Janssen Research & Development, LLC *

Clinical Protocol

A Phase 2b, Multicenter, Double-masked, Randomized Study Evaluating the Safety and Clinical Response of Subretinal Administration of CNTO 2476 in Subjects with Visual Acuity Impairment Associated with Geographic Atrophy Secondary to Age Related Macular Degeneration

Protocol CNTO2476MDG2002; Phase 2b
AMENDMENT 3

CNTO 2476

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status: Approved
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Prepared by: Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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LIST OF IN-TEXT TABLES AND FIGURES

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	1 July 2015
Amendment 1	21 December 2015
Amendment 2	29 September 2016
Amendment 3	15 December 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (15 December 2017)

The overall reason for the amendment: The palucorcel development program is discontinued for strategic business reasons. For this reason, this study protocol is amended to eliminate the 2nd Safety Cohort and the randomized masked portion of the study; to reduce the study sample size; to reduce the length of total follow-up period from 60 months to 36 months; and to eliminate most secondary and exploratory efficacy assessments.

Applicable Section(s)	Description of Change(s)
Rationale: To allow elimination of the 2nd Safety Cohort and randomized masked portion of the study.	
Synopsis, Objectives and Hypothesis; Efficacy evaluations/endpoints; 2. Objectives and Hypothesis 9.2.2 Endpoints	**Primary objectives and endpoints**: "The randomized Double-masked Treatment Phase of the study to assess the effects on visual acuity of a single subretinal administration of CNTO 2476 at 1 of 2 doses, compared with the control." was removed. The primary efficacy endpoint "The proportion of subjects in the randomized Double-masked Treatment Phase showing improvement from baseline of ≥15 letters in best corrected visual acuity (BCVA) at the 6-month visit following treatment with 1 of 2 doses of CNTO 2476 compared to the control arm" was removed. **Secondary objectives and endpoints**: Updated the major secondary objectives and secondary efficacy endpoints to reflect elimination of the Double-Masked Treatment phase. **Exploratory objectives and endpoints**: The exploratory objectives and endpoints related to the Double-masked Treatment phase were removed. **Hypothesis**: Added a statement about termination of the Double-masked Treatment phase.
Synopsis, Overview of study design, subject population; 3.1 Overview of Study Design; 3.2 Study Design Rationale 4 Subject Population;	The total subjects to be screened was decreased from 400 to 100 subjects to limit the total number of subjects in the open-label phase to 21 subjects. A sentence "This represents a significant reduction in scope and duration based on a decision to discontinue the palucorcel development program." was added. The Figure 1 representing the study design with the Double-masked treatment phase was removed. Updated the text to reflect the elimination of the Randomized Double-masked treatment phase.
Synopsis, Safety Run-in Phase	Updated the target number of subjects to be enrolled in the safety run-in phase from "approximately 75" to "approximately 21".
Synopsis, Randomized Double-masked Treatment Phase 3.2 Study Design Rationale	Updated the text to reflect that this planned phase of the study was eliminated. Updates made to the study design rationale to reflect that changes were made to minimize the visit burden on subjects and investigators.

Applicable Section(s)	Description of Change(s)
5. Treatment Allocation and Masking	Patient Reported Outcomes planned for the Double-Masked Treatment phase of the study were removed. Updated the control, masking, and randomization details to reflect that the open-label phase of the study do not require control, masking, or randomization. Procedures for randomization and stratification were removed and all subjects were planned to receive the same dose of 3.0×10^5 cells. Table 4 and Table 5 with masking procedures for subjects, site personnel, and team members were deleted.
Synopsis; Long-term follow-up phase 3.1 Overview of Study Design 8. Prestudy and Concomitant medications 16.1 Study specific design considerations 9.1.1.4 Long-term Follow-up Phase	The frequency of Long-term Follow-up Phase was updated from every 6 months for 4 years to every 6 months for 2 years. The total study duration was update to 3 years from 5 years.
Synopsis, Dosage and administration; 6.2 Randomized Double-masked Treatment Phase	Updated the dosing details to eliminate dosing information for the Randomized Double-masked treatment phase. The details of sham surgical procedure for the control group were removed.
Rationale: Updates were made to align the protocol with the decision to eliminate the randomized masked portion of the study.	

Applicable Section(s)	Description of Change(s)
Synopsis, Efficacy evaluations; 9. Study Evaluations 10.1. Completion 10.2 Discontinuation/Withdrawal	**Open-label Safety Run-in Phase**: Updated to remove the 2nd Safety Cohort and safety review by DSMB before the initiation of Randomized Double-masked treatment phase. **Randomized Double-masked treatment phase**: Text updated to remove this phase. **End of Treatment or Early withdrawal**: Updated to reflect that the final visit will be conducted on Month 36. The pharmacogenomic evaluations were eliminated.
Synopsis, Secondary efficacy measures; 9.2.1.2 Secondary efficacy measures	The additional assessments of contrast sensitivity, low luminescence BCVA (best corrected visual acuity), health related quality of life, and MN read were removed. Exploratory efficacy measures were removed. The use of software prediction tool to predict the treatment of dry AMD was eliminated.
14.4. Preparation, Handling and Storage	The sentence "To support the masking of the trial, a vapor-phase shipper containing no CNTO 2476 vials will be shipped for subjects assigned to the sham surgery arm" was removed.
Time and Events Schedule (Table 2)	The 'DNA blood samples for genetic testing' was removed. The columns for Months 42, 48, 54, and 60 (End of Study) visit were deleted. The assessments of low luminescence visual acuity, contrast sensitivity, MN read, microperimetry, and NEI-VFQ-25, and 3-item Near Vision Subscale, and SF-36, FRI were removed.
Footnotes for Time and Events Schedule (Table 1) Footnotes for Time and Events Schedule (Table 2)	The phrase "the Double-masked Treatment Phase" was removed from the Note 2 in the footnote. Bullet 'g)' was updated to reflect that the double-blind masked phase was eliminated from the study The follow-up phase was updated to 2 years The abbreviations and expanded forms of NEI-VFQ-25 and SF-36 were removed.
Synopsis, Statistical methods; 11. Statistical Methods	Updated to reflect that descriptive statistics will be used instead of previously planned formal statistical testing. The statistical methods planned for primary, secondary, exploratory endpoint analyses were removed. Updates were made to depict that all the subjects receiving treatment will be considered for safety analyses.
11.2 Sample size determination	Updated the text to reflect that 21 subjects will be included in the study for an adequate clinical assessment of safety and usability of the novel delivery system instead of using the BCVA response rates between the control group and CNTO 2476 group for sample size determination.
11.5 Pharmacogenomic analyses	The pharmacogenomic analyses were eliminated.
11.6 Data and Safety Monitoring Board	Updated the text to reflect that no further DSMB meetings will be held and DSMB will be disbanded until further decision from Janssen's to reform the DSMB.
Rationale: The first Safety Cohort having already been done and the efficacy portion of the study no longer planned, there is no need to describe the rationale for the sham surgical procedure.	
Synopsis; 3.2 Study Design Rationale 5. Treatment allocation and masking 16 Ethical Aspects	The rationale for performing the sham surgical procedure was removed.
Rationale: Minor errors were noted.	

Applicable Section(s)	Description of Change(s)
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (29 Sept 2016)

The overall reason for the amendment: to include modifications to inclusion and exclusion criteria taken from learning acquired through the first 21 subjects (the initial Safety Cohort), to include a 2nd Safety Cohort of 21 additional subjects agreed upon by the DSMB, to expand the screening to treatment window to 45 days and to include additional baseline assessments (axial length). Other modifications are in included to provide clarity to study sites where there was ambiguity, or the protocol was silent on logistical issues that have arisen. Editorial changes were made to improve the overall clarity of the Protocol.

Applicable Section(s)	Description of Change(s)
Overview of Study Design	Updated the target number of subjects to be enrolled in the study to "approximately 285 subjects". Specified the screening period of up to 45 days before initial randomization that subjects must be confirmed with a diagnosis of GA of the macular secondary to age-related macular degeneration with associated vision loss. Clarified vision between the patient's eyes as "not **clinically** equal" or "**clinically** equal" for the relevant disease state of the eyes. Updated the approximate number of subjects to 75 in the Safety Run-in Phase of the study. Specified the addition of the 2nd Safety Cohort. Also updated the number of sites for this phase of the study to 20.
Screening Phase	Clarified that subjects may have the option to donate their eyes for histological evaluation post mortem. Specified the screening period of up to 45 days between a subject giving written informed consent and occurrence of treatment. Also clarified that screening activities need not take place in one visit. Clarified that the BCVA examination to determine eligibility should be performed prior to any other ocular study procedures that might interfere with vision assessments (dilation, bright light examination, etc). Also specified that axial length will be recorded at baseline. Indocyanin green angiography will be performed for all subjects unless discussed with the Sponsor
Safety Run-in Phase	Clarified that a minimum of the first 3 eligible subjects at each center will receive active treatment in an uncontrolled, open-label Safety Run-in Phase. Clarified that the first 21 subjects at 8 (not 7) study sites will comprise the initial Safety Cohort, and specified the addition of the 2nd Safety Cohort
Subject Population	Updated protocol to specify that approximately 400 subjects will be screened to provide approximately 285 subjects enrolled. The change reflects the additional safety run-in subjects resulting from an increase in the number of sites, the 2nd Safety Cohort and an estimated increase in the percentage of screen failures. Also updated the protocol to specify that screening for eligible subjects will be performed within 45 days before administration of the treatment.
Inclusion Criteria	**Criterion 2 (renumbered to 2.2)** was updated to indicate AMD confirmed within 45 days prior to initial randomization. Diagnosis to be verified by the central reading center. Macular Photocoagulation Study (MPS) disc areas (DA) of ≥0.5 for all subjects. In the Safety Run-in Phase only there is no maximum DA as long as the criteria for photography can be met and the surgeon determines that the GA size will not impede cell delivery. **Criterion 3 (renumbered to 3.2)** was updated to indicate that the treatment eye will be that with the worse BCVA at screening. If BCVA is clinically equivalent, the eye with the larger GA determines the study eye.
Exclusion Criteria	**Criterion 1 (renumbered to 1.2)** was updated to state "subjects with a history of neovacular ("wet") AMD …… *or fluid. In cases where imaging is inconclusive, review of the case with the study site, considering history and imaging will determine eligibility"* **Criterion 7 (renumbered to 7.2)** was extended to include "Subjects who have received anti-VEGF treatment without a confirmed diagnosis of wet AMD or who have participated

Applicable Section(s)	Description of Change(s)
	in previous studies for AMD may be considered eligible if these treatments/study participation were given at least one year prior to enrollment" **Criterion 8 (renumbered to 8.2)** was updated to "previous intraocular surgery within 3 months prior to screening in either eye. Previous treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy in the study eye at any previous time point"
Time and Events Schedule (Table 1)	"Visual Acuity" was replaced with "Best Corrected Visual Acuity" (BCVA) Low Luminance Visual Acuity was added as a separate Study Assessment at Screening, Week 4, and at Months 2, 3, 6 and 12. Axial Length was added as a Study Assessment at Screening. Footnotes for several items on Table 1 were re-numbered to accurately reflect the new assessments added to the table.
Footnotes for Time and Events Schedule	Note 1 was updated to reflect that screening procedures could occur 45 days prior to treatment and over multiple days. Also it states that BCVA will be performed twice and the best value (lowest logMAR value) will be used as the subject's baseline BCVA value. Footnote (b) was updated. A new footnote (c) "Axial length should be recorded once at screening as a baseline measure. Any instrument may be used OR measurement taken from the subjects medical records may be utilized. Measurement, instrument and date of recording will be noted in the CRF. Indocyanin green angiography will be performed for all subjects unless discussed with the Sponsor" was added. Added footnote (l) to indicate that SD-OCT may optionally be performed at Day 1 post-operatively or Day 2
Time and Events Schedule (Table 2)	A separate line to detail "Low Luminance Visual Acuity: was added for Months 18, 24, 30, 36, 42, 48, 54 and 60 as it had previously been ambiguous when this assessment took place.
Section 1.3 The Cell Delivery System	This section was rewritten to be more general. Reference is made to the Investigational Product Manual for detailed Delivery System information.
Section 3.1 Overview of Study Design	Updated the target number of subjects to be enrolled in the study to "approximately 285 subjects". Specify the screening period of up to 45 days before treatment that subjects must be confirmed with a diagnosis of GA of the macular secondary to age-related macular degeneration with associated vision loss. Clarified vision between the patient's eyes as "not **clinically** equal" or "**clinically** equal" for the relevant disease state of the eyes. Updated the approximate number of subjects to 75 in the Safety Run-in Phase of the study. Also updated the number of sites for this phase of the study to 20. Also specified that a minimum of 7 different surgeons would be required during the safety run-in phase. Specified the addition of the 2nd Safety Cohort. **Screening Phase**: updated the protocol to specify that subjects may be screened over a period of 45 days prior to treatment, and that BCVA examinations would be done prior to any other ocular study procedures that would interfere with vision assessments such as dilation or bright light assessments. Also specified that at baseline, dilated fundus examination readings will be carried out on all subjects. In addition, axial length will be recorded in the CRF. Indocyanin green angiography will be performed on all subjects unless discussed with the Sponsor. **Safety Run-in Phase:** Updated the protocol to reflect that a minimum of the first 3 eligible subjects at each center will receive active treatment in an uncontrolled, open-label Safety Run-in Phase to assess the safety of the surgical procedure and Delivery System, and to ensure the familiarity of the surgeons with the device and the procedure. Also specified that the first 21 subjects at the first approximately 7 sites would comprise the initial Safety Cohort. Specified the addition of the 2nd Safety Cohort. **Double-masked Treatment Phase**: Included the sham surgical procedure among the treatments to be administered at the clinical site on Day 1.

