Experience With a Subretinal Cell-based Therapy in Patients With Geographic Atrophy Secondary to Age-related Macular Degeneration

ALLEN C. HO, TOM S. CHANG, MICHAEL SAMUEL, PAUL WILLIAMSON, ROBERT F. WILLENBUCHER, AND TERRI MALONE

• PURPOSE: To evaluate the safety and tolerability of and clinical response to a single, subretinal dose of human umbilical tissue–derived cells (palucorcel [CNTO-2476]) in the eyes of adults aged ≥50 years with bilateral geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

• DESIGN: Phase 1/2a, multicenter, open-label, dose-escalation, fellow-eye–controlled study.

• METHODS: In the phase 1 portion, eyes were assigned to receive a single, subretinal dose of palucorcel (ranging from 6.0×10^4 to 5.6×10^5 viable cells). In the phase 2a portion, eyes were assigned to one of 2 palucorcel doses (6.0×10^4 or 3.0×10^5 cells) determined during the phase 1 portion. The intervention eye was the eye with worse baseline visual acuity.

• RESULTS: A total of 35 eligible subjects underwent at least a partial surgical procedure. Palucorcel was administered in 33 eyes. Overall, 17.1% (6/35) of subjects experienced retinal detachments and 37.1% (13/35) experienced retinal perforations. No episodes of immune rejection or tumor formation were observed. At 1 year, ≥10- and ≥15-letter gains in best-corrected visual acuity were observed in 34.5% (10/29) and 24.1% (7/29) of eyes receiving palucorcel, respectively, and in 3.3% (1/30; for both) of fellow eyes.

• CONCLUSIONS: The subretinal delivery procedure in this study was associated with a high rate of retinal perforations (n = 13) and retinal detachments (n = 6). When cells were sequestered in the subretinal space, palucorcel was well tolerated and may be associated with improvements in visual acuity. Larger randomized controlled studies are required to confirm these results. Future studies would require a modified surgical approach. (Am J Ophthalmol 2017;179:67–80.

AJO.com Supplemental material available at AJO.com.

Accepted for publication Apr 8, 2017.

From Wills Eye Hospital/Mid Atlantic Retina, Philadelphia, Pennsylvania (A.C.H.); Retina Institute of California, Pasadena, California (T.S.C., M.S.); and Cell Therapy, Janssen Research & Development, Spring House, Pennsylvania (P.W., R.F.W., T.M.).

Inquiries to Allen C. Ho, Wills Eye Hospital/Mid Atlantic Retina, 840 Walnut St, Suite 1020, Philadelphia, PA 19107; e-mail: achomd@gmail.com

AGE-RELATED MACULAR DEGENERATION (AMD) IS A degenerative retinal disorder that affects the elderly population and is the leading cause of central vision loss in the United States (and other developed countries) for adults aged >55 years, and there is currently no treatment for the advanced atrophic form of AMD.[1,2] AMD is a complex and multifactorial disease with a number of contributing genetic risk factors (eg, mutations in complement factor H) and environmental factors (eg, smoking).[1] Dysfunction of the retinal pigment epithelium (RPE) is central to the pathogenesis of AMD.[3] In intermediate AMD, drusen (deposits of lipids and proteins located between RPE cells and the Bruch membrane in the area of the macula) reach sizes of >125 μm in diameter; the presence of these large drusen is indicative of a higher risk of developing advanced AMD.[4] In advanced AMD, eyes may develop geographic atrophy (GA) or exudative neovascular ("wet") AMD.[3] GA, which accounts for 35%–40% of cases of advanced AMD, involves a gradual degeneration of the RPE and photoreceptor cells, along with the choriocapillaris, in the central retina.[4]

Palucorcel (CNTO-2476) is a novel cell-based potential therapy being evaluated for the treatment of AMD. Palucorcel comprises human umbilical tissue–derived cells (hUTCs) in a proprietary cryopreserved formulation. hUTCs are derived from extraembryonic mesoderm and differ from both fibroblasts and mesenchymal stem cells (MSCs) in a number of ways: hUTCs expand significantly more than MSCs and fibroblasts[5]; unlike MSCs, hUTCs express soluble vascular endothelial growth factor receptor 1 (sVEGF-R1 [Cao J, et al. *Molecular Ther* 2014;22(Suppl 1):S186–S187. Abstract 485]); and hUTCs express different cell surface receptors compared with MSCs.[6] These hUTCs do not meet the National Institutes of Health definition of a stem cell for 2 major reasons. First, these cells cannot grow for indefinite generations in culture; they senesce at approximately 40–60 population doublings.[5] Second, these cells are not rare and do not spontaneously differentiate in vitro, or when transplanted in vivo, into other cell types of the umbilical cord (endothelial cells or epithelial cells). In a rat

model of human retinal disease (Royal College of Surgeons [RCS] rat[7]), subretinal administration of palucorcel was associated with preservation of the architecture of the outer nuclear layer, compared with untreated animals, and resulted in a decreased rate of visual function loss.[5] hUTCs were shown to secrete several key neurotrophic factors thought to favorably influence RPE cell function and, thereby, photoreceptor function.[5] It should be noted that the RPE in RCS rats does not show the morphologic changes in the RPE typically seen in AMD; however, RCS rats suffer from RPE dysfunction and photoreceptor degeneration. In separate in vitro studies, hUTCs have been shown to secrete factors that rescue phagocytic dysfunction in RPE cells (eg, hepatocyte growth factor) and promote synaptogenesis (eg, thrombospondin family proteins).[8,9]

In this phase 1/2a study, the safety and clinical response to a single, subretinal administration of palucorcel in eyes with visual acuity impairment associated with GA secondary to AMD has been evaluated. This multicenter, open-label, single-dose, dose-escalation, fellow-eye–controlled study included a phase 1, dose-escalation portion and a phase 2a portion that enrolled additional subjects who were randomized to 1 of the 2 doses (determined during the phase 1 portion). The primary objective of both the phase 1 and 2a portions of this study was to evaluate the safety and tolerability of palucorcel, administered subretinally using the iTrack™ Model 275 (iScience Interventional Corporation, Menlo Park, California, USA) microcatheter and to evaluate modifications that could improve the safety of the surgical delivery procedure for the cells. Secondary objectives of both the phase 1 and 2a portions of this study were to evaluate the effects of palucorcel on clinical response (based on the change from baseline in visual acuity and the yearly rate of increase from baseline in the area of GA), immunogenicity, and other visual functions; and to evaluate the safety and performance of the surgical instruments and delivery system.

METHODS

THIS MULTICENTER, OPEN-LABEL, SINGLE-DOSE, DOSE-escalation, fellow-eye–controlled study was compliant with the Health Insurance Portability and Accountability Act and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Institutional Review Board approval was obtained at both study sites (Wills Eye Hospital and the Retina Institute of California) for the study protocol, all protocol amendments, written study subject information, the informed consent form, and any other appropriate study-related information. This study was conducted under the supervision of an independent Data Safety Monitoring Board (DSMB). This trial was registered and is publicly available at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT01226628). The original protocol and amendments are summarized in Supplemental Table 1 (Supplemental Material available at AJO.com), and key amendments are highlighted in the methods. These amendments were, in part, based on guidance from the DSMB.

• **SUBJECTS:** Key selection criteria included adults ≥50 years of age with a confirmed diagnosis of bilateral GA of the macula caused by AMD and confirmed within 21 days prior to administration of palucorcel by fundus examination, optical coherence tomography (OCT) imaging, fundus photography, and fundus autofluorescence (FAF). The intervention eye, which was designated at the time of study entry, was the eye with worse visual acuity or the eye selected by the investigator in the phase 1 portion of the study and was the worse eye in the phase 2a portion of the study. The intervention eye had ≥1 GA lesion involving the center of the macula, with a diameter of ≥360 μm, as determined by screening FAF images. Visual acuity in the intervention eye was characterized by best-corrected visual acuity (BCVA) as no better than 20/200 in the phase 1 portion and as no better than 20/80 in the phase 2a portion. Subjects with exudative AMD in either eye; evidence of other significant ophthalmic disease; or any ophthalmic condition that reduced the clarity of the media and would interfere with study-related examinations, surgery, or imaging were excluded from the study. Additional inclusion and exclusion criteria are summarized in Table 1.

