.4	Ocular Medical History	Safety Population	
14.1.5	**Prior and Concomitant Medications, Treatments and Therapies**		
14.1.5.1	Concomitant Medications	Safety Population	
14.2	**Efficacy Data**		
14.2.1.1	Best Corrected Visual Acuity (E-ETDRS), Average Number of Letters Correct by Visit: Study Eye	Safety Population	
14.2.1.2	Best Corrected Visual Acuity (E-ETDRS), Average Number of Letters Correct by Visit: Non-Study Eye	Safety Population	
14.2.2.1	Low Luminance Mobility Test (LLMT): Study Eye	Safety Population	
14.2.2.2	Low Luminance Mobility Test (LLMT): Both Eyes	Safety Population	
14.2.3.1	Kinetic Visual Fields (KVF): Study Eye	Safety Population	
14.2.3.2	Kinetic Visual Fields (KVF): Non-Study Eye	Safety Population	
14.2.4.1	Contrast Sensitivity Test (CST): Study Eye	Safety Population	
14.2.4.2	Contrast Sensitivity Test (CST): Non-Study Eye	Safety Population	
14.3	**Safety Data**		
14.3.1	**Extent of Exposure**		
14.3.1.1	Study Drug Administration	Safety Population	

Table Number	Table Title	Analysis Set	Comment
14.3.2	**Displays of Adverse Events**		
14.3.2.1	Overall Summary of TEAEs	Safety Population	
14.3.2.2	TEAEs by System Organ Class and Preferred Term	Safety Population	
14.3.2.3	TEAEs by System Organ Class, Preferred Term and Maximum Severity	Safety Population	
14.3.2.4	Related TEAEs by System Organ Class and Preferred Term	Safety Population	
14.3.2.5	Serious TEAEs by System Organ Class and Preferred Term	Safety Population	
14.3.3	**Ophthalmic Safety Examinations**		
14.3.3.1	Slit Lamp Exam: Study Eye	Safety Population	
14.3.3.2	Slit Lamp Exam: Non-Study Eye	Safety Population	
14.3.3.3	Dilated Funduscopic Exam: Study Eye	Safety Population	
14.3.3.4	Dilated Funduscopic Exam: Non-Study Eye	Safety Population	
14.3.3.5	Intraocular Pressure (IOP): Study Eye	Safety Population	
14.3.3.6	Intraocular Pressure (IOP): Non-Study Eye	Safety Population	
14.3.3.7	Clinical Vitreous Exam: Study Eye	Safety Population	
14.3.3.8	Categorical Analysis of Optical Coherence Tomography (OCT)	Safety Population	
14.3.4	**Other Safety Data**		
14.3.4.1	Hematology	Safety Population	
14.3.4.2	Chemistry	Safety Population	
14.3.4.3	Vital Signs	Safety Population	

Abbreviations: ECG=electrocardiogram; E-ETDRS= electronic visual acuity testing algorithm; FA=full analysis; ICH=International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; PP=per-protocol; TEAE=treatment-mergent adverse events

Index of Section 16.2

ICH Listing Number	Listing Title	Analysis Set	Comments
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition	All Subjects	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations	All Subjects	
16.2.3	**Demographic Data**		
16.2.3.1	Demographics and Baseline Characteristics	Safety Population	
16.2.3.2	Medical History	Safety Population	
16.2.3.3	Ocular Medical History	Safety Population	
16.2.3.4	Prior and Concomitant Medications	Safety Population	
16.2.4	**Individual Efficacy Response Data**		
16.2.4.1.1	Best Corrected Visual Acuity (E-ETDRS): Study Eye	Safety Population	
16.2.4.1.2	Best Corrected Visual Acuity (E-ETDRS): Non-Study Eye	Safety Population	
16.2.4.2.1	Low Luminance Mobility Test (LLMT): Study Eye	Safety Population	
16.2.4.2.2	Low Luminance Mobility Test (LLMT): Both Eyes	Safety Population	
16.2.4.3.1	Kinetic Visual Fields (KVF): Study Eye	Safety Population	
16.2.4.3.2	Kinetic Visual Fields (KVF): Non-Study Eye	Safety Population	
16.2.4.4.1	Contrast Sensitivity Test (CST): Study Eye	Safety Population	
16.2.4.4.2	Contrast Sensitivity Test (CST): Non-Study Eye	Safety Population	
16.2.5	**Compliance and/or Drug Concentration Data**		
16.2.5.1	Study Drug Administration	Safety Population	
16.2.6	**Adverse Events**		
16.2.6.1	Adverse Events	Safety Population	
16.2.6.2	Serious Adverse Events	Safety Population	
16.2.6.3	Related Adverse Events	Safety Population	
16.2.7	**Ophthalmic Safety Examinations**		
16.2.7.1.1	Slit Lamp Exam: Study Eye	Safety Population	
16.2.7.1.2	Slit Lamp Exam: Study Eye -Vitreous Findings	Safety Population	

ICH Listing Number	Listing Title	Analysis Set	Comments
16.2.7.2.1	Slit Lamp Exam: Non-Study Eye	Safety Population	
16.2.7.2.2	Slit Lamp Exam: Non-Study Eye - Vitreous Findings	Safety Population	
16.2.7.3.1	Dilated Funduscopic Exam: Study Eye	Safety Population	
16.2.7.3.2	Dilated Funduscopic Exam: Non-Study Eye	Safety Population	
16.2.7.4.1	Intraocular Pressure (IOP): Study Eye	Safety Population	
16.2.7.4.2	Intraocular Pressure (IOP): Non-Study Eye	Safety Population	
16.2.7.5	Optos Photography	Safety Population	
16.2.7.6	Clinical Vitreous Exam: Study Eye	Safety Population	
16.2.7.7	Optical Coherence Tomography (OCT)	Safety Population	
16.2.8	**Listing of Individual Laboratory Measurements by Subject, When Required by Regulatory Authorities**		
16.2.8.1	Hematology	Safety Population	
16.2.8.2	Chemistry	Safety Population	
16.2.8.3	Urinalysis	Safety Population	
16.2.8.4	Urinalysis: Microscopic Exam	Safety Population	
16.2.8.5	Coagulation	Safety Population	
16.2.8.6	Pregnancy Test	Safety Population	
16.2.8.7	Antibody Testing	Safety Population	
16.2.9	**Other Data**		
16.2.9.1	Vital Signs	Safety Population	
16.2.9.2	Physical Examination	Safety Population	
16.2.9.3	Exploratory Slit Lamp Biomicroscopy	Safety Population	
16.2.9.4	Exploratory Ultrasound Imaging	Safety Population	
16.2.9.5.1	Exploratory Optical Coherence Topography Exam – Part 1	Safety Population	
16.2.9.5.2	Exploratory Optical Coherence Topography Exam – Part 2	Safety Population	
16.2.9.6	Procedures	Safety Population	

Abbreviation: ICH=International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

APPENDIX D: TABLE, FIGURE, LISTING LAYOUTS

Appendix D1: Study-Specific Shells for Section 14

Appendix D2: Study-Specific Shells for Section 16.2

Signature: *Electronically signed by: Shamima Bibi*
Reason: I am the author
Date: Nov 10, 2022 11:13 GMT

Email: shamima.bibi@synteract.com

Title: Biostatistician II

Signature: Adrian Morris *Electronically signed by: Adrian Morris*
Reason: I am the approver
Date: Nov 11, 2022 11:40 GMT

Email: adrian.morris@jcyte.com

Title: Chief Development Officer

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