Applicable Section(s)	Description of Change(s)
	Figure 6 Schematic Representation of Study CNTO2476MDG2002 was updated and now becomes Figure 1 as the original Figures 1-5 in Section 3.1 were removed from the protocol and are now located in the Investigational Product Manual.
Section 3.2 Study Design Rationale	Specified the addition of the 2nd Safety Cohort.
Section 3.2.2	Replaced "suture" with "conjunctival incision, a scleral mark and a masking stitch"
Section 3.2.6 Patient-Reported Outcomes	Corrected a typographical error, replacing "retinal" with "retinal experts"
Section 4 Subject Population	Updated the subject population to indicate that "Approximately 400 subjects will be screened to provide approximately 285 subjects enrolled. Screening for eligible subjects will be performed within 45 days before administration of the treatment.
Section 4.1 Inclusion Criteria	Changes to the Inclusion Criteria are described in the Summary of Changes in the Synopsis (see Page 6).
Section 4.2 Exclusion Criteria	Changes to the Inclusion Criteria are described in the Summary of Changes in the Synopsis (see Page 7).
Table 4	A correction was made in footnote "a" to indicate that potential to become unmasked upon ophthalmic examination and/or review of AEs, SAEs and ocular procedure results
Section 9.1.1 Overview	The following was added to the protocol "New technology assessments, eg, Optical Coherence Tomography Angiography (OCT-A) and intraoperative Optical Coherence Tomography, may be performed at the surgeon or investigator's discretion but do not substitute for any of the mandatory evaluations listed in this protocol"
Section 9.1.1.1 Screening Phase	Text was added to specify that a subject failing screening for a reason determined to be temporary could be re-screened per the following criteria: • Elevated IOP, uncontrolled blood pressure, elevated liver enzymes , decreased platelets and decreased renal function, if correctable with treatment or time • Acute infections, after successful treatment • Time-bound restrictions (eg, Exclusions 8, 9, 12, 20, 21 and 25) after an appropriate waiting period such that the exclusion no longer applies • Use of prohibited prior medications, after an appropriate waiting period. In addition, Potential patients who fail screening for visual acuity, retinal anatomy or other ocular findings should not be rescreened. Any rescreening request not mentioned here should be discussed with the study Medical Monitor. For rescreened subjects, imaging studies do not have to be repeated if performed in the 60 days prior to start of new screening. For rescreened subjects, clinical laboratory exams (bloodwork) do not have to be repeated if performed in the 45 days prior to start of the new screening. Furthermore, Axial length will be recorded at baseline. Indocyanin green angiography will be performed for all subjects unless discussed with the Sponsor. Changes in concomitant medications will be recorded on Day 1
Section 9.1.1.2 Open-Label Safety Run-in Phase	Clarified that the study will begin with a minimum of 7 surgeons performing approximately 3 open-label procedures to complete an initial Safety Cohort of 21 subjects. A minimum of 7 surgeons were chosen for the Safety Cohort based on the amount of device users needed to identify complications with a surgical procedure and device. Added "significant loss of vision defined as loss of ≥15 letters compared to baseline in the first month post-surgery," as an event of special interest. Specified the addition of the 2nd Safety

Applicable Section(s)	Description of Change(s)
	Cohort.
Section 9.1.1.3 Randomized Double-Masked Treatment Phase	Clarified that a sham surgical procedure will take place on Day 1 (pre-operative visit on the treatment day).
Section 9.2.1.2 Secondary Measures	Included "visual assessment" among assessments to be performed.
Section 9.2.2 Endpoints	**Major Secondary Endpoints:** specified that "RS plateau" was being measured
Section 9.3.3 Immunogenicity Assessments	Clarified that Blood samples will only be collected during study assessments for the safety run-in phase and the randomized double-masked treatment phase from screening through the Month 12 postoperative visit
Section 9.7.1 Adverse Events	Updated the text of the protocol to indicate that adverse events will be reported by the **investigator or** the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study
Section 9.7.2 Clinical Laboratory Tests	Aligned the text of the penultimate paragraph with the Inclusion Criteria, ie, "Female subjects must be post-menopausal with last menses 12 months prior, or longer, OR a measured follicle stimulating hormone ≥26 mIU/mL"
Section 11 Statistical Methods	Updated the text of the protocol to state that data from approximately 75 subjects participating in the open-label safety run-in, after have completed 1 month of follow-up, will be analyzed for simple descriptive statistics for key safety and efficacy measures. Also specified the analysis of data after the 21 subjects of the 2nd Safety Cohort have completed 1 month of follow-up.
Section 11.7 Data Safety Monitoring Board	Specified the addition of the 2nd Safety Cohort.
Section 12.1.1 Adverse Event Definitions and Classifications	Under Adverse Event Associated With the Use of the Drug, the following was added to the text of the protocol "The surgical procedure and delivery of CNTO 2476 result in a small retinal detachment per procedure guidelines. This in itself should not be listed as an adverse event".
Section 14.2 Packaging	It was clarified in the protocol that each vial of product is for single us. In addition, the following text was added "Each vial is enclosed in a paperboard carton with appropriate labeling on the carton".
Section 14.4 Preparation, Handling and Storage	The text in the protocol was updated to exclude temperature deviations that were applicable to manufacturing only. In addition, the following was added to the protocol "CNTO 2476 is shipped to the clinical site in a liquid nitrogen vapor-phase shipper that is also used for short-term storage up to 7 calendar days after shipment. The distribution is on a just-in-time basis for each treatment in the trial. The shipment for a subject will be triggered when enrolled or randomized through the IWRS. To support the masking of the trial, a vapor-phase shipper containing no CNTO 2476 vials will be shipped for subjects assigned to the sham surgery arm"
Section 14.5 Investigational	The text in the protocol was updated to the following "The investigator is responsible for ensuring that all CNTO 2476, Delivery System devices received at the site are inventoried and accounted for throughout the study, per the requirements in the Investigational Product

Applicable Section(s)	Description of Change(s)
Product and Device Accountability	Manual. All CNTO 2476 will be stored and disposed of according to the sponsor's instructions, per the Investigational Product Manual. Study-site personnel must not combine contents of the CNTO 2476 containers”
Section 16.1 Study-Specific Design Considerations	Clarified there are 2 Safety Cohorts.
Section 17.8 Monitoring	The following text was added to the protocol “Representatives from the sponsor company, Janssen and/or its’ designees may be present at the clinical facility, in the operating room during surgery or observing remotely. This is to ensure oversight of aspects of the surgical procedure and protocol”
Throughout the Protocol	“Maximum Reading Speed, MRS” has been replaced with “Reading Speed, RS” “**Discontinue** from the study”, “**Drop out** of the study” replaced with “Withdrawal ….” **Withdrawa**l from the study”

Amendment 1 (21 Dec 2015)

The overall reason for the amendment: Include the Functional Reading Index (FRI) as a major secondary objective, update the Time and Events Schedule to reflect tests no longer to be done, update some Exclusion Criteria, correct the stratification data and clarify how informed consent is to be obtained. Editorial changes were made to improve the overall clarity of the Protocol.

Applicable Section(s)	Description of Change(s)
Synopsis, Objectives and Hypotheses;	Added Functional Reading Index (FRI) to the list of major secondary objectives
Synopsis, Overview of Study Design	Updated target number of subjects to 255. Also update the subjects in the safety run-in phase to 45, and the number of sites to 15. Described the screening process including BCVA examinations performed to determine patient eligibility
Synopsis, Subject Population	Updated the total number of subjects to be screened, and also update the number of subjects to be enrolled (open-label safety phase and subjects randomized in 1:1:1 ratio)
Synopsis Exclusion Criteria	Modified Criteria 7.1 and 20.1 (Details in Section 4.2 Exclusion Criteria, below)
Synopsis, Secondary Efficacy Endpoints	Added FRI as a secondary efficacy endpoint
Synopsis, Statistical Methods	Updated the baseline BCVA stratification criteria
Time and Events Schedule	Removed Visual Acuity Tests on Day 2, and on Days 7 & 15 NEI-VFQ-25, SF-36, Near Vision Subscale (3-item) and FRI will no longer be done on Treatment Day 1 (pre-op) Clarified that an additional optional pre-screening visit may be performed to determine potential subject BCVA for eligibility purposes this was already noted in the original protocol Clarified that Pharmacodynamic Marker Testing will not be done. Clarified that no samples will be collected for immunogenicity testing after the Month 12 visit Removed reference to blood sample volume after Month 12 (no samples will be collected)
Introduction	Editorial changes to capture additional files names previously listed as “data on file”
Section 1.1.1.1 Mechanism of Action	Re-wrote for clarity
Section 1.1.1.2 Section 2.1 Objectives	Re-wrote for clarity Added the Functional Reading Index as a Secondary Objective
Section 3.1 Overview of Study Design Section 3.2.4	Updated the number of subjects in run-in phase and the number of sites. Updated Figure 6 to capture the number of subjects and sites Specified how stratification would be done
Section 3.2.6 Patient-Reported Outcomes	Re-wrote the description of the NEI-VFQ-25 for clarity Updated the section with a description of the Functional Reading Index
Section 4 Subject	Updated the number of subjects enrolled into the study, including those from the

Applicable Section(s)	Description of Change(s)
Population	open-label safety run-in phase
Section 4.2 Exclusion Criteria	Bullet point 7 was renumbered 7.1, and "AMD" changed to "AMD (dry or wet)" Bullet point 20 was renumbered to 20.1 and the text "… *has participated in other ophthalmic investigational drug studies within 6 months of Day 1, or is currently enrolled in an investigational study*" deleted
Section 5. Treatment Allocation and Masking	Definition of BCVA was added Text describing the stratification used was clarified and corrected to the below: • 0.6 log MAR (20/80) to 1.3 logMAR (20/400) inclusive (i.e. the moderate loss stratum) • 1.32 logMAR (20/400$^{-1 \text{ letter}}$) to 1.6 logMAR (20/800) inclusive, ie, the low vision stratum
Section 8 Prestudy and Concomitant Therapy	The use of peri-operative and post-operative medications was clarified
Section 9.1.1 Overview	Table 6 was simplified and updated with corrected volumes of blood to be collected from each subject during the course of the study Text was introduced to describe how patient eligibility would be determined based on the results of BCVA examinations done at the screening visit
Section 9.2.2	The Functional Reading Index was added as a major secondary endpoint The major secondary endpoint of LL BCVA was re-written as the following to provide clarification and additional detail • Mean change from baseline at 6 and 12 months in low luminance BCVA (LL BCVA) letters following treatment with CNTO 2476 compared to the control arm. • Proportion of subjects with gain of >=15 letters from baseline at 6 and 12 months in LL BCVA following treatment with CNTO 2476 compared to the control arm.
Section 11. Statistical Methods	BCVA was defined and the stratification re-written as below: • 0.6 log MAR (20/80) to 1.3 logMAR (20/400) inclusive (i.e. the moderate loss stratum), and • 32 logMAR (20/400$^{-1 \text{ letter}}$) to 1.6 logMAR (20/800) inclusive (i.e the low vision stratum) A description was provided for how data analysis would be performed after the first 21 subjects, and after all subjects participating in the open-label safety run-in phase had completed 1 month of follow-up.
Section 11.3.2 Major Secondary Endpoint Analyses	Text was clarified to include subjects gaining ≥15 LLBCVA letters. The sensitivity analyses were also clarified to include LLBCVA letters
Section 16.2.3. Informed Consent	Clarified that all study sites will be asked by the Sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. An additional description of the process of obtaining informed consent is provided

SYNOPSIS

A Phase 2b, Multicenter, Double-masked, Randomized Study Evaluating the Safety and Clinical Response of Subretinal Administration of CNTO 2476 in Subjects with Visual Acuity Impairment Associated with Geographic Atrophy Secondary to Age Related Macular Degeneration

CNTO 2476 is an allogeneic somatic cell therapy medicinal product derived from the isolation and ex-vivo expansion of human umbilical tissue-derived cells (hUTC) that is to be injected in the subretinal space of the eye of subjects with retinal degeneration. In addition to impacting retinal pigment epithelium (RPE) cells, CNTO 2476 appears to preserve photoreceptors, and inner retinal cells.

Study CNTO2476MDG2002 is a Phase 2b study to evaluate the safety and usability profile of the procedure and the Delivery System, as well as to assess the clinical efficacy, safety, and tolerability of a single subretinal administration of CNTO 2476 at 1 of 2 doses, compared with the control.

OBJECTIVES AND HYPOTHESIS

Primary Objectives

The primary objective of the open-label Safety Run-in Phase is to evaluate the safety and performance profile of the suprachoroidal surgical approach and the Delivery System.

Major Secondary Objectives

The major secondary objectives of this study are the following:

- to assess the safety and performance profile of the Delivery System, the safety and tolerability of the suprachoroidal surgical approach, and the safety and tolerability of CNTO 2476 cells in the open-label Safety Run-in Phase
- to assess the effects of CNTO 2476 on anatomic correlates of treatment, including change in the area of geographic atrophy (GA)
- to assess the effects of CNTO 2476 on additional and alternative efficacy outcomes including duration of clinical response.

Hypothesis

The primary hypothesis of the open label safety phase of this study is that the novel subretinal delivery system is sufficiently safe and usable to deliver cells to the subretinal space. An additional hypothesis is that palucorcel is safe and well tolerated when delivered as a single dose to the subretinal space.

OVERVIEW OF STUDY DESIGN

This is a multicenter Phase 2b study. A target of approximately 21 subjects will be enrolled in this study. This protocol amendment represents a significant reduction in scope and duration of the study based on a decision to discontinue the palucorcel development program.

The target population will be subjects at least 55 years of age and no older than 90 years, inclusive with a confirmed diagnosis of GA of the macula secondary to age-related macular degeneration, with associated vision loss, confirmed within 45 days prior to initial randomization by the central reading center using fundus and/or autofluorescence, fluorescein angiography, and fundus photography. In subjects with neovascular AMD in 1 eye, the eye with GA must be the worse eye. In subjects with bilateral GA and the vision between both eyes not clinically equal, the eye with the worse vision will be treated in order to minimize risk to the subject's vision. In cases where the BCVA of the 2 eyes is clinically equal, the eye with more extensive GA as demonstrated on the imaging studies will become the study eye.

The Safety Run-in Phase consists of approximately 21 subjects (the first 3 subjects at each of approximately 8 sites) who will first be enrolled in an open-label assessment of the safety profile of the procedure and the Delivery System. During the Safety Run-in Phase, subjects will receive a CNTO 2476 dose of 3.0 x 10^5 cells in 50 µL. The first 21 subjects in the Safety Run-in Phase will be the initial Safety Cohort.

The safety profile of the procedure and the Delivery System will be assessed after the first 21 subjects (the initial Safety Cohort) have been treated and followed for a minimum period of 1 month. An external Data and Safety Monitoring Board (DSMB) will be commissioned for this study.

The Randomized Double-masked Treatment Phase of the study was planned to follow the DSMB's evaluation of the safety phase data and its supportive recommendation to advance to the randomized Double-masked Treatment Phase. This cohort was to consist of approximately 210 subjects for evaluation of both efficacy and safety. However, the Double-masked Treatment Phase has been eliminated from this study protocol.

The study will consist of a 12-month acute phase, followed by a 2-year maximum duration follow-up period (3 years total) for all subjects.

Screening Phase

Prior to the full study screening phase, optional BCVA pre-screening may be done to evaluate subjects for BCVA eligibility. In this case, subjects must sign an optional pre-screening informed consent form (ICF) prior to testing. The site will determine results of local testing and indicate if the subject is eligible for full study screening. If the BCVA test indicates the subject meets the necessary eligibility criteria, he or she will enter the full screening phase after signing the full study ICF for determination of full study eligibility.