The study was planned to enroll approximately 45 eligible subjects, with 30 subjects participating in the phase 1 dose-escalation portion of the study and 15 subjects participating in the phase 2a portion of the study. In the phase 2a portion of the study, only 4 subjects were enrolled before trial enrollment was suspended in favor of the development of a more refined surgical technique for cell delivery.

• **STUDY DESIGN AND DELIVERY PROCEDURE:** The phase 1 portion of the study did not contain any degree of masking, whereas during the dose-randomized phase 2a portion of the study, the centralized reading center was masked to the dose.

Palucorcel was surgically delivered via an ab externo approach (Figure 1); the iTrack 275 microcatheter delivery system was placed in the subretinal space after a peripheral scleral cutdown (approximately 3 mm long and 8–11 mm posterior to the limbus), choroidotomy, and creation of a subretinal bleb with a wire-tip microcannula and sodium hyaluronate viscoelastic (Healon; Abbott Medical Optics, Abbott Park, Illinois, USA). The iTrack 275 microcatheter was guided in the subretinal space with visualization to deliver palucorcel in a subretinal fluid bleb adjacent to the area of GA. Intraocular visualization was achieved with indirect ophthalmoscopy or intraocular endoscopy (Endo Optiks E2 System; Beaver Visitec, Waltham,

TABLE 1. Inclusion and Exclusion Criteria for the Study of Cell-based Therapy in Eyes With Geographic Atrophy Secondary to Age-related Macular Degeneration

Inclusion Criteria

- Women and men ≥50 years of age
- Women were incapable of childbearing
- Confirmed diagnosis of bilateral GA of the macula caused by AMD, and confirmed within 221 days prior to administration of palucorcel using fundus photography
- Intervention eyes had ≥1 GA lesion involving the center of the macula, with a diameter of ≥360 μm, as determined by screening FAF images
- Visual acuity was characterized by BCVA as no better than 20/200 in the intervention eye in the phase 1 portion and as no better than 20/80 in both eyes in the phase 2a portion
  - GA must have been able to be photographed in its entirety and not be contiguous with peripapillary atrophy, which was able to be clinically delineated and confirmed with fundus photography and FAF[a]
  - Images must have included the Modified 7-Standard Field images as defined by the University of Wisconsin standards. Retinal photographs and angiography of sufficient quality, allowing assessment of the macular area according to standard clinical practice, must have been obtained. A central reading center (Digital Angiography Reading Center, New York, New York, USA) was used for the digital ophthalmology photographic images.
- Subjects must have been suitable candidates for ophthalmic surgery
- Preoperative hematology and blood chemistry parameters were within the normal limits, as follows: hemoglobin ≥10 g/dL; white blood cells ≥3.5×10^3 cells/μL; neutrophils >1.5×10^3 cells/μL; platelet ≥100×10^3 cells/μL; alanine aminotransferase and aspartate aminotransferase ≤1.5 times the upper limit of normal, as defined by the central laboratory; and creatinine ≤1.5 mg/dL
  - If any abnormalities outside these ranges were present, they must have been considered by the investigator as not clinically significant

Exclusion Criteria

- Exudative AMD in either eye, evidence of other significant ophthalmologic disease, or any ophthalmologic condition that reduced the clarity of the media and would, in the opinion of the investigator and reading center, interfere with study-related examinations, surgery, or imaging
- Ocular hypertension (defined as morning intraocular pressure ≥24 mm Hg) despite treatment, a history of choroidal or scleral rupture in either eye, myopia >6 diopters, a history of ocular herpes zoster, or any systemic inflammatory or autoimmune conditions (eg, rheumatoid arthritis, systemic lupus erythematosus)
- Previous cell therapy other than blood components
- Previous treatment for AMD other than antioxidant or zinc supplements (eg, Age-related Eye Disease Study formula) or other vitamin supplements
- Systemic corticosteroids or immunosuppressives within the 6 months prior to screening
- Unstable IOL implant in the intervention eye for subjects with implanted IOL as confirmed by dynamic slit-lamp examination
- A history of intraocular surgery within 6 months prior to screening
- Retinal laser within 3 months of screening
- Prior vitrectomy, scleral buckling procedure, glaucoma filtration surgery, or any other extraocular or orbital procedure in the intervention eye that, in the opinion of the surgeon, would hamper the transscleral, subretinal cannulation procedure
- Participation in another interventional clinical trial within 60 days or 5 half-lives prior to day 1 or were expecting to participate in other clinical trials during this trial

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; FAF = fundus autofluorescence; GA = geographic atrophy; IOL = intraocular lens.

[a]Amendment 10 to the protocol modified this inclusion criterion as follows, "GA must be able to be photographed in its entirety and can be continuous with peripapillary atrophy. The peripapillary atrophy must be able to be clinically delineated and confirmed with fundus photography and FAF." Until Amendment 10 (February 2013), GA must have been able to be photographed in its entirety and not be contiguous with peripapillary atrophy.

Massachusetts, USA; procedure amendment after first 10 subjects). If the surgeon suspected that an inadvertent retinal perforation had occurred, the area could be treated prophylactically by peripheral cryopexy or laser retinopexy. If a retinal perforation posterior to the equator was observed, the investigator was not to inject palucorcel. For retinal perforations observed anterior to the equator, injection of the cells was based on the investigator's clinical judgment. In the phase 1 portion of the study, palucorcel was administered subretinally in a total volume of 27 μL (3.0×10^5 viable cells, given over 16 seconds) or 50 μL (6.0×10^4, 1.2×10^5, or 5.6×10^5 viable cells, given over 30 seconds). In the phase 2a portion of the study, palucorcel was administered subretinally in a total volume of either 27 μL (3.0×10^5 viable cells, given over 16 seconds) or 50 μL (6.0×10^4 viable cells, given over 30 seconds). Cell delivery was confirmed with either direct or indirect visualization using intraocular endoscopy or ophthalmoscopy, respectively, with a wide-field lens attached to the microscope prior to closure of the surgical incisions. After

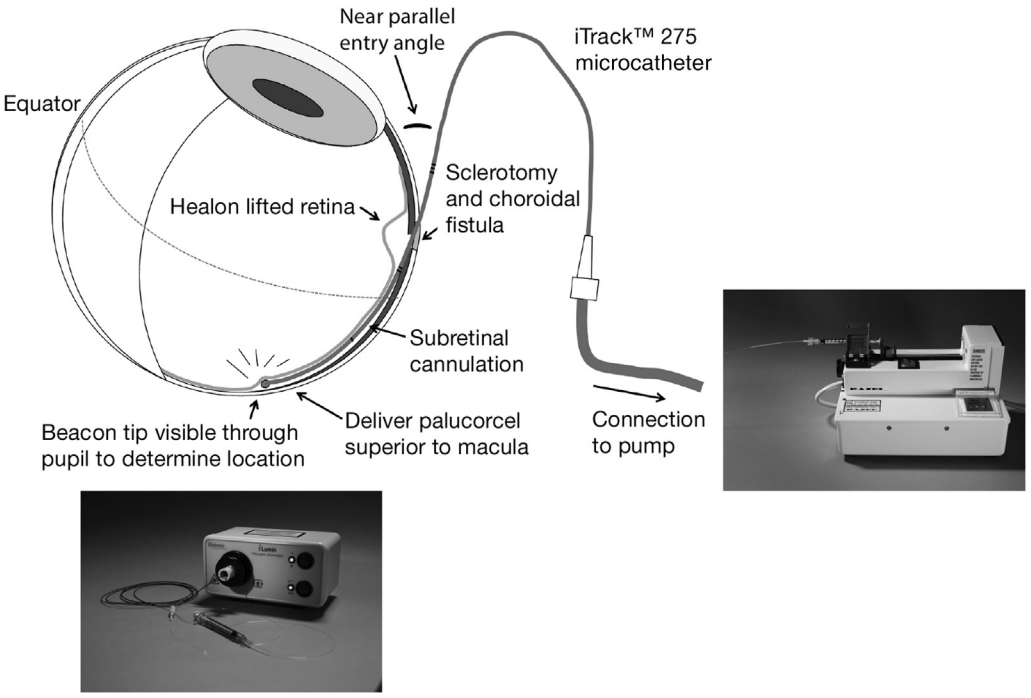


FIGURE 1. Surgical delivery of palucorcel is performed via an ab externo approach through a scleral cutdown and a choroidotomy. A peripheral subretinal bleb is created and the iTrack 275 microcatheter is passed into the subretinal space to deliver palucorcel cells adjacent to macular geographic atrophy.

the completion of cell delivery, the microcatheter was slowly withdrawn and the scleral and conjunctival incisions were sutured closed.