All subjects will be required to give written informed consent to participate in the trial.

After giving written informed consent, subjects may be screened over a period of up to 45 days prior to treatment to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study. The screening process may occur over a period of days and need not take place in one visit.

Patient eligibility will be determined based on the results of 2 BCVA examinations performed at the screening visit. These examinations can occur on the same day or subsequent days. The better of the 2 logMAR BCVA scores will be used for eligibility and randomization. These examinations should be performed prior to any other ocular study procedures that might interfere with vision assessments (dilation, bright light examination etc).

Visual acuity tests, contrast sensitivity, MN Read, intraocular pressure (IOP), slit lamp examinations (including lens mobility examination), microperimetry, fundus photography, spectral domain optical coherence tomography (SD-OCT), fundus autofluorescence, and fluorescein angiography, will be performed for all subjects. Axial length will be recorded at baseline. Indocyanin green angiography will be performed for all subjects unless discussed with the Sponsor.

Other assessments will include medical history, genomic material from consented subjects, demographics, a targeted physical examination, vital signs, routine laboratory and routine urinalysis In addition blood samples for immunogenicity, medication history, concomitant medications, the NEI-VFQ-25 and Near Vision subscale, the SF-36 and FRI will be collected.

Safety Run-in Phase

The first 3 eligible subjects at each center will receive active treatment in an uncontrolled, open-label Safety Run-in Phase to assess the safety of the surgical procedure and Delivery System, and to ensure the familiarity of the surgeons with the Delivery System and the procedure. The first 21 subjects at the first

8 study sites will comprise the initial Safety Cohort. Enrollment into the Safety Run-in Phase will be staggered across sites to ensure that the outcomes and learnings from earlier procedures can be transferred to all participating surgeons who will perform subsequent procedures. A 1-week interval for information sharing is appropriate since most procedure-related adverse events (AEs) are expected to be apparent within hours of surgery.

Long-Term Follow-up Phase

Following the 12-month acute phase of the study, subjects will be followed every 6 months for 2 years in the Long-term Follow-up Phase.

SUBJECT POPULATION

Approximately 100 subjects will be screened to provide approximately 21 subjects enrolled.

Screening for eligible subjects will be performed within 45 days before administration of the treatment.

Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Subject must be a man or woman at least 55 years to 90 years of age, inclusive.

2.2 Diagnosis of GA secondary to AMD confirmed within 45 days prior to initial randomization. Diagnosis verified by the central reading center using fundus photographs and including the following;

- The study eye must have at least 1 GA lesion that involves the fovea, and a Macular Photocoagulation Study (MPS) disc areas (DA) of ≥0.5 and ≤7 (1 MPS disc area equivalent to 2.54 mm^2 on the retina) determined by screening images of fundus autofluorescence photographs as calculated by the reading center. If GA is multifocal, at least one lesion must be ≥0.5 DA.
    - In the Safety Run-in Phase only, DA of ≥0.5 is allowed with no maximum specified area, as long as the criteria below for photography can be met and the surgeon determines that the GA size will not impede cell delivery.
- Geographic atrophy must be able to be photographed in its entirety and may be contiguous with peripapillary atrophy.
- Retinal photographs, fundus autofluorescence images, and angiography of sufficient quality, allowing assessment of the macular area according to standard clinical practice, can be obtained.
- The imaging center must be able to delineate and confirm peripapillary atrophy with fundus photography and fundus autofluorescence.
- Images must include the central field 1, 2, and 3 field images as defined by the University of Wisconsin standards as well as a supero-temporal image to capture the subretinal injection area if possible.

3.2 Study eyes will have a BCVA of 20/80 to 20/800 (Early Treatment Diabetic Retinopathy Study [ETDRS] log of the minimal angle of resolution (logMAR) value 0.6-1.6). The treatment eye will be that with the worse BCVA at screening. If BCVA is clinically equivalent, the eye with the larger GA determines the study eye.

4. Subject is a suitable candidate for ophthalmologic surgery, is willing and able to comply with the

surgical procedure, scheduled visits, treatment plan, laboratory tests and other study procedures. Subject has met criteria of the surgery center anti-coagulation protocol, if applicable.

5. Female subjects must be post-menopausal with last menses 12 months prior, or longer, OR a measured follicle stimulating hormone ≥26 mIU/mL.

6. Male subjects must be sterile or willing to use 2 approved methods of contraception from first day post-operatively to 3 months post-operatively (approved methods of contraception include condom with spermicide, a sterile sexual partner, a sexual partner using oral or implantable contraceptive or an intrauterine device with spermicide, a diaphragm with spermicide, or cervical cap with spermicide).

7. Each subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study

1.2 Subject has a history of neovascular ("wet") AMD in the treatment eye, including evidence of retinal pigment epithelium rips or evidence of subretinal or choroidal neovascularization or fluid. In cases where imaging is inconclusive, review of the case with the study site, considering history and imaging will determine eligibility. History or evidence of neovascular AMD in the fellow eye is allowed, if anti-vascular endothelial growth factor (VEGF) therapy has not been required for at least 8 weeks prior to screening.

2. Geographic atrophy secondary to any causes other than AMD in either eye

3. A diagnosis of glaucoma with an IOP ≥25 mmHg while being treated with an ocular hypotensive drug. Treatment should be no more than 1 drug preparation/combination, which can contain 1 or 2 ocular hypotensive active ingredients; subjects receiving more than 2 ocular hypotensive active ingredients are excluded. Note: subjects with a diagnosis of ocular hypertension (not glaucoma) are eligible to participate whether or not they are being medically treated.

4. Nuclear sclerotic cataract, cortical spoking, posterior subcapsular cataract above Grade 2 per Age-Related Eye Disease Study (AREDS) scale or any other ophthalmologic condition that reduces the clarity of the media that, in the opinion of the investigator or reading center, interferes with ophthalmologic examination (eg, corneal abnormalities, inadequate pupillary dilation), surgery or imaging in the study eye

5. Myopia >-8 diopters and subjects with >4 diopters of astigmatism, and >+10 diopters of hyperopia. Note: clinical evidence of retinal degeneration secondary to pathological myopia will exclude the subject as will a scleral ectasia with or without high myopia.

6. Evidence of other significant ophthalmologic disease (eg, intraocular inflammatory disease, diabetic retinopathy, Stage II, III, or IV macular hole, clinically evident vitreoretinal traction, choroidal or retinovascular disease, cystoid macular edema, significant epiretinal membrane, significant blepharitis, keratitis, conjunctivitis or staphyloma) in the study eye

7.2 Previous treatment for confirmed AMD (dry or wet) in the study eye with treatments *other than* antioxidant or zinc supplements (eg, AREDS1 or AREDS2 formula) or other oral vitamin supplements. Subjects who have received anti-VEGF treatment without a confirmed diagnosis of wet AMD or who have participated in previous studies for AMD may be considered eligible

if these treatments/study participation were given at least one year prior to enrollment.

8.2 Previous intraocular surgery within 3 months prior to screening in either eye. Previous treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy in the study eye at any previous time point.

9. Previous laser photocoagulation in the study eye (peripheral laser for treatment of a tear is allowed if more than 6 months prior to screening *except* when, in the opinion of the surgeon, this would hamper the suprachoroidal cannulation procedure in the study eye)

10. Previous vitrectomy, retinal detachment repair, submacular surgery, other surgical interventions targeting AMD, scleral buckling or glaucoma filtration surgery or any other extraocular or orbital procedure in the study eye that, in the opinion of the surgeon, would hamper the suprachoroidal cannulation procedure in the study eye

11. History of choroidal or scleral rupture in either study or fellow eye due to uveitis (previous trauma in the study eye or fellow eye in the case of good vision in that eye is not an exclusion criterion)

12. Uveitis or other intraocular inflammatory disease within past 3 months

13 Active infections of the anterior segment

14. Keratoconus, penetrating keratoplasty, Descemet's stripping endothelial keratoplasty (DSEK), radial keratotomy (RK), laser-assisted in situ keratomileusis (LASIK) in the study eye

15. Monocular subjects

16. Subject has known allergies, hypersensitivity, or intolerance to CNTO 2476 or its excipients (refer to Investigator's Brochure)

17. Medically not qualified for monitored anesthesia care intravenous sedation

18. Previous cell therapy other than standard blood and platelet transfusions

19. Subject has taken any disallowed therapies as noted in Section 8, (Prestudy and Concomitant Therapy) before the planned first dose of treatment

20.1 Subject has received an investigational drug (including investigational vaccines) within 30 days before the planned first dose of treatment

21. Active malignancy (requiring therapy) or history of malignancy requiring therapy within 2 years prior to Day 1 (with exception of cases of basal cell and squamous cell carcinoma of the skin)

22. History of human immunodeficiency virus (HIV) disease

23. Significant cognitive impairment that interferes with a subject's ability to participate with the testing regimen

24. History of organ or bone marrow transplants

25. History of alcohol or drug abuse within past 2 years

26. Significant hepatic dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >3x upper limit of normal [ULN]), or significant renal dysfunction (estimated creatinine clearance ≤30mL/min), or on renal dialysis

27. Significant uncorrectable coagulopathy, thrombocytopenia (platelets $<100 \times 10^3/\mu L$) or other

significant bleeding risk. Note: subjects on an anticoagulant therapy should be considered at low risk for new thromboembolic events, and must agree to stop all anticoagulation therapy prior to surgery, as follows:

- Warfarin ≥5 days
- Aspirin ≥7 days
- Oral Factor Xa inhibitors ≥3 days (or longer, depending on renal function)
- Dabagatran ≥3 days
- Low molecular weight heparin ≥1 day
- Clopidogrel and ticagrelor ≥5 days
- Prasugrel ≥7 days
- Ticlopidine ≥10 days

28 Uncontrolled systemic hypertension on the day of surgery, defined as a systolic blood pressure ≥180 mm Hg. Note: if the subject's systolic blood pressure can be controlled later by the subject's medical doctor, eligibility for surgery can be re-assessed.

29. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

30. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator

31. Known allergy to iodinated contrast dyes

DOSAGE AND ADMINISTRATION

During the Safety Run-in Phase, subjects will receive a CNTO 2476 dose of 3.0×10^5 cells in 50 µL. CNTO 2476 will be delivered using the custom-designed Delivery System and surgical procedure.

Each subject in each target dose group will receive a single subretinal administration of CNTO 2476.

EFFICACY EVALUATIONS/ENDPOINTS

Primary Efficacy Endpoint

The primary efficacy measure will be the BCVA testing performed after refraction and under standardized photopic lighting conditions and distance using an ETDRS logMAR chart.

The endpoints of the open-label Safety Run-in Phase are all related to the objective of evaluating the safety profile of the procedure, Delivery System, and of the implanted hUTC cells.

Secondary Efficacy Endpoints

Assessments will be performed at the 6- and 12-month visits to evaluate:

- Proportion of subjects losing ≥15 BCVA letters from baseline at 12 months following treatment with CNTO 2476
- Change in mean number of BCVA letters from baseline at the 6- and 12-month visits following treatment with CNTO 2476

- Growth rate of GA lesion documented at baseline to 6 and 12 months following treatment with CNTO 2476 compared to the control arm. The area of GA is determined based primarily on fundus autofluorescence as well as fluorescein angiography and fundus photos

Safety Endpoint

- Treatment-related ocular AEs and SAEs and other safety outcomes including markers of immunogenicity, safety of the surgical procedure and performance of the Delivery System

IMMUNOGENICITY EVALUATIONS

Serum antibody levels pre- and post-administration of CNTO 2476 will be assessed. The titer of confirmed positive samples will be reported.

SURGICAL EVALUATIONS

Data on the conduct of the procedure, including the success of individual elements of the surgical procedure and Delivery System performance will be collected and tabulated, as well as any complications of the procedure or any product quality defects.

SAFETY EVALUATIONS

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. In addition to AEs, clinical laboratory tests for hematology, serum chemistry, and urinalysis will be performed and reported. In addition, vital signs and physical examination will be measured and reported.

STATISTICAL METHODS

- All outcome assessments will be tabulated using descriptive statistics; no formal statistical testing is planned for outcome in the Safety Cohort.

Sample Size Determination

The sample size of 21 subjects is based on the number of subjects required for an adequate clinical assessment of the safety and usability of the novel delivery system.

Efficacy Analyses

The BCVA response is defined as an increase of 15 letters or more from baseline in ETDRS letters, a magnitude of change that is determined to be clinically important.

The BCVA, LL BCVA, LLD, contrast sensitivity and growth rate of GA lesion will be summarized with descriptive statistics as specified in the SAP.

Other Analyses

Safety analyses will be performed and reported for AEs, the Delivery System and surgical procedure, clinical laboratory tests, immunogenicity, vital signs, and physical examination.

Specifically, the number and percentage of subjects who experienced at least 1 treatment-emergent serious ocular AE will be presented in summary tables by treatment group and preferred term according to terminology from the Medical Dictionary for Regulatory Activities (MedDRA) as well as by affected eyes (events occurring in the treated eye only, in the fellow eye only, and in both eyes).

Ocular TEAEs will be summarized by treatment group and preferred term according to MedDRA terminology, as well as by affected eyes (events occurring in the treated eye only, in the fellow eye only, and in both eyes).

The number and percentage of subjects who experienced at least 1 treatment-emergent serious AE (SAE) will be presented in summary tables by treatment group and preferred term, as well as by preferred term within system-organ class according to MedDRA terminology.

The number and percentage of subjects who experienced at least 1 treatment-emergent AE will be presented in summary tables by treatment group and preferred term, as well as by preferred term within system-organ class according to MedDRA terminology.

Data regarding the Delivery System and surgical procedure will be tabulated by treatment group. A listing of all data pertaining to the Delivery System and surgical procedure, as well as any surgical deviations and surgical medications, will be provided. Adverse events for subjects who receive surgery but not CNTO 2476 cells will be listed.

TIME AND EVENTS SCHEDULES

Table 1: Schedule of Study Assessments for the Safety Run-in Phase and the Randomized Double-masked Treatment Phase from Screening through the Month 12 Postoperative Visit

	Optional Pre-Screening	Screen (see note)	Treatment Day 1 (pre-op)	Day 2	Days 7 & 15 (±3d)	Week 4 (±3d)	Month 2 (±3d)	Month 3 (±3d)	Month 6 (±3d)	Month 12 (±7d)
Visit number		1	2	3	4, 5	6	7	8	9	10
Informed consent	x[a]	x								
Inclusion/Exclusion criteria		x								
Medical History and demographics		x								
Vital signs		x	x	x	x	x	x	x	x	x
Physical exam		x								x
Best Corrected Visual Acuity (BCVA)	x	x[b]				x	x	x	x	x
Low Luminance Visual Acuity		x				x	x	x	x	x
Axial Length		x[c]								
Contrast sensitivity		x						x	x	x
MN Read		x						x	x	x
IOP		x		x	x	x	x	x	x	x
Slit lamp biomicroscopy/ophthalmoscopy		x		x	x	x	x	x	x	x
Microperimetry assessments		x						x	x	x
Fundus photography		x			x	x	x	x	x	x
SD-OCT[l]		x			x	x	x	x	x	x
Fundus autofluorescence		x			x	x	x	x	x	x
Fluorescein angiography		x						x		x
Indocyanin green angiography		x								
Routine laboratory[d]		x				x				x
Routine urinalysis		x				x				x
Blood samples for immunogenicity[f]		x			x	x	x	x	x	x
Medication History		x	x							
NEI-VFQ-25, SF-36[i], and Near Vision Subscale (3-item), FRI		x							x	x
Randomization (for the Double-masked Treatment Phase only)[g]										
CNTO 2476 Administration			x[h]							
PGIC-S									x	x
PGIC-Q									x	x
CGIC									x	x
Change in concomitant medications			<----------Continuous---------->							
Adverse events		<----------Continuous---------->								
Blood samples volume[l]		16.3 mL	0	0	20 mL[k]	16.3mL	10 mL	10 mL	10 mL	16.3 mL

BCVA=Best Corrected Visual Acuity; CGIC=Clinician Global Impression of Change; ETDRS=Early Treatment Diabetic Retinopathy Study; IOP=intraocular pressure; MN Read=Minnesota reading test; NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire; PGIC-Q=Patient Global Impression of Change – Quality of Life; PGIC-S=Patient Global Impression of Change – Symptoms; SD-OCT=spectral domain optical coherence tomography; SF-36=Short Form (36) Health Survey, FRI= Functional Reading Index questionnaire

Note 1: Screening procedures must occur within 45 days prior to treatment and may occur over multiple days. An additional optional pre-screening visit may be performed to determine potential subject BCVA for eligibility purposes. At the next screening visits, BCVA will be performed twice and the best value (lowest logMAR value) will be used as the subjects' baseline BCVA value.

Note 2: If a subject withdraws early from the Safety Run-in Phase, the end-of-study assessments (described in Table 2) should be performed.

a) Subjects will be presented with an optional pre-screening ICF to allow the determination of their BCVA results prior to full study screening. The subjects who meet the BCVA eligibility criteria will be further screened to determine the full study eligibility. For the full study eligibility assessments, the subject will be presented a separate ICF within 45 days prior to treatment. The pre-screening visit is optional

b) Best Corrected Visual Acuity testing includes BCVA using the ETDRS chart under high illumination and standardized conditions at 4 meters and 1 meter (as needed). .

c) Axial length should be recorded once at screening as a baseline measure. Any instrument may be used OR measurement taken from the subjects medical records may be utilized. Measurement, instrument and date of recording will be noted in the CRF.

d) Includes routine hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count, prothrombin time, and partial thromboplastin time) and serum chemistry (sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, uric acid, calcium, albumin, and total protein) and urinalysis (dipstick).

e) Optional blood draw (ie, for subjects who provide consent for this blood draw)

f) Includes samples for antibody assay testing.

g) Enrollment and randomization of subjects in the Double-masked Treatment Phase was to follow the DSMB's evaluation of the Safety Run-in Phase and its supportive recommendation to advance the study to the Double-masked Treatment Phase. However, the Double-masked Treatment Phase has been eliminated from this study protocol.

h) Includes assessment of Delivery System.

i) SF-36 is included to assess the measurement properties of the NEI-VFQ-25 and Near Vision subscale.

j) Blood sample estimates based upon the following volumes per sample: Screening=16.3 mL, DNA=8.5 mL, Day 7=10 mL, Day 15=10 mL, Week 4=16.3 mL, Month 2=10 mL, Month 3=10 mL, Month 6=10 mL, Month 12=16.3 mL Total volume of blood through Month 12 = approximately 107.4 mL.

k) Includes 10 mL samples each for Day 7 and Day 15

l) Optional SD-OCT at day 1 (post-operatively) and day 2 may be performed

Table 2 Schedule of Study Assessments During the Long-term Follow-up Phase*

	Time Post-treatment			
	Month 18 (±2 wk)	Month 24 (±2 wk)	Month 30 (±2 wk)	Month 36 (±2 wk)
Visit number	11	12	13	14
Best Corrected Visual Acuity testing	x	x	x	x
IOP	x	x	x	x
Slit lamp biomicroscopy / ophthalmoscopy	x	x	x	x
SD-OCT	x	x	x	x
Fundus photography	x	x	x	x
Fundus autofluorescence	x	x	x	x
Concomitant medications	<----------Continuous---------->			
Adverse events[b]	<----------Continuous---------->			

Footnotes

* After the 12-month acute phase of the study subjects will be followed for 2 years. Subjects will come in for a follow-up visit every 6 months.

AE=adverse event; IOP=intraocular pressure; SAE=serious adverse event; SD-OCT=spectral-domain optical coherence tomography.

a) If a subject is withdrawn from the study, he/she will be asked to have the End-Of-Study Visit assessments performed.

b) Only SAEs, ophthalmologic AEs, ongoing AEs from acute phase or any AEs designated as related to treatment or surgical procedure are recorded.

ABBREVIATIONS

ABCA4	ATP-binding cassettes A4
AE	adverse event
AMD	age-related macular degeneration
AMD-GA	age-related macular degeneration with geographic atrophy
AREDS	Age Related Eye Disease Study
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCVA	best corrected visual acuity
BSS	balanced salt solution
CFR	Code of Federal Regulations
CGIC	Clinician Global Impression of Change
CPS	critical print size
CRO	Contract Research Organization
DA	disc area
DARC	Digital Angiography Reading Center
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
eDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FRI	Functional Reading Index questionnaire
GA	geographic atrophy
GCP	Good Clinical Practice
GTP	Good Tissue Practice
HIV	human immunodeficiency virus
hUTC	human umbilical tissue-derived cells
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
LASIK	laser-assisted in situ keratomileusis
LL BCVA	low luminance best corrected visual acuity
LLD	low luminance difference
logMAR	log of the minimum angle of resolution
MAIA2	Macular Integrity Assessment
MCID	minimal clinical important difference
MDS	microcatheter delivery system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MN Read	Minnesota reading test
MertK	Mer tyrosine kinase
MPS	Macular Photocoagulation Study
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire
NOAEL	no-observed-adverse-effect level
PGIC-Q	Patient Clinician Global Impression of Change – Quality of Life
PGIC-S	Patient Clinician Global Impression of Change – Symptoms
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
pUTC	pig umbilical tissue-derived cells
RA	reading acuity
RCS	Royal College of Surgeons
RGC	retinal ganglion cell

RK	Radial keratotomy
ROS	rod outer segments
RPE	retinal pigment epithelium
RS	reading speed
SAE	serious adverse event
SAP	statistical analysis plan
SD-OCT	spectral domain optical coherence tomography
SF-36	Short Form (36) Health Survey
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor

1. INTRODUCTION

CNTO 2476, BB-IND 13198, is an allogeneic somatic cell therapy medicinal product derived from the isolation and ex vivo expansion of human umbilical tissue-derived cells (hUTC) that is to be injected in the subretinal space of the eyes of subjects with retinal degeneration. In addition to impacting retinal pigment epithelium (RPE) cells, CNTO 2476 appears to preserve photoreceptors, and inner retinal cells. As a result, treatment with CNTO 2476 may have a positive impact on visual function. The putative mechanisms of action of CNTO 2476 relevant to age-related macular degeneration (AMD) are stimulating RPE phagocytosis of rod outer segments, promoting RPE survival and promoting synaptogenesis and neuron survival.

Age-related macular degeneration with geographic atrophy (AMD-GA) is a retinal degenerative disease involving the macula. The pathogenesis of AMD, though not conclusively defined, involves the loss of photoreceptors and RPE cells. This loss is thought to be induced by toxic agents such as lipofuscin in RPE. The accumulation and deposition of lipofuscin and the formation of drusen has been associated with dysfunction and subsequent loss of RPE, resulting in degeneration of the overlying photoreceptors[1,6,9,4,13], and synaptic loss and mislocalization.[8,15]

Biological functions of RPE cells include phagocytosis of rod outer segments (ROS) and recycling of visual cycle products. Genetic mutations that affect the normal phagocytosis and visual cycle functions of the RPE cells result in significant deficiencies, underscoring their importance maintaining retinal homeostasis.[12] In particular, mutations in RPE Mer tyrosine kinase (MertK) and ATP-binding cassettes A4 (ABCA4) induce AMD-like retinal degeneration. The MertK mutation interferes with Mer receptor mediated phagocytosis in RPE cells and causes retinitis pigmentosa, another degenerative disease of the retina in human.[5] Mutation of lipid visual cycle transporter—ABCA4 in the eye increases a toxic byproduct of the visual cycle, A2E, a component in lipofuscin, and results in early onset macular degeneration in children.[1] Both of these mutations lead to the loss or dysfunction of RPE cells and consequently in the accumulation of lipofuscin, the formation of drusen, and loss of overlying photoreceptors.[9,11,6] Therefore, overcoming RPE deficiencies could have a significant impact on photoreceptor function.

Animal models of AMD-GA presenting all clinical and histological signs of the human disease are lacking. Nevertheless, several key elements of AMD-GA pathogenesis can be identified in the Royal College of Surgeons (RCS) rat model, such as phagocytosis and visual cycle lipid metabolism. The RCS rat carries the MertK mutation resulting in diminished phagocytosis of ROS and leading to photoreceptor cell death.[14] The RPE cells from dystrophic RCS rats showed reduced phagocytosis in vitro. Furthermore, deterioration of the visual cycle associated with disease progression was identified by gene profiling in dystrophic RCS rats. The visual cycle transporter (ABCA4) was down-regulated with disease progression over time, potentially leading to an accumulation of A2E. This is supported by the finding that A2PE, a precursor of A2E, is increased in the RCS retina.[11] Therefore, the RCS rat RPE cells have functional deficits in phagocytosis and visual cycle functions, which are similar to deficiencies that may lead to AMD-GA in humans. Finally, RCS rats exhibit early changes in synaptic connectivity that lead to mislocalization and loss of synapses.[2]

Data from preclinical studies with CNTO 2476 support the hypothesis that CNTO 2476 can improve the phagocytic function of dystrophic RCS RPE cells. In vitro, CNTO 2476 restored dystrophic RPE phagocytosis function to the level of normal RPE cells (SCIV-DR14). In vivo, subretinal injections of CNTO 2476 into dystrophic RCS rats led to preservation of visual function and photoreceptors (SCIV-DR1, SCIV-DR2). Moreover, the presence of CNTO 2476 resulted in an increase of phagosomes in the RPE and a reduced layer of debris between the photoreceptor and RPE (SCO-TD-2009-0035). This increase in phagocytosis may lead to a reduction of photoreceptor apoptosis. Additionally, in vitro studies utilizing a purified rat retinal ganglion cell (RGC) culture system, further confirmed CNTO 2476 secrete factors that enhanced neuronal survival, supported neurite outgrowth and strongly promoted excitatory synaptic connectivity (SCO-DR-2015-0001). In addition, CNTO 2476 also promoted survival reduced apoptosis of RPE cells exposed to oxidative stress (SCO-DR-2009-0004 and SCO-DR-2015-0002). Finally, subretinal injections of CNTO 2476 to the RCS rat also preserved the gene expression of ABCA4, a visual cycle transporter (SCO-DR-2009-0005).

For the most comprehensive nonclinical and clinical information regarding CNTO 2476, refer to the latest version of the Investigator's Brochure for CNTO 2476.[7]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Nonclinical Studies

1.1.1.1. Mechanism of Action

Mechanism of action studies indicated that CNTO 2476 can affect phagocytic function of dystrophic RCS retinal pigment epithelial (RPE) cells, both in vitro and in vivo. Additionally, studies performed in human RPE cells demonstrated hUTC promoted survival and reduced apoptosis of RPE cells exposed to oxidative stress. Finally, in vitro studies utilizing a purified rat retinal ganglion cell (RGC) culture system further confirmed CNTO 2476 secrete factors that enhanced neuronal survival, supported neurite outgrowth and strongly promoted excitatory synaptic connectivity. Together, these data suggest that CNTO 2476 can potentially improve vision by enhancing the phagocytic function of dysfunctional RPE cells, promoting RPE survival and enhancing neuronal survival and function.

1.1.1.2. Pharmacokinetic Profile

The disposition of hUTC were characterized with respect to persistence and systemic biodistribution in xenogeneic settings. These studies have indicated that following subretinal administration, hUTC persist for approximately 2 to 3 months. In non-target organs in RCS rats treated with immunosuppressants, human cell equivalents were detected by polymerase chain reaction in the peripheral blood, kidney, liver, and testis up to 14 days following subretinal administration of hUTC. However, in a study conducted in nude rats designed to evaluate systemic distribution of hUTC to the ovaries, testes, and seminal fluid, no human cells could be detected. Taken together, these results indicate that following subretinal administration,

umbilical tissue-derived cells do not engraft and that in contrast to subretinal persistence, systemic exposure is limited over time for CNTO 2476.

1.1.1.3. Immunogenicity

The in vivo immunogenicity of umbilical tissue-derived cells was characterized following subretinal administration to pigs. No antibodies to pUTC or cellular immune responses were observed in the allogeneic setting following single or repeated subretinal administration of pUTC to pigs. In the xenogeneic setting, following single or repeated subretinal administration of hUTC to pigs, antibodies to hUTC developed when surgical methods used for cell administration caused an intentional or inadvertent retinal perforation. No antibody responses were observed when targeted subretinal delivery of hUTC was achieved without retinal perforation. Following repeated subretinal delivery, focal mononuclear cell infiltrates and subretinal granulomas were observed at the cell administration site. In all animals with subretinal granulomas antibodies to hUTC were detected consistent with the premise that they were a manifestion of a xenogeneic immune response intended to wall off foreign antigens that were too large to phagocytose. This finding was monitorable by spectral domain optical coherence tomography (SD-OCT), which revealed resolution into small focal areas of fibrosis over time suggesting the finding was reversible.

1.1.1.4. Toxicology

The toxicology program was conducted in rats and mini-pigs. No tumorigenicity of CNTO 2476 was observed in nude rats following subretinal administration at a maximum feasible dose which corresponded to approximately a 5-fold multiple of an efficacious dose in the RCS rat model. No systemic toxicity of CNTO 2476 was observed in rats following a single intravenous dose of up to 1.5×10^6 cells (corresponding to approximately a 5-fold multiple of an efficacious dose in the RCS rat model) when intravenous injection rates were limited to approximately 1×10^6 cells/minute.