Subjects received standard postoperative care without systemic immunosuppression. Follow-up visits were scheduled for postoperative days 2, 7, and 15; weeks 3 and 4; and months 2, 3, 6, and 12. During follow-up visit at day 7, OCT, FAF, slit-lamp biomicroscopy, and fundus photography were performed to evaluate cell safety. After the initial 12-month postoperative follow-up period, subjects continued in a 4-year, long-term safety follow-up period of general safety surveillance, which is ongoing. Different measures of safety, tolerability, and clinical response were assessed at each follow-up visit as described below.

• **CELL THERAPY AND DOSING:** The procedures used for the culture, characterization, and storage of the cells are summarized in Supplemental Appendix 1 (Supplemental Material available at AJO.com). In the phase 1 portion of the study, study subjects were assigned to receive a single dose of palucorcel (ranging from 6.0×10^4 to 5.6×10^5 viable cells) in 7 cohorts (Cohorts A-G), with 3 subjects per cohort in each of the first 4 cohorts (A-D) and 6 subjects per cohort in the remaining 3 cohorts (E-G). In the phase 2a portion of the study, subjects were randomized to a single dose of 1 of the 2 doses of palucorcel (6.0×10^4 or 3.0×10^5 cells) determined during the phase 1 portion of the study. The progression of subjects through the phase 1 study cohorts and the process for selecting the doses for the phase 2a portion are summarized in Supplemental Appendix 2 (Supplemental Material available at AJO.com).

• **STUDY ASSESSMENTS:** *Safety and Tolerability Assessments*. Adverse events (AEs) were recorded during and after surgical administration of palucorcel. Additional standard safety assessments included routine laboratory assessments (performed at screening, at week 4, and at month 12), vital sign measurements (assessed at each visit), electrocardiogram (ECG) evaluations (assessed at screening and at month 12), and physical examinations (assessed at screening and at month 12). The presence of antibodies to palucorcel was evaluated using a proprietary assay, with blood samples obtained at screening and at days 7 and 15, weeks 3 and 4, and months 2, 3, 6, and 12 after palucorcel administration in the acute period.

Ophthalmologic safety assessments included intraocular pressure via Goldmann applanation tonometry (GAT), slit-lamp biomicroscopy and funduscopy, FAF, spectral-domain OCT (SDOCT), color fundus photography (CFP), and fluorescein angiograms (FA). The Digital Angiography Reading Center (DARC, New York, New York, USA) was used for the digital ophthalmology photographic images, which included the Modified 7-Standard Field photography (University of Wisconsin) standard images. Ophthalmologic safety assessments were performed at follow-up days

2, 7, and 15 and at months 1, 2, 3, 6, and 12. Long-term ophthalmologic safety follow-up visits were performed every 6 months for a subsequent 4 years.

Clinical Response Assessments. Clinical response assessments included evaluations of visual function: BCVA, refractive error, low-luminance BCVA, low-luminance deficit (LLD), and contrast sensitivity threshold (evaluated using the Pelli-Robson test). BCVA testing was performed using the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol. After a protocol amendment instituted in June 2012, BCVA was measured at 2 separate visits during screening (once at the first screening visit and twice at the second screening visit) to improve accuracy; BCVA was the only visual acuity testing performed at the second screening visit and on day 2.

Reading speed and reading acuity were evaluated via MNREAD charts at baseline, at months 3 and 12 during the acute period, and at months 24, 36, 48, and 60. Reading acuity (RA) was defined as 1.4 − [number of sentences read × 0.1] + [words missed × 0.01] in units of logMAR; this measure reflects the print size of an average reading speed before it becomes limited by print size. Maximum reading speed (MRS) for an eye was defined as the MRS (in words per minute) at any font size. Critical print size (CPS) was defined as the font size in logMAR units associated with MRS. For subjects unable to read the largest print size at a standard distance of 40 cm, both RA and CPS were substituted by a maximum logMAR value of 1.4 and the subject's BCVA at that visit, and the MRS value was assigned to 0. Visual field assessments were performed via Humphrey automated perimetry at baseline and at months 3, 12, 24, and 60 during follow-up.

In addition, anatomic response was evaluated based on changes in the area of GA (evaluated using FAF) at screening and at all postbaseline visits starting with day 7 by the DARC. The National Eye Institute Visual Function Questionnaire–25 item (NEI VFQ-25) was also used to evaluate clinical response; these results are in a separate report.

• **STATISTICAL ANALYSES:** This analysis encompasses all subjects through month 12 follow-up. Continuous variables were summarized using descriptive statistics, including number of subjects, mean, median, standard deviation, maximum, and minimum. Categorical variables were summarized using counts of subjects and percentages. Efficacy and tolerability data are summarized for all palucorcel doses in the current report. No statistical hypothesis testing was performed in this pilot study.

The results of ophthalmologic assessments are presented for each eye (identified as the intervention eye and fellow eye). For numerical measurement summaries, a median value across readers was used; and for categorical parameters, a category provided by the majority of readers was used.

The baseline value was defined as the last available value prior to the administration of palucorcel. For study subjects enrolled prior to the June 2012 protocol amendment (n = 19), the baseline BCVA was defined as the last available assessment prior to the administration of palucorcel. For subjects enrolled under the June 2012 amendment or later (n = 16), with BCVA measured 3 times over 2 separate visits during screening to improve accuracy, baseline BCVA was defined as the median BCVA for subjects with all 3 assessments performed or as the assessment showing better visual acuity for subjects with only 2 assessments performed.

Partial data available for all subjects who received palucorcel are included in the summaries and data listings.

No imputation or carrying forward for missing data was performed for the purposes of primary or secondary analyses. All statistical procedures were performed using Statistical Analysis Software (SAS; SAS Institute Inc, Cary, North Carolina, USA), version 9.2 or higher.

Given that the primary objective of this study was to evaluate the safety and tolerability of palucorcel delivered subretinally and that the sample size of the study was small, statistical testing of any hypotheses was not considered appropriate. Furthermore, the study protocol specified that only descriptive statistics would be used to summarize study findings.

RESULTS

• **SUBJECTS:** A total of 109 potential subjects were screened and 35 subjects enrolled in this phase 1/2a study. Overall, 35 eligible study subjects underwent at least a partial surgical procedure. Of those 35 subjects, 33 received palucorcel; the remaining 2 subjects, both in the phase 1 portion of the study, underwent a partial surgical procedure but did not receive palucorcel. A total of 3 subjects (all from phase 1) discontinued prior to completing the 12-month follow-up visit (Figure 2).

Baseline and demographic characteristics for all 35 subjects who underwent at least a partial surgical procedure are summarized in Table 2. Overall, 54.3% (19/35) of subjects were female, and the median (range) age was 82.0 (66–94) years. The median (range) total area of GA at baseline was 14.26 (5.7–35.9) mm^2 in the intervention eye and 11.05 (3.1–33.6) mm^2 in the fellow eye. The majority of subjects had ≤10 discrete areas of GA in the intervention eye (88.6% [31/35]) and in the fellow eye (80.0% [28/35]). The median (range) baseline BCVA (logMAR score) was 1.10 (0.7–1.6) in the intervention eye and 0.60 (0.2–1.5) in the fellow eye, and the median (range) baseline BCVA (number of letters) was 26.0 (2–50) letters and 56.0 (10–77) letters, respectively. The median baseline BCVA (Snellen equivalent) was 20/250 in the intervention eye and 20/80 in the fellow eye.