Toxicology studies conducted in the Göttingen mini-pigs allowed development and evaluation of surgical techniques based on the similar size and anatomy of the pig eye relative to human eyes. Both CNTO 2476 and pUTC were employed to characterize safety following single and repeated dosing in the xenogeneic and allogeneic setting. No evidence of systemic toxicity was observed in these studies. Vitreoretinal reaction characterized by traction, tractional retinal detachments and formation of membranes were identified as the major adverse effects in these pig toxicology studies following subretinal administration of cells using the initial surgical procedure. This procedure was used in the initial pig toxicology studies, and clinical Study CNTO2476RPG1001 employed full or partial 3-port pars plana vitrectomy, retinotomy, and creation of bleb to provide a subretinal space for subretinal injection of cells. A new surgical procedure was subsequently developed that used a microcatheter to achieve targeted subretinal delivery of cells that mitigated vitreoretinal adverse effects observed in nonclinical studies with the initial surgical procedure. Based on these preclinical observations, the microcatheter delivery method was implemented in clinical Study CNTO2476RPG1002. Following a single subretinal injection of CNTO 2476 in pigs the no-observed-adverse-effect level (NOAEL) was considered to be 3×10^5 cells and 1.5×10^6 cells using the initial surgical procedure and microcatheter procedure, respectively.

Following repeated subretinal administration 6 x 10^4 and 1.5 x 10^6 cells were considered the NOAELs following repeated subretinal dosing with a microcatheter for CNTO 2476 and pUTC, respectively based on the observation of subretinal granulomas.

1.1.2. Clinical Studies

Study CNTO2476RPG1001 was a Phase 1 open-label, noncomparative study to evaluate the safety of a single, unilateral, subretinal administration of CNTO 2476 (using a transvitreal approach) in subjects with advanced retinitis pigmentosa. Seven subjects were enrolled in the study and completed 5-year follow-up. Study CNTO2476MDG1002 is a Phase 1/2a, multicenter, randomized, dose escalation, fellow-eye controlled study to evaluate the safety and clinical response of a single, subretinal administration of CNTO 2476 in subjects with visual acuity impairment associated with geographic atrophy (GA) secondary to AMD. In September 2014, enrollment in this study was discontinued but long-term follow-up is ongoing. Per the interim report, dated 22 January 2015, 35 subjects enrolled in the study; 33 were evaluable for efficacy and safety. Among the 33 subjects, 29 were in the Phase 1 portion of the study and 4 were in the Phase 2a portion of the study.

1.1.2.1. Human Pharmacokinetics

No data on pharmacology, pharmacokinetics, and metabolism of CNTO 2476 in humans are available.

1.1.2.2. Efficacy

Although Study CNTO2476RPG1001 was not designed as an efficacy study, secondary objectives included preliminary evaluations of changes from baseline in retinal structure and visual function. Overall, changes from baseline in visual acuity and retinal thickness were mixed. At the Month 3 visit, 3 subjects had measurable increases in retinal thickness in the treated eye, 3 subjects had decreases in retinal thickness, and 1 subject had no change from baseline values. The data were insufficient to make any meaningful conclusions. No durable changes in visual acuity were evident and data were variable. At 12 months post-treatment, no subject had any worsening of visual acuity. At the end of the study (Month 60), 3 subjects reported lower visual acuity (ie, no light perception or a shift from hand motion to light perception) at Month 12.

Study CNTO2476MDG1002, as described above, is currently ongoing and the efficacy results reflect combined data from both the Phase 1 and 2a portions of the study. At baseline, the median best corrected visual acuity (BCVA) for the 33 treated subjects was log of the minimum angle of resolution (logMAR) 1.2 (20/320) and logMAR 0.6 (20/80) in the treated eye and fellow eye, respectively. At 12 months post-treatment, median BCVA for 26 subjects was logMAR 1.1 (20/250) and logMAR0.6 (20/80) in the treated eye and fellow eye, respectively, suggesting an improvement in BCVA in the treated eye compared with no change in the fellow eye. The mean change from baseline was 5 letters between fellow and treated eye at 6 months and 6.8 letters at 12 months.

BCVA gains and losses at 6 and 12 months post-treatment were as follows:

- At the 6-month assessment of BCVA gain, 10 subjects out of 27 (37%) had their treated eyes showing a ≥3-line gain in BCVA. At the same time, 1 subject out of 27 (4%) had their fellow eyes showing a ≥3-line gain in BCVA.
- At the 6-month assessment of BCVA loss, 6 subjects out of 27 (22%) had their treated eyes showing a ≥3-line loss in BCVA. At the same time, 1 subject out of 27 (4%) had the fellow eye showing a ≥3-line loss in BCVA.
- At the 12-month assessment of BCVA gain, 10 subjects out of 26 (39%) had their treated eyes showing a ≥3-line gain in BCVA. At the same time, 1 subject out of 26 (4%) had their fellow eyes showing a ≥3-line gain in BCVA.
- At the 12-month assessment of BCVA loss, 6 subjects out of 26 (23%) had their treated eyes showing a ≥3-line loss in BCVA. At the same time, 3 subjects out of 26 (12%) had their fellow eyes showing a ≥3-line loss in BCVA.

Recognizing the study was designed for safety, interim efficacy data suggest that subretinal administration of CNTO 2476 may result in BCVA letter gain in some subjects with vision loss secondary to GA.

1.1.2.3. Safety

Study CNTO2476RPG1001

This was a Phase 1 open-label, noncomparative study to evaluate the safety of a single, unilateral, subretinal administration of CNTO 2476 in 7 subjects with advanced retinitis pigmentosa.

Adverse events (AEs) observed during the study were consistent with the postoperative course for the surgical procedure.

- There were no adverse clinical observations suggesting an immune response in the treated eye. These observations suggest that a single, subretinal injection of CNTO 2476 was not immunogenic and did not cause an adverse immune response through 60 months after treatment.
- Two subjects who received the targeted doses of 3.0×10^5 or 5.6×10^5 CNTO 2476 cells had serious AEs (SAEs) of retinal detachment. In these cases, the mechanism of retinal detachment was traction due to proliferation of RPE cells in the vitreous after retinotomy. This suggests that transvitreal delivery of CNTO 2476 is not appropriate.

Ocular and visual assessments during the 4-year safety surveillance period remained similar to those noted at Month 12.

Study CNTO2476MDG1002

This was a Phase 1/2a study a to evaluate the safety and tolerability of CNTO 2476, administered subretinally using the iScience microcatheter delivery system (MDS), in subjects with visual

acuity impairment associated with GA secondary to AMD. The study was limited by the inability to deliver cells to the subretinal space without a retinal tear.

Thirty-three subjects received CNTO 2476 (29 subjects in the Phase 1 portion of the study and 4 subjects in the Phase 2a portion of the study) and were evaluable for safety. Of the 29 subjects treated in Phase 1, 28 (96.6%) had at least 1 treatment-emergent AE (TEAE). The most common TEAEs by preferred term were retinal tear (9 subjects, 31.0%), conjunctival haemorrhage (7 subjects, 24.1%), and hypertension (7 subjects, 24.1%). Of the 4 subjects treated in Phase 2a, 3 (75.0%) had at least 1 TEAE, the most common of which were conjunctival haemorrhage and retinal tear (reported for 3 subjects [75.0%] each). Most AEs were considered related to the surgical delivery procedure, or to various co-morbidities. Serious AEs reported for subjects from both the Phase 1 and 2a portions of the study combined are summarized in Table 3. The most commonly reported SAE was retinal detachment (5 of 33 subjects, 15.2%). The incidence of AEs and SAEs did not appear to be dose related.

Table 3: Study CNTO2476MDG1002: Number (%) of Subjects with 1 or More Treatment-emergent Serious Adverse Events by Preferred Term (Subjects Treated in Phases 1 and 2a Combined)

	6.0×10^4 cells	1.2×10^5 cells	3.0×10^5 cells	5.6×10^5 cells	Total
Subjects Treated	12	3	15	3	33
Subjects with 1 or more Treatment-emergent SAEs	6 (50.0%)	2 (66.7%)	3 (20.0%)	2 (66.7%)	13 (39.4%)
Preferred Term					
Appendicitis	1 (8.3%)	0	0	0	1 (3.0%)
Atrial Flutter	0	0	1 (6.7%)	0	1 (3.0%)
Chronic Obstructive Pulmonary Disease	1 (8.3%)	0	1 (6.7%)	0	2 (6.1%)
Device Dislocation	0	0	1 (6.7%)	0	1 (3.0%)
Grand Mal Convulsion	1 (8.3%)	0	0	0	1 (3.0%)
Intestinal Obstruction	1 (8.3%)	0	0	0	1 (3.0%)
Metastatic Squamous Cell Carcinoma	0	0	1 (6.7%)	0	1 (3.0%)
Nephrolithiasis	0	0	0	1 (33.3%)	1 (3.0%)
Osteoarthritis	1 (8.3%)	0	0	0	1 (3.0%)
Pneumonia	0	1 (33.3%)	0	0	1 (3.0%)
Pneumonia Aspiration	1 (8.3%)	0	0	0	1 (3.0%)
Retinal Detachment	2 (16.7%)	1 (33.3%)	1 (6.7%)	1 (33.3%)	5 (15.2%)
Retinopathy Proliferative	1 (8.3%)	0	0	1 (33.3%)	2 (6.1%)
Suicide Attempt	1 (8.3%)	0	0	0	1 (3.0%)
Thoracic Vertebral Fracture	0	1 (33.3%)	0	0	1 (3.0%)
Urinary Tract Infection	0	1 (33.3%)	0	0	1 (3.0%)
Urosepsis	0	1 (33.3%)	0	0	1 (3.0%)

Note: A treatment-emergent AE was defined as any event that started during or after the administration of study treatment. A subject experiencing the same AE multiple times is counted once within the corresponding preferred term. Percentages are based on the number of treated subjects.

There were no clinically significant changes in vital signs, physical examination, or clinical laboratory parameters.

Safety data available from this study suggest that CNTO 2476 is without substantial toxicity when subretinal administration occurs without a retinal break. However, the iScience MDS is not

suitable for further development, and an alternative approach to subretinal delivery will be required.

A single administration of CNTO 2476 did not appear to elicit an immune response. No relevant treatment group differences in shift changes were noted for positive antibody titers. There were no clinically meaningful changes in median values from baseline for antibody titers within the treatment groups. One subject appeared to have pre-existing antibody to CNTO 2476, and 1 subject had a de novo immunologic response to treatment with CNTO 2476. The presence of serum antibodies directed against CNTO 2476 was not associated with ocular adverse or inflammatory events.

There have been 3 deaths among the 33 treated subjects, 1 each of depression/suicide, cancer of the lung and chronic obstructive pulmonary disease/pneumonia. None was considered to be treatment related.

1.2. Overall Rationale for hUTC Development and Delivery System Innovation

Geographic atrophy related to AMD is the most common cause of blindness in the developed world among persons over age 60; in the United States (US) alone, approximately 8 million persons age 55 or older have intermediate or advanced AMD, and the prevalence of GA specifically in person over age 40 is 0.8%, or approximately 970,000 individuals.[10] The prevalence of AMD and GA is similar in other developed nations and will increase with the aging of the population. There are currently no approved therapies for the treatment of the dry form of AMD, including GA.

Human umbilical tissue cells are easily available without the need to obtain or manage differentiation of stem cells; they are fully differentiated and have low potential for uncontrolled proliferation or teratoma formation; and they are readily expanded in vitro. Potency and viability assays are available to ensure quality and consistency of scaled up manufacturing.

Both in vitro and in vivo data indicate that hUTCs have beneficial effects on RPE cells. As described above, hUTCs improve RPE phagocytic function in vitro and in vivo, with corresponding improvement in vision the RSC rat model. HUTCs also appear to modulate oxidative stress and neuroplasticity, factors which are disordered in GA.

Furthermore, Phase 1 human data suggest that subretinal delivery of CNTO 2476 improve vision by at least 15 letters in BCVA, as compared to a fellow-eye control, and this benefit appears to be maintained through Month 12. CNTO cells appear to be safe when delivered as intended. These findings strongly support the further development of the therapy.

The safe delivery of CNTO 2476 to the appropriate location is currently the most important factor in the development of this program, and delivery of viable cells in the subretinal space requires some type of surgical procedure. Experience in the clinic has shown that leakage or reflux of cells into the vitreous may lead to proliferation of cells with membrane formation with to traction and retinal detachment. Thus, delivery of CNTO 2476 to the subretinal space without a break to the retina is of paramount importance. In the Phase 1 study, the iScience microcatheter

delivery system was used with an *ab externo* surgical approach. That approach was found to be challenging, requiring 2 operators, and resulting in an unacceptable rate of retinal tears and retinal detachments. That surgical approach is inadequate for further development.

Given the limitations of the iScience MDS, a newly developed Delivery System will be utilized in this Phase 2b study. The Delivery System was developed to facilitate delivery of CNTO 2476 cells to the targeted perimacular subretinal delivery site via a suprachoroidal approach. The suprachoroidal surgical procedure was selected and the new Delivery System was developed with the goal of improving the delivery device and procedure usability and facilitating the safe targeted delivery of CNTO 2476.

The Delivery System is being developed in accordance with 21 Code of Federal Regulations (CFR) Part 4, Current Good Manufacturing Practice regulations for Combination Products, including 21 CFR Part 820.30, Medical Device Design Controls. Verification and validation testing for the device portion of the combination product will be performed prior to this clinical study to demonstrate that the devices perform safely according to the intended use of infusing cells.

The Delivery System is investigational in this clinical study for the intended use of delivery of CNTO 2476 cells. This is a first-in-human clinical use of an innovative Delivery System. As such, the proposed Phase 2b study will employ a Safety Run-in Phase as a Delivery System pilot study, prior to randomization of subjects into the controlled Double-masked Treatment Phase of the study.

1.3. The Cell Delivery System

The Delivery System is investigational for the intended use of delivering CNTO 2476 cells in this study. The Delivery System was developed to facilitate delivery of CNTO 2476 cells to the targeted perimacular subretinal delivery site via a suprachoroidal approach. The devices that comprise the Delivery System are described in the Investigational Product Manual.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objectives

The primary objective of the open-label Safety Phase is to evaluate the safety and performance profile of the suprachoroidal surgical approach and the Delivery System.

Major Secondary Objectives

The major secondary objectives of this study are the following:

- to assess the safety and performance profile of the Delivery System, the safety and tolerability of the suprachoroidal surgical approach, and the safety and tolerability of CNTO 2476 cells in the open-label Safety Run-in Phase.
- to assess the effects of CNTO 2476 on anatomic correlates of treatment, including change in the area of GA

- to assess the effects of CNTO 2476 on additional and alternative efficacy outcomes including duration of clinical response.