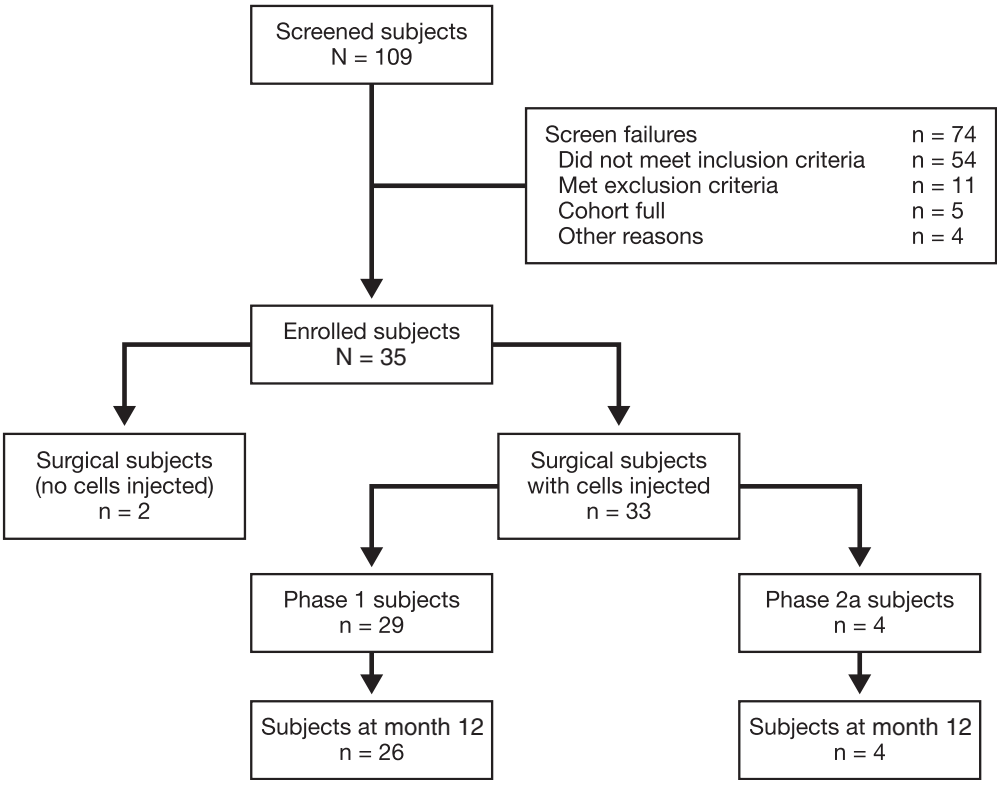


FIGURE 2. Disposition of subjects in the study of cell-based therapy for geographic atrophy secondary to age-related macular degeneration.

TABLE 2. Baseline and Demographic Characteristics of Patients With Geographic Atrophy Secondary to Age-related Macular Degeneration

Characteristic		All Surgical Subjects (N = 35)
Sex, n (%)		
Male		16 (45.7)
Female		19 (54.3)
Race, n (%)		
White		35 (100)
Median (range) age, y		82.0 (66–94)
Median (range) weight, kg		68.95 (49.4–113.9)
Baseline Ophthalmologic Characteristics	**Intervention Eye**	**Fellow Eye**
Median (range) total area[a] of GA, mm^2	14.26 (5.7–35.9)	11.05 (3.1–33.6)
Median (range) IOP, mm Hg	13.0 (7–22)	14.0 (9–22)
Median (range) BCVA, logMAR score[b]	1.10 (0.7–1.6)	0.60 (0.2–1.5)
Median (range) BCVA, Snellen equivalent	20/250 (20/100 to 20/800)	20/80 (20/30 to 20/600)
Median (range) BCVA, letters	26.0 (2–50)	56.0 (10–77)

BCVA = best-corrected visual acuity; GA = geographic atrophy; IOP = intraocular pressure.

[a]Measurement was obtained from 2 or 3 readers interpreting the same image, and a median value across readers was used for each eye.

[b]For subjects enrolled under the protocol amendment in June 2012, baseline BCVA was defined as the median visual acuity when 3 assessments were performed or as the assessment showing better visual acuity when only 2 assessments were performed.

• **PALUCORCEL EXPOSURE AND ADMINISTRATION:** In this phase 1/2a study, palucorcel was delivered in the subretinal space in 33 of 35 subjects. Overall, 51.5% (17/33) of subjects received palucorcel in the right eye and 48.5% (16/33) received palucorcel in the left eye. A total of 12 subjects received 6.0×10^4 cells, 3 received 1.2×10^5 cells, 15 received 3.0×10^5 cells, and 3 received 5.6×10^5 cells. Two subjects did not receive palucorcel because retinal perforations were noted during the surgical procedure. Palucorcel was placed in the targeted location (superior to the macula and area of GA) in all 33 subjects (Table 3).

• **SAFETY AND TOLERABILITY:** *Adverse Events—All Surgical Subjects*. A total of 97.1% (34/35) of subjects who underwent at least a partial surgical procedure in the study experienced ≥1 AE, with 80.0% (28/35) experiencing eye disorder AEs. The most common nonocular AEs were hypertension (20.0% [7/35]), depression (14.3% [5/35]), urinary tract infection (11.4% [4/35]), and chronic obstructive pulmonary disease (11.4% [4/35]). The most common ocular AEs were retinal perforation, conjunctival hemorrhage, retinal detachment, retinal hemorrhage, eye pain, and reduced visual acuity (Table 4). Retinal perforations were most often located at the site of the subretinal bleb formation in the peripheral retina.

Three subjects in the phase 1 portion of the study died during the study. One death was reported as a completed suicide; 1 death was as a result of metastatic squamous cell lung cancer; and 1 death resulted from methicillin-resistant *Staphylococcus aureus* pneumonia and end-stage chronic obstructive pulmonary disease. None of these deaths were considered related to palucorcel administration or the study surgical procedures, in the opinion of the investigator.

Adverse Events—Subjects Who Received Palucorcel. A total of 97.0% (32/33) of subjects who received palucorcel experienced ≥1 AE, with 78.8% (26/33) of subjects experiencing eye disorder AEs. The most common eye disorder AEs among subjects who received palucorcel were retinal perforation (36.4% [12/33]), conjunctival hemorrhage (30.3% [10/33]), retinal detachment (15.2% [5/33]), retinal hemorrhage (15.2% [5/33]), eye pain (12.1% [4/33]), and reduced visual acuity (12.1% [4/33]). Overall, 39.4% (13/33) of subjects who received palucorcel experienced a serious AE, with 15.2% (5/33) experiencing a serious ocular AE (retinal detachment, 15.2% [5/33]; proliferative retinopathy, 6.1% [2/33]). Severe AEs were reported for 51.5% (17/33) of subjects who received palucorcel, with 12.1% (4/33) experiencing severe ocular AEs. Severe ocular AEs included retinal detachment (9.1% [3/33]), retinal perforation (6.1% [2/33]), periorbital edema (3.0% [1/33]), and reduced visual acuity (3.0% [1/33]).

The relationship of ocular AEs to eye surgery, the surgical delivery system, and palucorcel were evaluated (Table 5). Approximately 76% (25/33) of subjects who received palucorcel experienced ≥1 AE related to eye surgery, the surgical delivery system, and/or palucorcel. Approximately 58% of subjects experienced an AE considered to be reasonably related to the surgical delivery system, most notably retinal tears. In subjects

TABLE 3. Summary of Palucorcel Administration in Patients With Geographic Atrophy Secondary to Age-related Macular Degeneration

Administration Characteristic	Subjects Who Received Palucorcel (n = 33)
Intervention eye, n (%)	
Left eye	16 (48.5)
Right eye	17 (51.5)
Successful product placement in anticipated location (superior to macula), n (%)	33 (100)[a]

[a]Palucorcel was delivered to the targeted location in all 33 subjects; however, specific data for this outcome were not collected for the first 2 subjects who received palucorcel.