2.2. Hypothesis

The primary hypothesis of the open label safety phase of this study is that the novel subretinal delivery system is sufficiently safe and usable to deliver cells to the subretinal space. An additional hypothesis is that palucorcel is safe and well tolerated when delivered as a single dose to the subretinal space.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter Phase 2b study. A target of approximately 21 subjects will be enrolled in this study. This protocol amendment represents a significant reduction in scope and duration of the study based on the sponsor's decision to discontinue the palucorcel development program.

The study includes only an initial open-label safety phase.

The target population will be subjects at least 55 years of age and no older than 90 years with a confirmed diagnosis of bilateral GA of the macula secondary to age-related macular degeneration, with associated vision loss, confirmed within 45 days prior to initial randomization by the central reading center using fundus and/or autofluorescence photography. In subjects with neovascular AMD in 1 eye, the eye with GA must be the worse eye. In subjects with bilateral GA and the vision between both eyes is not clinically equal, the eye with the worse vision will be treated in order to minimize risk to the subject's vision. In cases where the BCVA of the 2 eyes is clinically equal, the eye with the larger GA as demonstrated on the imaging studies will become the study eye.

The Safety Run-in Phase consists of approximately 21 subjects (the first 3 subjects at each of approximately 8 sites) who will first be enrolled in an open-label assessment of the safety profile of the procedure and the Delivery System. The first 3 subjects at the first 8 sites (approximately 21 subjects in total) will be the initial Safety Cohort. A minimum of seven different surgeons are required to ensure most of the possible failure modes will be identified.[16] Enrollment will be actively managed to ensure that experience and learning from earlier procedures are promptly transferred to the subsequent procedures, and to ensure that an appropriate number of subjects are enrolled at the time of the planned safety assessments.

The safety profile of the procedure and the Delivery System will be assessed after the first 21 subjects (the initial Safety Cohort) have been treated and followed for a minimum period of 1 month. An external Data and Safety Monitoring Board (DSMB) will be commissioned for this study. The 2nd Safety Cohort and the double blind portion of this study have been eliminated from this study protocol.

The study will consist of a 12-month acute phase, followed by a 2-year maximum duration follow-up period (3 years total) for all subjects.

Screening Phase

All subjects will be required to give a written informed consent to participate in the trial. In a separate consent, subjects will have the option of providing a DNA sample for genotyping. Subjects may also have the option of donating their eyes for histological evaluation post mortem, using a supplemental informed consent.

Subjects may be screened over a period of up to 45 days prior to treatment to assess their eligibility for the study based on the inclusion and exclusion criteria defined for this study. Patient eligibility will be determined based on the results of 2 BCVA examinations performed at the screening visits. These examinations can occur on the same day or subsequent days. The better of the 2 logMAR BCVA scores will be used for eligibility and randomization. These examinations should be performed prior to any other ocular study procedures that would interfere with vision assessments such as dilation or bright light assessments.

Visual acuity tests, contrast sensitivity, MN Read, intraocular pressure (IOP), slit lamp examinations, microperimetry, fundus photography, SD-OCT, fundus autofluorescence, fluorescein angiography and dilated fundus examination readings will be carried out on all subjects. At baseline, axial length will be recorded in the CRF. Indocyanin green angiography will be performed on all subjects unless discussed with the Sponsor.

Other assessments will include medical history, genomic material from consented subjects, demographics, a targeted physical examination, vital signs, routine laboratory and routine urinalysis In addition blood samples for immunogenicity, medication history, concomitant medications, and the NEI-VFQ-25 and the Near Vision subscale, and the SF-36 and FRI, will be collected.

Additional details of the screening phase are provided in Section 9.1.1.1 (Screening Phase).

Open-label Safety Run-in Phase

A minimum of the first 3 eligible subjects at each center will receive active treatment in an uncontrolled, open-label Safety Run-in Phase to assess the safety of the surgical procedure and Delivery System, and to ensure the familiarity of the surgeons with the Delivery System and the procedure. The first 21 subjects from the designated Safety Cohort study sites will comprise the initial Safety Cohort. Enrollment into the safety Run-in Phase will be staggered across sites to ensure that the outcomes and learnings from earlier procedures can be transferred to all participating surgeons who will perform subsequent procedures. A 1-week interval for information sharing between the first few subjects is appropriate since most procedure-related AEs are expected to be apparent within hours of surgery.

Long-term Follow-Up Phase

After the 12-month acute phase of the study, subjects will be followed every 6 months for 2 years in the Long-term Follow-up Phase of the study, as shown in the Time and Events Schedule (see Table 2).

A DSMB will be established to monitor study data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. Refer to Section 11.6, Data and Safety Monitoring Board, for details. The committee will meet periodically to review interim study data. After the review, the DSMB will make recommendations regarding the safety and continuation of the study. The details will be provided in a separate DSMB charter.

3.2. Study Design Rationale

This protocol amendment represents a significant reduction in the scope and duration of the planned trial, based on the sponsor's decision to discontinue the palucorcel development program. The intent of the current study design is to ensure adequate long-term safety follow-up of the subjects previously enrolled, while minimizing the visit burden on subjects and investigators.

The target population for this study is adult subjects (at least 55 years of age and no older than 90 years) with GA of the retina secondary to age related macular degeneration, with a baseline visual acuity of approximately logMAR 0.6 (20/80) to logMAR 1.6 (20/800). The best visual acuity of logMAR 0.6 (20/80) was selected because in this range, vision is compromised to a degree that restricts certain activities of daily living, and the potential benefit to the subjects justifies risks associated with the procedure and treatment.

A critical requirement of the program is the ability to deliver viable cells safely and efficiently to the subretinal space, without damaging the retina, and without leakage of cells into the vitreous. Currently, there is no alternative to surgical delivery. Previous studies using a transvitreal approach or an ab externo surgical approach have led to an unacceptable rate of retinal tears and detachments. The new suprachoroidal surgical procedure was selected and the new Delivery System designed with the goal of simplifying the procedure and facilitating the safe targeted delivery of CNTO 2476.

The use of the Delivery System in the Safety Cohort is a first-in-man study and AEs and device quality will be assessed by an independent DSMB after the first 21 subjects have been treated (or sooner, if a stopping threshold is reached).

Dose Selection

The breadth of the dose range is constrained by the cell density during cryopreservation and the minimal volumes that can be accurately administered to minimize the detachment at the subretinal injection site; the feasible doses were all studied in the Phase 1/2a study. The greatest experience to date is with the 3.0×10^5 cell dose (15 subjects). Although that dose was administered in a 27 µL volume in the prior study, there is no reason to believe that the volume

of administration is relevant to either safety or efficacy; the AE profile for this dose/volume combination is comparable to a smaller dose (6.0 x 10^4 cells) given in a 50 µL volume.

3.2.1. Control

The open-label phase of this study does not require a control group.

3.2.2. Masking

The open-label phase of this study does not require masking.

3.2.3. Randomization

The open-label phase of this study does not require randomization.

3.2.4. Primary Outcome Measure

Change in BCVA is considered meaningful to patients and has been accepted by the US Food and Drug Administration (FDA) as an approvable endpoint in trials of therapeutic agents for AMD. In addition, BCVA reflects holistically both the potential benefits (gain in visual acuity from therapy) and harms (loss of visual acuity due to AEs). Assessment of BCVA is known to be partly effort-dependent, and every effort will be made to standardize these assessments. The Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 meters is considered the 'gold standard' for visual acuity testing in clinical research for its physical and statistical properties.

4. SUBJECT POPULATION

Approximately 100 subjects will be screened to enroll approximately 21 subjects in the open-label safety phase of this study.

Screening for eligible subjects will be performed within 45 days before administration of the treatment.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Subject must be a man or woman at least 55 years to 90 years of age, inclusive.

2.2 Diagnosis of GA secondary to AMD confirmed within 45 days prior to initial randomization. Diagnosis verified by the central reading center using fundus photographs and including the following;

- The study eyes must have at least 1 GA lesion that involves the fovea, and a Macular Photocoagulation Study (MPS) disc areas (DA) of ≥0.5 and ≤7 (1 MPS disc area equivalent to 2.54 mm^2 on the retina) determined by screening images of fundus autofluorescence photographs as calculated by the reading center. If GA is multifocal, at least 1 lesion must be ≥0.5 DA.
    - In the Safety Run-in Phase only, DA of ≥0.5 with no maximum specified area, as long as the criteria below for photography can be met and the surgeon determines that the GA size will not impede cell delivery.
- Geographic atrophy must be able to be photographed in its entirety and may be contiguous with peripapillary atrophy.
- Retinal photographs, fundus autofluorescence images, and angiography of sufficient quality, allowing assessment of the macular area according to standard clinical practice, can be obtained.
- The imaging center must be able to delineate and confirm peripapillary atrophy with fundus photography and fundus autofluorescence.
- Images must include the central field 1, 2, and 3 field images as defined by the University of Wisconsin standards as well as a supero-temporal image to capture the subretinal injection area if possible.

3.2 Study eyes will have a BCVA of 20/80 to 20/800 (ETDRS logMAR value 0.6-1.6). The treatment eye will be that with the worse BCVA at screening. If BCVA is clinically equivalent, the eye with the larger GA determines the study eye.

4. Subject is a suitable candidate for ophthalmologic surgery, is willing and able to comply with the surgical procedure, scheduled visits, treatment plan, laboratory tests and other study procedures. Subject has met criteria of the surgery center anti-coagulation protocol, if applicable.

5. Female subjects must be post-menopausal with last menses 12 months prior, or longer, OR a measured follicle stimulating hormone ≥26 mIU/mL.

6. Male subjects must be sterile or willing to use 2 approved methods of contraception from first day post-operatively to 3 months post-operatively (approved methods of contraception include condom with spermicide, a sterile sexual partner, a sexual partner using oral or implantable contraceptive or an intrauterine device with spermicide, a diaphragm with spermicide, or cervical cap with spermicide).

7. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1.2 Subject has a history of neovascular ("wet") AMD in the treatment eye, including any evidence of retinal pigment epithelium rips or evidence of subretinal or choroidal neovascularization or fluid. In cases where imaging is inconclusive, review of the case with the study site, considering history and imaging will determine eligibility. History or evidence of neovascular AMD in the fellow eye is allowed, if anti-vascular endothelial growth factor (VEGF) therapy has not been required for at least 8 weeks prior to screening.

2. Geographic atrophy secondary to any causes other than AMD in either eye

3 A diagnosis of glaucoma with an IOP ≥25 mmHg while being treated with an ocular hypotensive drug. Treatment should be no more than 1 drug preparation/combination, which can contain 1 or 2 ocular hypotensive active ingredients; subjects receiving more than 2 ocular hypotensive active ingredients are excluded. Note: subjects with a diagnosis of ocular hypertension (not glaucoma) are eligible to participate whether or not they are being medically treated.

4. Nuclear sclerotic cataract, cortical spoking, posterior subcapsular cataract above Grade 2 per Age-Related Eye Disease Study (AREDS) scale or any other ophthalmologic condition that reduces the clarity of the media that, in the opinion of the investigator or reading center, interferes with ophthalmologic examination (eg, corneal abnormalities, inadequate pupillary dilation), surgery or imaging in the study eye

5. Myopia >-8 diopters and subjects with >4 diopters of astigmatism, and >+10 diopters of hyperopia. Note: clinical evidence of retinal degeneration secondary to pathological myopia will exclude the subject as will a scleral ectasia with or without high myopia.

6. Evidence of other significant ophthalmologic disease (eg, glaucoma, intraocular inflammatory disease, diabetic retinopathy, Stage II, III, or IV macular hole, clinically evident vitreoretinal traction, choroidal or retinovascular disease, cystoid macular edema, significant epiretinal membrane, significant blepharitis, keratitis, conjunctivitis, or staphyloma) in the study eye

7.2 Previous treatment for confirmed AMD (dry or wet) in the study eye with treatments *other than* antioxidant or zinc supplements (eg, AREDS1 or AREDS2 formula) or other oral vitamin supplements. Subjects who have received anti-VEGF treatment without a confirmed diagnosis of wet AMD or who have participated in previous studies for AMD may be considered eligible if these treatments/study participation were given at least one year prior to enrollment.

8.2 Previous intraocular surgery within 3 months prior to screening in either eye. Previous treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy in the study eye at any previous time point.

9. Previous laser photocoagulation in the study eye (peripheral laser for treatment of a tear is allowed if more than 6 months prior to screening except when, in the opinion of the surgeon, this would hamper the suprachoroidal cannulation procedure in the study eye)

10. Previous vitrectomy, retinal detachment repair, submacular surgery, other surgical interventions targeting AMD, scleral buckling or glaucoma filtration surgery or any other extraocular or orbital procedure in the study eye that, in the opinion of the surgeon, would hamper the suprachoroidal cannulation procedure in the study eye

11. History of choroidal or scleral rupture in either study or fellow eye due to uveitis (previous trauma in the study eye or fellow eye in the case of good vision in that eye is not an exclusion criterion)

12. Uveitis or other intraocular inflammatory disease within past 3 months

13 Active infections of the anterior segment

14. Keratoconus, penetrating keratoplasty, Descemet's stripping endothelial keratoplasty (DSEK), radial keratotomy (RK), Laser-assisted in situ keratomileusis (LASIK) in the study eye

15. Monocular subjects

16. Subject has known allergies, hypersensitivity, or intolerance to CNTO 2476 or its excipients (refer to Investigator's Brochure)

17. Medically not qualified for monitored anesthesia care intravenous sedation

18. Previous cell therapy other than standard blood and platelet transfusions

19. Subject has taken any disallowed therapies as noted in Section 8, (Prestudy and Concomitant Therapy) before the planned first dose of treatment

20.1 Subject has received an investigational drug (including investigational vaccines) within 30 days before the planned first dose of treatment

21. Active malignancy (requiring therapy) or history of malignancy requiring therapy within 2 years prior to Day 1 (with exception of cases of basal cell and squamous cell carcinoma of the skin)

22. History of human immunodeficiency virus (HIV) disease

23. Significant cognitive impairment that interferes with a subject's ability to participate with the testing regimen

24. History of organ or bone marrow transplants

25. History of alcohol or drug abuse within past 2 years

26. Significant hepatic dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >3x upper limit of normal [ULN]), or significant renal dysfunction (estimated creatinine clearance ≤30 mL/min), or on renal dialysis

27. Significant uncorrectable coagulopathy, thrombocytopenia (platelets <100 x 10^3/µL) or other significant bleeding risk. Note: subjects on an anticoagulant therapy should be considered at low risk for new thromboembolic events, and must agree to stop all anticoagulation therapy prior to surgery, as follows:

    - Warfarin ≥5 days
    - Aspirin ≥7 days
    - Oral Factor Xa inhibitors ≥3 days (or longer, depending on renal function)
    - Dabagatran ≥3 days
    - Low molecular weight heparin ≥1 day
    - Clopidogrel and ticagrelor ≥5 days
    - Prasugrel ≥7 days
    - Ticlopidine ≥10 days

28 Uncontrolled systemic hypertension on the day of surgery, defined as a systolic blood pressure ≥180 mm Hg. Note: if the subject's systolic blood pressure can be controlled later by the subject's medical doctor, eligibility for surgery can be re-assessed.

29. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

30. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator

31. Known allergy to iodinated contrast dyes

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of treatment is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

a. A man who is sexually active with a woman of childbearing potential must use a double-barrier method of birth control (ie, male condom, female diaphragm or cervical cap, or condom) and all men must also not donate sperm for 3 months after receiving the last dose of study drug.

b. Subjects must agree to defer blood, blood component, or tissue donation until 12 months post treatment

5. TREATMENT ALLOCATION AND MASKING

Treatment Allocation

All subjects in the Safety Cohort will receive the same dose of 3.0 x 10^5 cells in 50 µL.

Masking

Masking is not applicable to the open-label safety phase of this study.

6. DOSAGE AND ADMINISTRATION

6.1. Open-label Safety Run-in Phase

Subjects in the Safety Run-in Phase will receive 3.0 x 10^5 cells in 50 µL dosing volume. CNTO 2476 will be delivered using the custom-designed Delivery System and surgical procedure.

Each subject in the Safety Run-in Phase will receive a single subretinal administration of CNTO 2476. A high-level overview of the procedure for administering the single dose of CNTO 2476 in 1 eye is described below:

- An eyelid speculum will be placed and a chandelier is inserted targeting illumination of the superiotemporal quadrant
- A trap-door conjunctival incision will be made in the superiotemporal quadrant to expose the sclera
- With aid of measuring template, a “suture loop” will be created between the limbus and the sclerotomy site
- A sclerotomy incision will be created approximately 3mm in length
- The cannula will be inserted through the suture loops, through the sclerotomy, and 5 mm into the suprachoroidal space

- The retina will be visualized through the pupil and the cannula is advanced to the target location superior to the macula
- Under direct visualization of the cannula tip, the needle will be advanced and a small saline entry bleb is created
- When successful subretinal entry has been established, the surgeon will administer 50 µL of CNTO 2476 cells subretinally
- The needle will be withdrawn, and the cannula removed from the suprachoroidal space
- The suture loops are removed and the sclera and conjunctiva will be closed

A detailed description of the surgical procedure will be available and updated as a part of the physician training materials.

7. TREATMENT COMPLIANCE

The investigational product will be administered subretinally as a single dose by the retinal surgeon. The administration of the investigational product will take place in an operating room using the Delivery System. Compliance will not require any activity by the subject.

8. PRESTUDY AND CONCOMITANT THERAPY

All pre-study therapies administered up to 30 days before first dose of treatment must be recorded at screening.

Peri-operative (subconjuntival vancomycin) and post-operative (PRED FORTE® and Polytrim®) or equivalent medication regimens are required in order to have standardization in treatments across sites.

Systemic concomitant therapies must be recorded throughout the study beginning with start of treatment to 1 year after the last dose of treatment. Systemic therapies for eye disease or any concomitant therapies given by ophthalmic routes must be recorded for the entire 3 years. Concomitant therapies associated with an SAE should also be recorded for the entire 3 years.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements different from the study drug) must be recorded in the eCRF.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Prohibited Concomitant Medications

The following are prohibited in the 30 days prior to dosing, and discouraged thereafter:

- Hydroxychloroquine (unless taking less than 6.5 mg/kg/day)
- Chloroquine (unless taking less than 3 mg/kg/day)
- Thioridazine
- Chlorpromazine

- Tamoxifen,
- Isotretinoin
- Clofazimine
- Cisplatin
- Carmustine
- Systemic corticosteroids ≥20mg/day prednisone (or equivalent) for > 14 days.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULES is a summary of the frequency and timing of efficacy, immunogenicity, pharmacogenomic, PROs, and safety measurements applicable to the study.

The Time and Events Schedule lists the day associated with each visit until Day 15, and then the month associated with each visit through Month 12, and Month 18 through Month 36 of the long-term follow-up phase. From Day 7 through Month 6 a visit window of ±3 business days will be allowed; for the Month 12 visit, a visit window of ±7 days will be allowed. From Month 18 through Month 36 a visit window of ±2 weeks (14 days) will be allowed. The data on the visit should always be calculated from the baseline visit, and not from the prior visit.

All visit-specific, PRO assessments should be performed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

The BCVA, low luminance BCVA (LL BCVA), and contrast sensitivity will all be performed using a validated testing protocol. BCVA is the best vision one can achieve with best correction ETDRS acuity testing, and is a done using a standard ETDRS chart for visual acuity testing.

The MN Read will be used to determine reading speed (RS, [measured in characters per minute]), critical print size (CPS, [measured in logMAR]), as well as RA (measured in logMAR).

Microperimetry will be performed using the MAIA2 system measuring the sensitivity in decibels.

New technology assessments, eg, Optical Coherence Tomography Angiography (OCT-A) and intraoperative Optical Coherence Tomography, may be performed at the surgeon or investigator's discretion but do not substitute for any of the mandatory evaluations listed in this protocol.

A standard full ophthalmology examination will be performed and will include IOP, slit lamp examinations, and dilated fundus examinations. The order of multiple ophthalmologic assessments within 1 protocol time point will be the same throughout the study.

The following imaging data will also be collected and analyzed by the Digital Angiography Reading Center (DARC):

- fundus photography
- SD-OCT
- fundus autofluorescence
- fluorescein angiography
- Indocyanin green angiography

The NEI-VFQ-25 and the Near Vision subscale, and the SF-36 contained in the appendices, will be used in the study to evaluate quality of life.

Blood may be drawn using a cannula or by other venipuncture. The exact times for each blood draw or assessment will be recorded. The total volume of blood to be collected from each subject is 107.4 mL. For each subject the amount of blood drawn is summarized in Table 4.

Table 4: Volume of Blood to be Collected From Each Subject

Time Point for Blood Collection	Amount of Blood Collected (mL)
Screening	16.3
DNA Collection	8.5
Day 7	10.0
Day 15	10.0
Week 4	16.3
Month 2	10.0
Month 3	10.0
Month 6	10.0
Month 12	16.3

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

A DSMB will be established to monitor study data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. Refer to Section 11.6, Data and Safety Monitoring Board for details. The committee will meet periodically to review interim study data. After the review, the DSMB will make recommendations regarding the safety and continuation of the study. The details will be provided in a separate DSMB charter.

9.1.1.1. Screening Phase

Prior to the full study screening phase, optional BCVA pre-screening may be done to evaluate subjects for BCVA eligibility. In this case, subjects must sign an optional pre-screening ICF prior to testing. The site will determine results of local testing and indicate if the subject is eligible for full study screening. If the BCVA test indicates the subject meets the necessary eligibility criteria, he or she will enter the full screening phase under the full study ICF for determination of full study eligibility.

All subjects will be required to give written informed consent to participate in the trial. In a separate consent, subjects will have the option of providing a DNA sample for genotyping. Subjects will also have the option of donating their eyes for histological evaluation post mortem, using a supplemental informed consent.

After giving written informed consent, subjects may be screened over a period of up to 45 days prior to treatment to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study. The screening process may occur over a period of days. If a subject fails screening for a reason determined to be temporary, they may be rescreened to determine eligibility by following these criteria:

- Elevated IOP, uncontrolled blood pressure, elevated liver enzymes , decreased platelets and decreased renal function, if correctable with treatment or time
- Acute infections, after successful treatment
- Time-bound restrictions (e.g., Exclusions 8, 9, 12, 20, 21 and 25) after an appropriate waiting period such that the exclusion no longer applies
- Use of prohibited prior medications, after an appropriate waiting period.

Potential patients who fail screening for visual acuity, retinal anatomy or other ocular findings should not be rescreened. Any rescreening request not mentioned here should be discussed with the study Medical Monitor. For rescreened subjects, imaging studies do not have to be repeated if performed in the 60 days prior to start of new screening. For rescreened subjects, clinical laboratory exams (bloodwork) do not have to be repeated if performed in the 45 days prior to start of the new screening.

Patient eligibility will be determined based on the results of 2 BCVA examinations performed at the screening visit. These examinations can occur on the same day or subsequent days. The better of the 2 logMAR BCVA scores will be used for eligibility and randomization. These examinations should be performed prior to any other ocular study procedures that would interfere with vision assessment such as dilation or bright light assessments.

Visual acuity tests, contrast sensitivity, MN Read, IOP, slit lamp examinations (including lens mobility examination), microperimetry, fundus photography, SD-OCT, fundus autofluorescence, fluorescein angiography and dilated fundus examination readings will be carried out on all subjects. At baseline, axial length will be recorded in the CSF. Indocyanin green angiography will be performed for all subjects unless discussed with the Sponsor.Medical history, genomic material from consented subjects, demographics, physical examination, vital signs, routine laboratory and routine urinalysis data will also be collected during the screening visit. In addition, blood samples for immunogenicity, medication history, and the NEI-VFQ-25 and Near Vision subscale, SF-36 and FRI, will be done during the screening visit. Changes in concomitant medications will be recorded on Day 1.

9.1.1.2. Open-label Safety Run-in Phase

The study will begin with a minimum of 7 surgeons performing approximately 3 open-label procedures to complete an initial Safety Cohort of 21 subjects. A minimum of 7 surgeons were chosen for the Safety Cohort based on the amount of users needed to identify complications with a surgical procedure and Delivery System. According to usability standards for medical devices, 5 to 8 surgeons performing 1 to 5 procedures at each site for a total of 21 procedures find between 75% and 90% of usability defects.[16]

After a total of 21 subjects are enrolled in the study, a safety review of the Delivery System and procedure will be performed. The data will be reviewed in a meeting with the surgeons, Principal Investigators, and the DSMB. The data will be assessed in the context of the predefined stopping rules described in the DSMB Charter. Events of special interest are choroidal hemorrhage, endophthalmitis or infections, retinal detachments, leakage of cells into the vitreous/need for vitrectomy, significant loss of vision defined as loss of ≥15 letters compared to baseline in the first month post-surgery, and failure to deliver cells/device failure.

9.1.1.3. End of Treatment or Early Withdrawal

Every attempt should be made to follow subjects through their final visit (Month 36). In the event that a subject prematurely discontinues from the study for any reason, an end-of-study visit should be completed (see Section 10.2 for criteria for treatment discontinuation). Assessments and procedures to be completed at the end-of-study visit are listed in the Time and Events Schedule (Table 2).

If a subject withdraws from the study due to an AE, every reasonable attempt will be made to follow the subject until the AE resolves or until the investigator, in conjunction with the sponsor, deems the AE to be chronic or stable. All SAEs will continue to be followed as instructed in Section 12.3.2.

9.1.1.4. Long-term Follow-up Phase

Subjects who complete the 12-month acute phase of the study will be followed every 6 months for 2 years in the Long-term Follow-up Phase, as indicated in the Time and Events Schedule (Table 2).

9.2. Efficacy

9.2.1. Evaluations

Subjects who successfully complete the screening visit will present to the clinical site on Day 1 (pre-operative visit on the treatment day), at which time CNTO 2476 will be administered. The Delivery System will also be assessed at this time. All study assessments are listed in the Time and Events Schedule (Table 1 and Table 2).

9.2.1.1. Primary Efficacy Measure

The primary efficacy measure will be the BCVA testing performed after refraction and under standardized photopic lighting conditions and distance using an ETDRS logMAR chart.

9.2.1.2. Secondary Efficacy Measures

The BCVA will be assessed at the 6- and 12-month visits to evaluate the major secondary endpoints described in Section 9.2.2.

An additional assessment of growth rate of GA lesion documented at baseline to 12 months will be performed. Lesion size will be determined by the DARC will also be performed.

9.2.2. Endpoints

Primary Endpoints

The endpoints of the open-label Safety Run-in Phase are all related to the objective of evaluating the safety profile of the procedure, Delivery System, and of the implanted hUTC cells.

Major Secondary Endpoints

- Proportion of subjects losing ≥15 BCVA letters from baseline at 12 months following treatment with CNTO 2476
- Change in mean number of BCVA letters from baseline at the 6- and 12-month visits following treatment with CNTO 2476
- Growth rate of GA lesion documented at baseline to 6 and 12 months following treatment with CNTO 2476. The area of GA is determined based primarily on fundus autofluorescence as well as fluorescein angiography and fundus photos

9.3. Immunogenicity

The evaluations, analytical procedures, and immunogenicity assessments done are described in the sections following. Additional instructions sample handling and disposition are provided in a separate laboratory manual.

9.3.1. Evaluations

Venous blood samples will be collected by the investigator site for immunogenicity assessment. The measurements will be taken at screening, Day 7 and 15, Week 4, Month 2, 3 6, and 12. This will allow dynamic monitoring of the serum antibody levels. Additional information on the blood volumes to be collected is provided in the Time and Events Schedule (Table 1).

Serum antibody levels pre- and post-administration of CNTO 2476 will be assessed by co-incubating subject serum samples and CNTO 2476. An antibody detection system will then be added and the bound serum antibodies are measured via flow cytometry. The titer of confirmed positive samples will be reported.

The serum will be separated at the investigator site laboratory and transferred to the appropriate storage vials supplied in the sample kit. The tubes will be stored at the prescribed temperature and shipped to the laboratory/storage of the Contract Research Organization (CRO), according to instructions. The CRO will send the samples to the laboratory assessing the serum antibodies on a monthly basis. The laboratory will assess the serum antibody levels and deliver the results to the CRO.

9.3.2. Analytical Procedures

Serum samples will be screened for the presence of antibodies binding to CNTO 2476. The detection and characterization of antibodies to CNTO 2476 will be performed using a validated assay method by or under the supervision of the sponsor. Other analyses may be performed to verify the stability of antibodies to CNTO 2476 and/or further characterize the immunogenicity of CNTO 2476.

All samples collected for detection of antibodies to CNTO 2476 will also be evaluated for CNTO 2476 serum concentration to enable interpretation of the antibody data.

9.3.3. Immunogenicity Assessments

Blood samples for determination of antibodies to CNTO 2476 will be collected from all subjects according to the Time and Events Schedule. Samples should also be collected at the final visit from subjects who are withdrawn from the study. Blood samples will only be collected during study assessments for the safety run-in phase and the randomized double-masked treatment phase from screening through the Month 12 postoperative visit.