TABLE 4. Significant Ocular Adverse Events Reported for All Subjects in the Study of Cell-based Therapy for Geographic Atrophy

AE, n (%)	All Surgical Subjects (N = 35)
Any AE	34 (97.1)
Eye disorders	28 (80.0)
Retinal perforation	13 (37.1)
Conjunctival hemorrhage	11 (31.4)
Retinal detachment	6 (17.1)
Retinal hemorrhage	5 (14.3)
Reduced visual acuity	5 (14.3)
Eye pain	4 (11.4)
Anterior chamber cell	4 (11.4)
Vitreous floaters	4 (11.4)
Cataract	3 (8.6)
Foreign body sensation in eyes	3 (8.6)
Vitreous hemorrhage	3 (8.6)
Chalazion	2 (5.7)
Conjunctival hyperemia	2 (5.7)
Conjunctival edema	2 (5.7)
Corneal edema	2 (5.7)
Eye discharge	2 (5.7)
Photophobia	2 (5.7)
Proliferative retinopathy	2 (5.7)
Subretinal fibrosis	2 (5.7)
Subretinal fluid	2 (5.7)
Vitreous detachment	2 (5.7)

AE = adverse event; AMD = age-related macular degeneration.

TABLE 5. Relationship of Adverse Events to Surgery, the Surgical Delivery System,[a] and Palucorcel[b]

Aes, n (%)	Subjects Who Received Palucorcel (N = 33)
AEs related to eye surgery	25 (75.8)
AEs related to surgical delivery system[a]	19 (57.6)
AEs related to palucorcel	5 (15.2)

AE = adverse event.

[a]The surgical delivery system includes the iScience microcatheter and ancillary devices used in the surgical procedure.

[b]Relationship was determined for AEs considered reasonably related to surgery, the surgical delivery system, and/or palucorcel.

experiencing AEs considered reasonably related to palucorcel, these AEs were also considered to be reasonably related to the eye surgery and/or the surgical delivery system. The most frequent AEs in this category were retinal detachments.

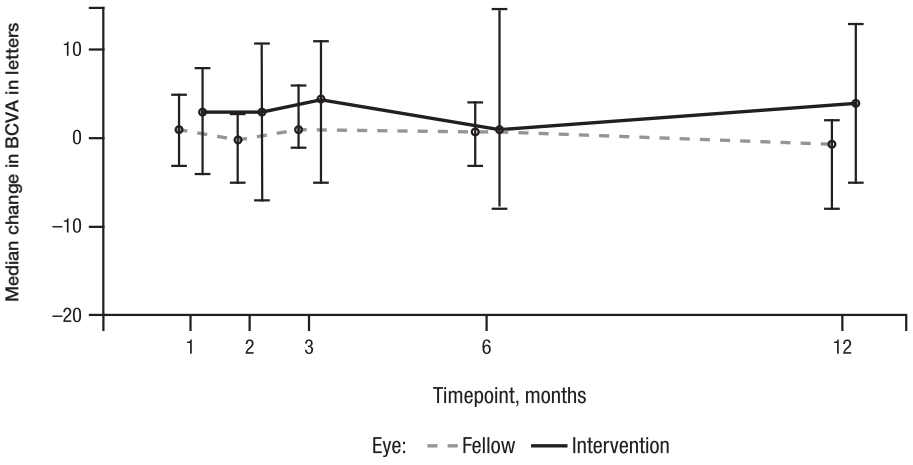
Ophthalmic endoscopy was introduced to provide surgeons with additional visualization during surgery after the first 10 subjects received palucorcel in the phase 1 portion of the study. The rate of retinal detachment decreased after the introduction of ophthalmic endoscopy, whereas the number of retinal perforations identified increased (likely owing to improved detection). Prior to the introduction of ophthalmic endoscopy, 90.0% (9/10) of subjects experienced ≥1 ocular AE in the intervention eye, including retinal perforations (20.0% [2/10]) and retinal detachment (30.0% [3/10]). After the introduction of ophthalmic endoscopy, 78.3% (18/23) of subjects experienced ≥1 ocular AE in the intervention eye, including retinal perforations (43.5% [10/23]) and retinal detachment (8.7% [2/23]).

Standard Safety Assessments and Concomitant Medication Use. There were no clinically meaningful changes from baseline to month 12 in mean values for hematology parameters, mean values for blood chemistry parameters, median values for urinalysis parameters, median values for vital signs, or changes in ECGs.

Immune Response, Tumor Formation, and Antibody Testing. No immune response or immune rejection was noted for intervention or fellow eyes. In addition, no evidence of tumor formation was observed. At baseline, 31 subjects tested negative for antibodies to palucorcel, 1 tested positive, and 1 was unknown (a sample was collected for this subject, but results were inconclusive). No relevant between-group differences in shift changes were observed for positive antibody titers, and there were no significant changes from baseline in median values for antibody titers. Administration of palucorcel did not sensitize naïve subjects; however, palucorcel may have induced a recall response (or immune response to subsequent administration of cells) in 1 subject. One subject in the 6.0×10^4 cell dose cohort had unknown results at baseline, tested negative for antibodies to palucorcel at all time points from day 7 thorough month 3, and tested positive for antibodies at month 6 (peak titer of 36). This subject tested negative for antibodies at subsequent time points (months 12, 24, and 36), and the single positive value at month 6 does not seem to be indicative of a true biologic response (Supplemental Figure 1, Top left, available at AJO.com). One subject in the 3.0×10^5 cell dose cohort was negative for antibodies at baseline, had positive antibody test results on day 15 through month 3 (peak titers ranged from 9 to 33), and tested negative at months 6, 12, and 24. The pattern of response in this subject was consistent with a recall response (Supplemental Figure 1, Bottom left). Another subject in the 3.0×10^5 cell dose cohort was negative at baseline and tested marginally positive only at the months 3 and 6 visits (Supplemental Figure 1, Bottom left). Finally, 1 subject in the 5.6×10^5 cell dose cohort tested positive for antibodies from baseline through month 48 (peak titers ranged from 11 to 32; Supplemental Figure 1, Bottom right). The presence of serum antibodies against palucorcel was not associated with the occurrence of ocular AEs or clinical events characterized by inflammation.

Ophthalmologic Safety Assessments. There were no significant safety findings in FAF readings regarding GA. There was no consistent pattern in the total area of drusen between the intervention and fellow eyes. The most common ocular AEs, including retinal perforation or detachment, conjunctival or retinal hemorrhage, reduced visual acuity, anterior chamber cell, eye pain, and vitreous floaters, were described in the previous section on AEs among all surgical subjects.

• **CLINICAL VISUAL FUNCTION AND IMAGING ASSESSMENTS:** Two subjects underwent a partial surgical procedure but did not receive cell therapy. One of the 2 subjects did not receive cells owing to an equipment failure of the endoscope during surgery (with inability to visualize the subretinal bleb) and subsequently developed 2 separate retinal detachments. That subject read 32 letters at baseline, 19 letters at month 3, and hand motion only at months 6 and 12. The other subject, who underwent a partial surgical procedure but did not receive cell therapy, had a retinal perforation at the time of the surgery; therefore, cells were not administered. That subject read 34 letters at baseline, 28 letters at month 3, 31 letters at month 6, and 23 letters at month 12. All other clinical efficacy outcomes presented are for subjects who underwent the surgical procedure and received palucorcel (n = 33).



Number of subjects

Fellow eye	33	33	30	31	29
Intervention eye	33	33	30	31	29

Median BCVA value (Snellen equivalent) at each timepoint

Timepoint, months	BL	1	2	3	6	12
Fellow eye	20/80	20/80	20/100	20/80	20/80	20/100
Intervention eye	20/300	20/300	20/300	20/280	20/250	20/250

FIGURE 3. Median (interquartile range) post-palucorcel change from baseline in best-corrected visual acuity (BCVA) over time.

Best-Corrected Visual Acuity. At month 12, the median (range) change in BCVA from baseline was 4.5 (−41 to 32) letters in the intervention eye and –0.5 (−30 to 15) letters in the fellow eye (Figure 3). The median BCVA (Snellen equivalent) in the intervention and fellow eyes is summarized under the graph in Figure 3. The percentage of subjects with a gain of ≥10 letters in BCVA was >30% at months 3, 6, and 12 in the intervention eye and peaked at approximately 13% at month 3 in the fellow eye (Figure 4, Top). Individual subject responses at month 12 are shown in Figure 4, Bottom. The proportion of subjects with a gain or loss of ≥10 or ≥15 letters in BCVA at month 6 in the treated eye varied across dose groups (Supplemental Table 2, available at AJO.com).

Additional Measures of Visual Function. At month 12, the median (range) increases in low-luminance BCVA were 5.5 (–25 to 29) letters in the intervention eye and 0 (−35 to 31) letters in the fellow eye (Supplemental Table 3). In the intervention and fellow eyes, respectively, the median low-luminance BCVA (Snellen equivalent) values were approximately 20/360 and 20/200 at month 12 (Supplemental Table 3, available at AJO.com).

At month 12, the median (range) changes from baseline in the LLD (logMAR score), or difference between BCVA and low-luminance BCVA, were 0.05 (−0.8 to 0.9) in the intervention eye and 0.00 (−1.1 to 0.8) in the fellow eye (Supplemental Table 4, available at AJO.com). In the intervention and fellow eyes, respectively, the median LLD (Snellen equivalent) values were 20/25 and 20/30 at month 12 (Supplemental Table 4).

There was considerable variability with low reliability in measures of contrast sensitivity (evaluated using the Pelli-Robson test) and reading acuity (logMAR equivalent). Visual field assessments (performed via Humphry automated perimetry) showed relatively small changes in the mean deviation and pattern standard deviation in the intervention eye during the first 12 months since application of palucorcel. Visual field reliability was also poor for many of these subjects with impaired visual functioning owing to GA.

Geographic Atrophy Area. The total area of GA (by FAF) increased over time in the intervention eye group; the median (range) change in the area of GA from baseline was 2.86 (1.0–8.1) mm^2 in the intervention eye and 2.37 (0.6–8.9) mm^2 in the fellow eye at month 12 (Figure 5). The median (range) change in the square root of the area of GA from baseline was 0.356 (0.14–0.91) mm in the intervention eye and 0.336 (0.09–1.28) mm in the fellow eye at month 12 (Supplemental Table 5, available at AJO.com).

Case Reports. Two subjects experienced proliferative vitreoretinopathy. In some subjects, catheter tracks and

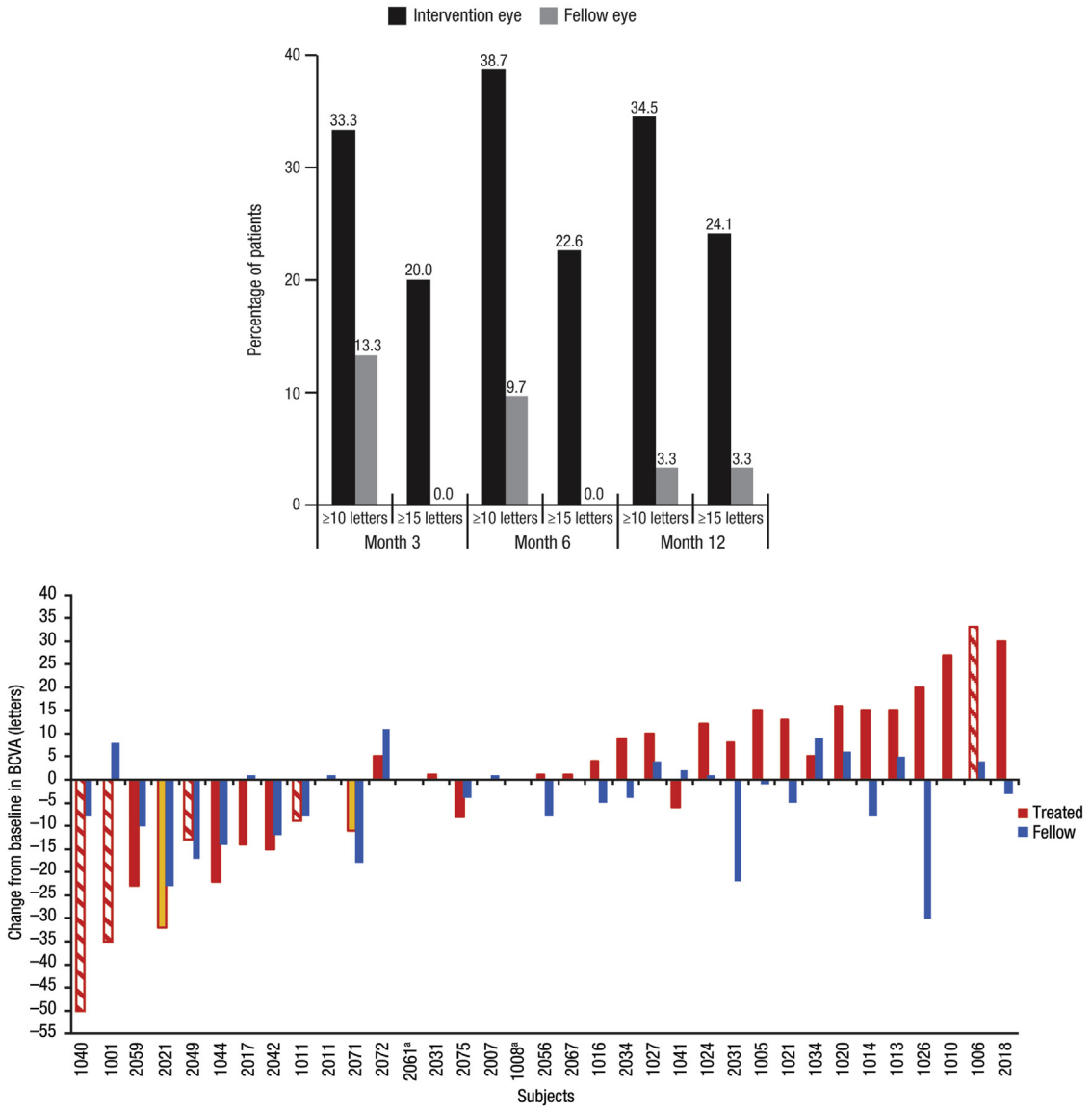
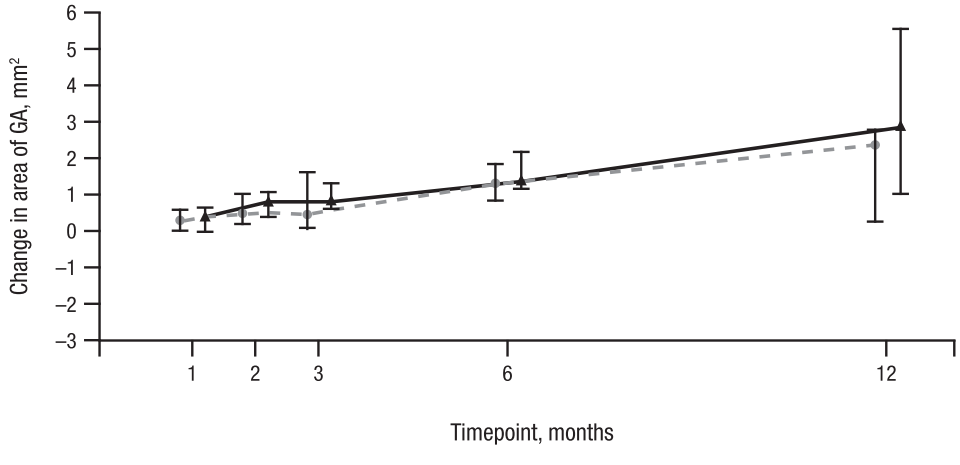


FIGURE 4. Best-corrected visual acuity (BCVA): (Top) Percentage of subjects with a gain of ≥10 and ≥15 letters at months 3, 6, and 12 after palucorcel treatment. (Bottom) Individual subject responses at month 12. Red indicates treated eyes; blue indicates fellow eyes; hashed bars indicate serious ocular adverse events; and gold bars indicate surgery without cell delivery. [a]Subjects were lost to follow-up after month 3.

linear fibrosis were observed on follow-up visits; sample images for 2 subjects (Subjects A and B) are shown in Figure 6 and 7, respectively. For Subject A (Figure 6), the dose assignment was 3.0×10^5 cells, and for Subject B (Figure 7), the dose assignment was 5.6×10^5 cells. For both subjects, no subretinal fluid, intraretinal cysts, or epiretinal membrane was observed. The OCT central foveal thickness ranged from 243 to 264 μm for Subject A and from 192 to 202 μm for Subject B. Based on these observed issues, the iTrack microcatheter delivery system was not adequate for continued development. The BCVA (Snellen equivalent) for Subject A was 20/800 at baseline and 20/200 by months 6 and 12. The BCVA (Snellen equivalent) for Subject B was 20/400 at baseline and 20/250 by months 6 and 12. Change from baseline in BCVA values (letters) over time is summarized in Supplemental Figure 2 (Supplemental Material available at AJO.com).