9.4. Intraoperative Delivery System and Procedure Evaluations

The Delivery System is designed to access the suprachoroidal space and the subretinal space, and to deliver the cells subretinally.

In order to evaluate the safety of the Delivery System for the intended use of delivering CNTO 2476 cells, device-related safety information will be collected. Relevant ophthalmic AEs will be evaluated. In addition, specific device performance data will be collected.

9.5. Safety Evaluations

Details regarding the DSMB are provided in Section 11.6.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the valuations of safety and tolerability according to the time points provided in the Time and Events Schedule (Table 1 and Table 2) and as described in the following sections.

9.5.1. Adverse Events

Adverse events will be reported by the investigator or the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.5.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory (Covance Laboratories), and by the local laboratory (Catalent) for immunology assessments:

- Hematology Panel

  hemoglobin
  hematocrit
  red blood cell (RBC) count
  white blood cell (WBC) count with differential
  platelet count
  prothrombin time (PT)
  partial thromboplastin time (PTT)

- Serum Chemistry Panel

  sodium
  potassium
  chloride
  blood urea nitrogen
  creatinine
  glucose
  aspartate aminotransferase (AST)
  alanine aminotransferase (ALT)
  gamma-glutamyltransferase (GGT)
  total bilirubin
  alkaline phosphatase
  lactic acid dehydrogenase (LDH)
  uric acid
  calcium
  albumin
  total protein

- Urinalysis (Dipstick)

  specific gravity
  -glucose
  -blood
  -bilirubin
  -nitrite
  pH
  protein
  ketone
  urobilinogen
  leukocyte esterase

Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick.

Female subjects must be post-menopausal with last menses 12 months prior, or longer, OR a measured follicle stimulating hormone ≥26 mIU/mL.

Additional instructions relating to the clinical laboratory tests are provided in the laboratory manual.

9.5.3. Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure will be collected at the time points indicated in the Time and Events Schedule. Blood pressure and pulse rate measurements will be assessed sitting. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

9.5.4. Physical Examination

The study investigator, or other authorized and appropriately qualified designee, will perform a targeted physical examination at the time points listed in the Time and Events Schedule.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study or early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

A targeted physical examination will be done at screening and at the 12-monthly visit only.

9.6. Sample Collection and Handling

The actual dates and times of blood and urine sample collection must be recorded in the eCRF to the nearest minute, or in laboratory requisition form.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual. Collection, handling, storage, and shipment of samples must be according to specifications contained in the laboratory manual.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the 12-month acute phase of the study if he or she has completed assessments at Month 12. Subjects who prematurely withdraw for any reason before completion of the 12-month assessments will *not* be considered to have completed the study.

A subject will be considered to have completed the Long-Term Follow-up Phase of the study if he or she has completed assessments at Month 36 of the study.

10.2. Discontinuation/Withdrawal from the Study

A subject should be withdrawn from the study if the investigator believes that for safety reasons (eg, an AE) it is in the best interest of the subject to discontinue.

If a subject discontinues from the study before the end of the 12-month acute phase, or before the end of the Long-term Follow-up Phase, end-of-study assessments (Table 2) should be performed.

In addition, if a subject undergoes surgery but product is not administered, and the subject subsequently discontinues from the study, the subject will be followed for safety assessments.

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Subjects who withdraw will not be replaced. If a subject withdraws from the study, end-of-study assessments (Table 2) should be performed.

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. In general, all data will be tabulated and displayed using descriptive methods only; no formal statistical testing is planned for outcome in the Safety Cohort.

Analyses will be conducted for all subjects who receive treatment in the open-label Safety Run-in phase.

After the first 21 subjects participating in the open-label safety run-in phase have completed 1 month of follow-up (the initial Safety Cohort), an analysis of data will be performed. These analyses will consist of simple descriptive statistics for key safety and efficacy measures, which will be described in the statistical analysis plan (SAP).

11.1. Subject Information

For all subjects, descriptive statistics of the baseline and demographic information by treatment group will be provided.

Subject disposition will be summarized for subjects who received cell injection. The number of subjects who discontinued study participation early will be summarized by reason for discontinuation. A list of subjects who discontinued study participation early will also be provided. The number of subjects with left or right treated eye will be summarized.

11.2. Sample Size Determination

The sample size of 21 subjects is based on the number of subjects require to allow for an adequate clinical assessment of the safety and usability of the novel delivery system.

11.3. Efficacy Analyses

The BCVA, LL BCVA, LLD, contrast sensitivity and growth rate of GA lesion will be summarized with descriptive statistics as specified in the SAP.

11.4. Immunogenicity Analyses

The incidence of antibodies to CNTO 2476 will be summarized for all subjects who receive a dose of CNTO 2476 and have appropriate samples for detection of antibodies to CNTO 2476 (ie, subjects with at least 1 sample obtained after their first dose of CNTO 2476).

11.5. Safety Analyses

Safety analyses will be performed for all subjects who receive treatment in the open-label Safety Run-in phase.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset from the surgery start date and onwards (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis.

The number and percentage of subjects who experienced at least 1 treatment-emergent serious ocular AE will be presented in summary tables by treatment group and preferred term according to MedDRA terminology as well as by affected eyes (events occurring in the treated eye only, in the fellow eye only, and in both eyes).

Ocular TEAEs will be summarized by treatment group and preferred term according to MedDRA terminology, as well as by affected eyes (events occurring in the treated eye only, in the fellow eye only, and in both eyes).

The number and percentage of subjects who experienced at least 1 treatment-emergent SAE will be presented in summary tables by treatment group and preferred term, as well as by preferred term within system-organ class according to MedDRA terminology.

The number and percentage of subjects who experienced at least 1 TEAE will be presented in summary tables by treatment group and preferred term, as well as by preferred term within system-organ class according to MedDRA terminology.

The following lists of individual subject data will also be provided:

- list of subjects with SAEs;
- list of subjects with ocular AEs;
- list of subjects who died while on study (after administration of CNTO 2476 cells);
- list of subjects who discontinued the study due to an AE;
- list of subjects with TEAEs of severe intensity;
- list of subjects with TEAEs related to eye surgery, surgical delivery system, protocol-related procedure or CNTO 2476 cells;
- list of subjects with treatment-emergent infections.
- list of all AEs for subjects who have the surgical procedure but do not receive CNTO 2476 cells.

Surgical Evaluation

Data regarding the Delivery System and surgical procedure will be tabulated by treatment group.

A listing of all data pertaining to the Delivery System and surgical procedure, as well as any surgical deviations will be provided.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges will be used in the summary of laboratory data. Frequency tabulations of the laboratory results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges) by treatment group. Frequency tabulations of the abnormalities by treatment group will also be made. A listing of subjects with any laboratory results outside the reference ranges will be provided.

Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point by treatment group.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point by treatment group. The percentage of subjects with values outside standard reference ranges will be summarized by treatment group. A listing of subjects with any vital signs results outside the standard reference ranges will be provided.

11.6. Data and Safety Monitoring Board

A DSMB will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The DSMB will consist of at least 1 medical expert in the relevant therapeutic area, and at least 1 statistician. The committee will meet periodically to

review interim data. After the review, the DSMB will make recommendations regarding the continuation of the study.

The first formal safety review will take place when 1 month safety follow-up data are available for the 21 subjects in the initial Safety Cohort. In addition, the DSMB charter will specify rules for interrupting the study enrollment in the event of device- or procedure-related safety events prior to the completion of the Safety Cohort. Events of special interest are choroidal hemorrhage, endophthalmitis or infections, retinal detachments, leakage of cells into the vitreous/need for vitrectomy, significant loss of vision defined as ≥15 letters lost compared to baseline (first month post-surgery only), and failure to deliver cells/device failure.

Since no additional subjects are to be enrolled under this amendment, there will be no further DSMB meetings and DSMB will be disbanded; Janssen retains the option to reform the DSMB should the need arise.

The DSMB's responsibilities, authorities, and procedures, will be documented in a separate charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (definition per the International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between CNTO 2476, the delivery system, or the device and the event, the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For CNTO 2476, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

The surgical procedure and delivery of CNTO 2476 result in a small retinal detachment per procedure guidelines. This in itself should not be listed as an adverse event.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of CNTO 2476, or the Delivery System.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of CNTO 2476, or the Delivery System. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of CNTO 2476, or the Delivery System. The relationship in time is suggestive. An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest for CNTO 2476 that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose
- Inadvertent or accidental exposure
- Medication error (with or without subject exposure to CNTO 2476, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of CNTO 2476, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 1.

All AEs, regardless of seriousness, severity, or presumed relationship to treatment, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARS). The investigator (or sponsor where required) must report SUSARS to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including Open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the mask.

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by the treatment will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study within 30 days of the last dose of CNTO 2476, whether or not the event is expected or associated with CNTO 2476, is considered an SAE.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product/device defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product/device, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product/device. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

The provisions for a PQC apply to the CNTO 2476 product, as well as the Delivery System.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. TREATMENT INFORMATION

14.1. Physical Description of CNTO 2476

CNTO 2476 is an allogeneic somatic cell therapy medicinal product derived from the isolation and ex vivo expansion of hUTC. It is a cryopreserved cell suspension that is thawed immediately (within 2 hours) prior to administration to patients and ready for administration after thaw.

14.2. Packaging

CNTO 2476 supplied for this study is manufactured and provided under the responsibility of the sponsor. CNTO 2476 cryopreserved drug product (CDP) is a cell suspension formulated in chemically defined freezing medium containing CryoStor™-SCO 4B (custom formulation) and Balanced Salt Solution® (BSS) Sterile Irrigating Solution. CNTO 2476 is filled in Crystal Zenith® resin vials and stored at < −120ºC. Each single-use vial contains 330 µL of cell suspension of which 50 µL will be administered. The overfill is required to transfer and fill the Delivery System. The cells will be administered in the subretinal space of the eye using the Delivery System.

Each vial is enclosed in a paperboard carton with appropriate labeling on the carton.

14.3. Labeling

Treatment labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling and Storage

Each site will be provided with an Investigational Product Manual with detailed instructions for proper preparation, handling and storage of CNTO 2476.

CNTO 2476 must be stored at controlled temperatures ranging from −321°F to −184°F (−196°C to −120°C). CNTO 2476 is shipped to the clinical site in a liquid nitrogen vapor-phase shipper that is also used for short-term storage up to 7 calendar days after shipment. The distribution is on a just-in-time basis for each treatment in the trial. The shipment for a subject will be triggered when enrolled or randomized through the IWRS.

At the time of surgery, CNTO 2476 will be thawed in a controlled manner per the instructions in the Investigational Product Manual.

14.5. Investigational Product and Device Accountability

The investigator is responsible for ensuring that all CNTO 2476, Delivery System devices received at the site are inventoried and accounted for throughout the study, per the requirements in the Investigational Product Manual. All CNTO 2476 will be stored and disposed of according to the sponsor's instructions, per the Investigational Product Manual. Study-site personnel must not combine contents of the CNTO 2476 containers.

15. STUDY-SPECIFIC MATERIALS

The following will be provided to the investigator/clinical site as reference materials:

- Investigator Brochure
- Ophthalmic Examination Manuals
- Investigational Product Manual
- Study Manual
- Laboratory Manual
- PRO questionnaires (NEI-VFQ-25, SF-36, and FRI)
- IWRS Manual
- eDC Manual
- Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Age-related macular degeneration is a debilitating and common cause of blindness in persons over 60 years of age. For GA, the severe dry form of AMD, there is no approved therapy. Preliminary clinical data suggests that CNTO 2476 may improve visual acuity in patients with GA.

The primary risk is related to the novel delivery procedure and subretinal access kit; there may also be risk associated with the cell therapy. For this reason, the study is designed with an open-label Safety Run-in Phase and Safety Cohort to ensure safety of the surgical procedure prior to the randomized portion of the study; an independent DSMB will provide oversight through the first 12 months of the study. Extensive training for proper use of the subretinal access kit will be provided to all surgeons, and all procedures will be monitored by representatives of the sponsor.

In addition to adherence to Good Clinical Practices (GCPs), the study will also follow Good Tissue Practices (GTPs) to maximize and manage the safety of injected human cells. Subjects will be asked to be followed for up to 36 months to assess the long-term safety outcomes of the cell therapy.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Consent will be provided in a format that is accessible to subjects with severe visual impairment.

The total blood volume to be collected is approximately 107.4 mL, and is considered to be within the normal range allowed for this subject population over the time period (3 years) proposed for this study, and is within the range of Red Cross blood donations.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, GTP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the treatment

- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional samples for research where local regulations permit. After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

All study sites will be asked by the sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. If both parties (sponsor and the study site) agree, and if participation is allowed by local regulations and IEC/IRB requirements, the means to facilitate such a process will be provided to the sites by sponsor. The actual mechanism of consenting will be facilitated by the use of an eTablet device (eg, iPad®), but overall the consent process will remain the same, as described in this section. At these study sites, subjects will still be required to review the entire informed consent as a written document on the eTablet and then to apply their handwritten signature electronically by the use of a stylus directly onto the eTablet.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand CNTO 2476, to understand visual acuity impairment associated with GA secondary to AMD, to understand differential responders, and to develop tests/assays related to CNTO 2476 and visual acuity impairment associated with GA secondary to AMD. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page[s] provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of CNTO 2476 and Delivery System to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; CNTO 2476 and devise receipt/dispensing/return records; treatment administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Demographics
- History of smoking
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination
- Patient Reported Outcomes

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in an electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets and intraoperative videos may be used for the capture of some data to facilitate completion of the eCRF (ie, data collection during cell delivery procedure). Any such worksheets and videos will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, PRO questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory and all outside vendors into the

study database into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor/designee will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If

electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

The sponsor will conduct on-site monitoring and support on Day 1 of the study, and throughout the surgical procedure. Representatives from the sponsor company, Janssen and/or its designees may be present at the clinical facility, in the operating room during surgery or observing remotely. This is to ensure oversight of aspects of the surgical procedure and protocol.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further treatment development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance

with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding CNTO 2476 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of CNTO 2476, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be

arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Fatal and non-fatal myocardial infarction
- Angina pectoris
- Fatal and non-fatal stroke
- Transient ischemic attack
- Chronic obstructive pulmonary disease (COPD), COPD exacerbation and chronic bronchitis

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All adverse events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

CNTO 2476
Clinical Protocol CNTO2476MDG2002 Amendment 3
INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): James Baldassarre, M.D.

Institution: Janssen Research & Development, L.L.C.

Signature: _____ Date: 15 12 2017
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 15 December 2017