DISCUSSION

ALTHOUGH AMD IS THE PRIMARY CAUSE OF CENTRAL vision loss among elderly adults in the United States,[1,2] there are no approved treatments for nonexudative



Fellow eye	30	29	27	29	27
Intervention eye	28	28	26	25	26

FIGURE 5. Median (interquartile range) postpalucorcel change from baseline in geographic atrophy (GA) measured via fundus autofluorescence.

("dry") AMD, including the advanced atrophic form, GA.[2,4] Current management strategies for "dry" AMD are limited to lifestyle modifications and supportive measures in advanced stages of the disease.[1,4] Cell therapies and different cell lines are being evaluated in patients with AMD with GA.[10–12] The use of hUTCs (palucorcel) delivered to the subretinal space is being evaluated as a novel approach for the treatment of GA secondary to AMD. The purpose of this study was to evaluate the safety and reliability of palucorcel and to refine the surgical delivery procedure based on safety findings related to the subretinal microcatheter surgical procedure.

This phase 1/2a pilot study had inherent study limitations. A limited number of study subjects were included by design. This study was fellow-eye controlled; however, as a primarily safety-focused study, this phase 1/2a study was not masked and did not have the methodologic benefit of true randomization. Without masking procedures, intervention bias can affect certain safety and clinical response assessments, and treatment benefits may be overestimated.[13,14] In addition, there were certain limitations associated with using the fellow eye as a control; the fellow eye was not matched with the intervention eye in terms of baseline BCVA and lesion area/severity. For example, this may have affected relative evaluations of GA area because the growth rate for GA lesions differs depending on the size of the lesion. Furthermore, it is possible that the trauma of surgery may be associated with a release of cytokines that may improve visual function; these improvements, however, are generally short-lived (on the order of weeks, rather than ≥6 months).[15] For the phase 1 portion of this study, the intervention eye was the eye with worse visual acuity. Spontaneous improvements in visual acuity with the worse eye have been observed in subjects with GA owing to subjects developing or improving their ability to employ eccentric fixation of the target; typically, approximately 5%–6% of subjects show a gain of ≥15 letters in the worse eye.[16–19] This "learned" improvement in visual acuity may complicate the interpretation of BCVA results. Regardless, clinical responses in GA studies that advance beyond pilot study investigation, such as that reported herein, should be verified in studies that employ masking.

Beyond study design limitations, administration of the cells with the iTrack microcatheter using an ab externo and subretinal surgical approach led to an unacceptably high rate of retinal perforations and retinal detachments. Retinal detachment occurred in 5 subjects who underwent the surgical procedure and received palucorcel and 1 subject who underwent a partial surgical procedure but did not receive palucorcel. Therefore, retinal detachment may or may not be related to the application of palucorcel. Based on the high rate of retinal perforations and detachments, as well as the 2 subjects who experienced proliferative vitreoretinopathy, improvements in the surgical method of delivery are needed and are currently in evolution.

Nevertheless, this study provided valuable safety and potential efficacy data for palucorcel and insight into the need for an improved surgical procedure. In this study, palucorcel appeared to be well tolerated when delivered without

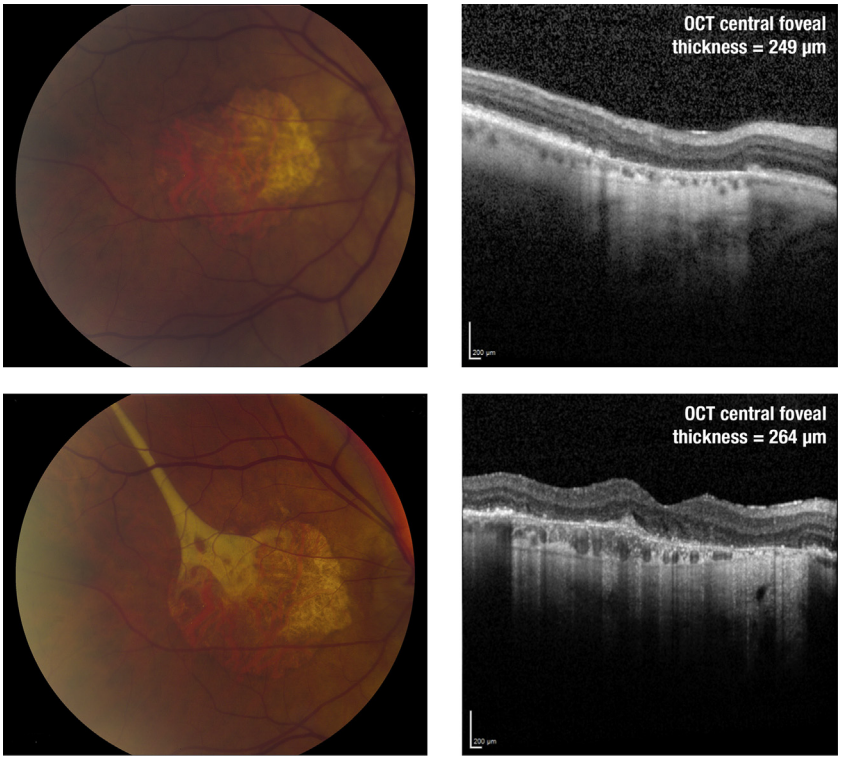


FIGURE 6. Fundus and optical coherence tomography (OCT) images at baseline and at month 6 postpalucorcel treatment. (Top) Subject A demonstrates baseline (screening) central macular geographic atrophy with a baseline best-corrected visual acuity of 20/800. (Bottom) At 6 months, subretinal palucorcel is visualized extending into the area of geographic atrophy and along the subretinal catheter track. Best-corrected visual acuity was 20/200 at months 6 and 12. OCT central foveal thickness did not change significantly.

retinal perforation and contained solely in the subretinal space. There was no evidence of immune response, cell rejection, or tumor formation, and this was noted without any protocol-specified systemic immunosuppression. During this early-stage study, the methods of administering the cells improved over time. Of particular relevance was the addition of intraocular endoscopy to improve visualization of retinal perforations resulting from the delivery of palucorcel to the intended site. The percentage of subjects with retinal perforations increased after the introduction of intraocular endoscopy; this was likely owing to improved detection of perforations with endoscopy. Identification of retinal perforations allowed for treatment with laser/cryotherapy prior to completing the surgery and resulted in a reduced incidence of retinal detachments. Furthermore, administration of palucorcel did not sensitize naïve subjects, and the presence of serum antibodies against palucorcel did not elicit an increase in ocular AEs or clinical events characterized by inflammation.

Administration of palucorcel was associated with improvements in BCVA; however, these results must be considered in the context of an unmasked clinical trial and with consideration given to the overall design of the study. On average, the intervention eye generally showed greater increases in BCVA from baseline over time compared with the fellow eye in the current study. Furthermore, the percentage of subjects with a gain of ≥10 and ≥15 letters in the intervention eye was numerically higher than in the fellow eye. Results of the current early-stage clinical study are consistent with preclinical findings in an RCS rat model, which showed that administration of palucorcel preserved RPE function and decreased the rate of visual function loss compared with untreated animals.[5] Palucorcel did not appear to reduce the rate of increase in the area of GA. Although data were summarized for all palucorcel doses in the current report, it should be noted that there did not appear to be a dose response for efficacy or safety.

Cell therapies offer a technology that can provide sustained delivery of cytokines and other factors, such as thrombospondins, which may improve the function of the aging or diseased retina.[5,8] These factors may be pleiotropic, acting on multiple cell types in the retina, such as RPE phagocytosis and synapse formation and retinal ganglion cell function.[9] GA is a chronic condition; thus, it may be expected that a therapeutic requires prolonged exposure to demonstrate effectiveness. hUTCs (palucorcel) can be delivered without the need for immune suppression and,

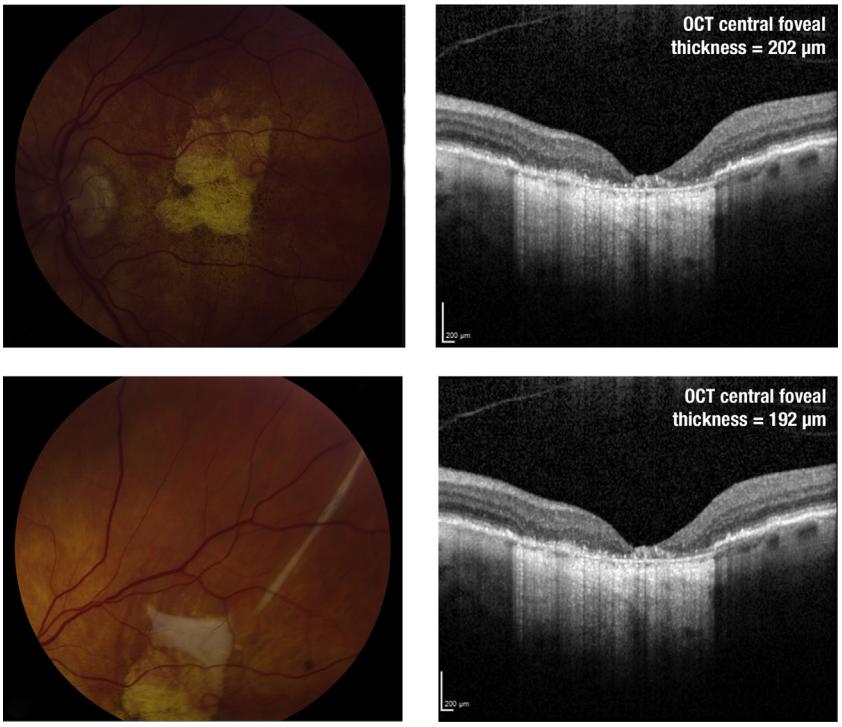


FIGURE 7. Fundus and optical coherence tomography (OCT) images at baseline and at month 6 post-palucorcel treatment. (Top) Subject B demonstrates baseline (screening) central macular geographic atrophy with baseline best-corrected visual acuity of 20/400. (Bottom) At 6 months, subretinal palucorcel is visualized extending into the area of geographic atrophy and along the subretinal catheter track. Best-corrected visual acuity was 20/250 at months 6 and 12. OCT central foveal thickness did not change significantly.

because they are not a polarized cell type, hUTCs can be delivered as a cell suspension. hUTCs secrete trophic factors that have been demonstrated to act on functional synapse formation and increase phagocytosis of RPE cells.[5,9,10] By knocking down the expression of specific factors, we have confirmed that these factors are important for the biologic activity of hUTCs.[8] Other studies suggest that the effects of cell therapy are maintained over months and act beyond the immediate area of cell delivery.[5] Thus, detaching the macula or fovea and interfering with the preferred retinal locus can be avoided. RPE transplantation requires immune suppression and delivery to the area of atrophy, increasing the risk to the patient.[20]

To summarize, results of this phase 1/2a study demonstrate that palucorcel was well tolerated as a single-dose therapy and when subretinal administration was achieved without a retinal perforation. Furthermore, in the current study, subretinal administration of palucorcel resulted in improvements in visual acuity in some subjects with vision loss secondary to GA; considering that there was no masking in this pilot study and there were limited numbers of study subjects, further studies that use an adequate control group are needed to determine the reproducibility and clinical relevance of these results. Further refinements of the surgical procedure and delivery system are needed to reduce the ocular complications associated with cell delivery in future studies. Nevertheless, the results of this pilot study, which showed good tolerability for palucorcel that remained in the subretinal space and potential efficacy for improving visual acuity, suggest that further study of palucorcel as a potential treatment for vision loss secondary to GA is warranted.

FUNDING/SUPPORT: JANSSEN RESEARCH & DEVELOPMENT, LLC, SPRING HOUSE, PA, SUPPORTED THIS STUDY. FINANCIAL DISclosures: Allen C. Ho and Tom S. Chang have served as consultants and received research grant funding from Janssen Research & Development, LLC. Robert F. Willenbucher and Terri Malone are employees of Janssen, and Paul Williamson was an employee of Janssen at the time this study was conducted. The following author has no financial disclosures: Michael Samuel. All authors attest that they meet the current ICMJE criteria for authorship.

Other Acknowledgements: Editorial support for the writing of this manuscript was provided by Megan Knagge, PhD, of MedErgy, and was funded by Janssen Research & Development, LLC. The authors thank the Independent Safety Monitoring Committee chair, Lee Jampol, MD, and committee members Dianne Catellier, PhD, Craig Greven, MD, and Michael Singer, MD, for their contributions to the study. In addition, the authors thank Digital Angiography Reading Center (DARC), New York, New York, USA, for providing digital angiography services.

REFERENCES

1. Buschini E, Fea AM, Lavia CA, et al. Recent developments in the management of dry age-related macular degeneration. *Clin Ophthalmol* 2015;9:563–574.
2. Hawkins BS, Bird A, Klein R, West SK. Epidemiology of age-related macular degeneration. *Mol Vis* 1999;5:26.
3. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol* 2000;45(2):115–134.
4. Grassmann F, Fleckenstein M, Chew EY, et al. Clinical and genetic factors associated with progression of geographic atrophy lesions in age-related macular degeneration. *PLoS One* 2015;10:e0126636.
5. Lund RD, Wang S, Lu B, et al. Cells isolated from umbilical cord tissue rescue photoreceptors and visual functions in a rodent model of retinal disease. *Stem Cells* 2007;25(3):602–611.
6. Alder J, Kramer BC, Hoskin C, Thakker-Varia S. Brain-derived neurotrophic factor produced by human umbilical tissue-derived cells is required for its effect on hippocampal dendritic differentiation. *Dev Neurobiol* 2012;72(6):755–765.
7. Strauss O, Stumpff F, Mergler S, Wienrich M, Wiederholt M. The Royal College of Surgeons rat: an animal model for inherited retinal degeneration with a still unknown genetic defect. *Acta Anat (Basel)* 1998;162(2–3):101–111.
8. Cao J, Murat C, An W, et al. Human umbilical tissue-derived cells rescue retinal pigment epithelium dysfunction in retinal degeneration. *Stem Cells* 2016;34(2):367–379.
9. Koh S, Kim N, Yin H, Harris I, Dejneka N, Eroglu C. Human umbilical tissue-derived cells (hUTC) promote synapse formation and neurite outgrowth via thrombospondin family proteins (TSPs). *J Neurosci* 2015;35(47):15649–15665.
10. Schwartz SD, Hubschman JP, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet* 2012;379(9817):713–720.
11. Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet* 2015;385(9967):509–516.
12. Schwartz SD, Tan G, Hosseini H, Nagiel A. Subretinal transplantation of embryonic stem cell-derived retinal pigment epithelium for the treatment of macular degeneration: an assessment at 4 years. *Invest Ophthalmol Vis Sci* 2016;57(5):ORSFc1–ORSFc9.
13. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273(5):408–412.
14. Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. *Ann Intern Med* 2002;136(3):254–259.
15. Nishijima K, Ng YS, Zhong L, et al. Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury. *Am J Pathol* 2007;171(1):53–67.
16. Sunness JS, Applegate CA, Gonzalez-Baron J. Improvement of visual acuity over time in patients with bilateral geographic atrophy from age-related macular degeneration. *Retina* 2000;20(2):162–169.
17. Bissell AJ, Yalcinbayir O, Akduman L. Bilateral geographic atrophy: spontaneous visual improvement after loss of vision in the fellow eye. *Acta Ophthalmol Scand* 2005;83(4):514–515.
18. Sunness JS, Applegate CA, Haselwood D, Rubin GS. Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and Stargardt disease. *Ophthalmology* 1996;103(9):1458–1466.
19. Sunness JS. Stem cells in age-related macular degeneration and Stargardt's macular dystrophy. *Lancet* 2015;386(9988):29.
20. Carr AJ, Smart MJ, Ramsden CM, Powner MB, da Cruz L, Coffey PJ. Development of human embryonic stem cell therapies for age-related macular degeneration. *Trends Neurosci* 2013;36(7):385–395.