Ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for treatment of geographic atrophy in age-related macular degeneration

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There is no treatment available for vision loss associated with advanced dry age-related macular degeneration (AMD) or geographic atrophy (GA). In a pilot, proof of concept phase 2 study, we evaluated ciliary neurotrophic factor (CNTF) delivered via an intraocular encapsulated cell technology implant for the treatment of GA. We designed a multicenter, 1-y, double-masked, sham-controlled dose-ranging study. Patients with GA were randomly assigned to receive a high-or low-dose implant or sham surgery. The primary endpoint was the change in best corrected visual acuity (BCVA) at 12 mo. CNTF treatment resulted in a dose-dependent increase in retinal thickness. This change was followed by visual acuity stabilization (loss of less than 15 letters) in the high-dose group (96.3%) compared with low-dose (83.3%) and sham (75%) group. A subgroup analysis of those with baseline BCVA at 20/63 or better revealed that 100% of patients in the high-dose group lost <15 letters compared with 55.6% in the combined low-dose/sham group (P = 0.033). There was a 0.8 mean letter gain in the high-dose group compared with a 9.7 mean letter loss in the combined low-dose/sham group (P = 0.0315). Both the implant and the implant procedure were well-tolerated. These findings suggest that CNTF delivered by the encapsulated cell technology implant appears to slow the progression of vision loss in GA, especially in eyes with 20/63 or better vision at baseline.

apoptosis | retina | photoreceptor degeneration

Age-related macular degeneration (AMD), the leading cause of blindness in people age 55 or older in developed countries (1–3), is a heterogeneous clinical entity in which retinal degeneration occurs predominantly in the macula and leads to impairment of central visual acuity (4, 5). AMD occurs in two general forms: wet AMD involving choroidal neovascularization with subsequent bleeding and fluid exudation, and dry AMD, which involves a constellation of clinical features that can include drusen, pigment clumping and/or retinal pigment epithelium (RPE) dropout, and geographic atrophy (GA) (4–6). GA can begin as a thinning of the RPE and lead subsequently to an atrophic change in the macula and loss of overlying photoreceptors (6, 7). GA is typically characterized by well-defined nummular patches of RPE loss or depigmentation, underlying choriocapillaris atrophy, and overlying photoreceptor degeneration (5). To date, no effective treatment for progressive vision loss is available for the atrophic form of macular degeneration.

Ciliary neurotrophic factor (CNTF) is a neurotrophic factor that retards loss of photoreceptor cells during retinal degeneration (8). CNTF is also a member of the IL-6 family of neuropoietic cytokines (9, 10). Its biological activities are mediated through a heterotrimeric complex consisting of CNTF receptor alpha (CNTFRα), gp130, and LIF receptor beta (LIFRβ), and the downstream signal transduction pathways (11). Although the intrinsic function of CNTF is not fully understood, exogenous CNTF affects the survival and differentiation of cells in the nervous system, including retinal cells (12, 13). CNTF effectively protected photoreceptors in 12 animal models of photoreceptor degeneration (14–18). Further, CNTF has passed appropriate milestones in a phase 1 human clinical study of retinitis pigmentosa (19). A key question for clinicians and researchers is whether CNTF can be used to treat retinal degenerations in humans.

Delivery of CNTF to the retina is a major challenge. The blood–retinal barrier prevents the penetration of a variety of molecules from the systemic circulation to the neurosensory retina. To overcome this challenge, encapsulated cell technology (ECT), and specifically the NT-501 implant, was developed to enable controlled, sustained delivery of therapeutic agents directly into the vitreous cavity, thus providing direct access to the retina (20). ECT uses cells encapsulated within a semipermeable polymer capsule that secretes therapeutic factors directly into the vitreous (17, 19). In addition, ECT implants can be retrieved, providing an added level of safety.

Histopathologic studies of multiple forms of retinal neurodegenerative diseases have demonstrated the possibility of using CNTF as an effective approach to reduce photoreceptor cell loss (14, 17, 18). Accordingly, the use of the implanted NT-501 implant, which secretes CNTF into the vitreous, may be beneficial in people with atrophic macular degeneration. The purpose of this phase 2 study was to demonstrate the safety profile of NT-501 in the GA patient population, evaluate the effect of CNTF on structure and function, and to determine the dose and primary endpoint for future studies.

Results

Study Patients. Between February and October 2007, 51 patients were enrolled and randomly assigned to study treatment. Groups were balanced for demographic and baseline ocular characteristics (Table 1). All patients completed the 12-mo endpoint, and no patients dropped out of the study.

Safety Profile. Cumulative adverse events for the 12-mo study period are summarized in Table 2. No serious adverse events related to the NT-501 implant or surgical procedures were reported during the 12-mo study period. No treatment-related severe adverse effects including retinal detachment, endophthalmitis, intraocular pressure (IOP) increase, or choroidal neovascularization

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(CNV) development were reported. No CNTF was detectable in the serum, and no serum antibodies against CNTF or encapsulated cells could be detected.

Structural and Functional Changes at 12 Mo. ***Changes in retinal thickness by optical coherence tomography (OCT).*** The total macular volume is an interpolated number that indicates retinal thickness averaged over the macular region and gives an estimate of macular retinal volume. It can be increased by increased retinal tissue cellularity, increased retinal cell volume, or increased interstitial fluid volume. It can be decreased by loss of retinal tissue, decreased size of retinal cells, or loss of interstitial retinal fluid.

There was a statistically significant difference in the change in total macular volume in the study eye compared with baseline in the high- or low-dose CNTF groups but not in the sham group (Table 3). The high- and low-dose CNTF groups had a significant increase in total macular volume compared with baseline at all time points (months 4, 6, and 12) ($P < 0.001$), and the high-dose group was significantly greater than the low-dose group at all time points ($P < 0.05$) (Table 3). This increase was associated with increased width of the outer layer complex (21), as seen on cross-sectional evaluation of high-resolution line scans. Fig. 1 shows an example of the OCT surface maps (Fig. 1*A*) and cross-section scans (Fig. 1*B*) of a high-dose treated eye at the baseline and 12 mo. The total macular volume increased from 6.42 mm^3 at baseline to 7.22 mm^3 at 12 mo after implant (Fig. 1*A*), and the cross-section scans showed that the width of the outer nuclear layer of photoreceptors increased at 12 mo after implant compared with the baseline (Fig. 1*B*).

Table 1. Baseline characteristics of the patients

Characteristics	Sham	Low dose	High dose
Sex			
Male	7 (58.3%)	7 (58.3%)	10 (37.0%)
Female	5 (41.7%)	5 (41.7%)	17 (63.0%)
Race			
Caucasian	12 (100.0%)	12 (100.0%)	27 (100.0%)
Ethnicity			
Nonhispanic/Latino	12 (100.0%)	12 (100.0%)	27 (100.0%)
Age			
Mean (SD)	74.5 (6.0)	78.3 (5.6)	74.9 (7.5)
Median	77.0	78.0	74.0
Range	64–82	65–88	56–87
BCVA			
Mean (SD)	55.3 (7.3)	49.9 (10.2)	53.5 (9.0)
Median	52.3	49.5	52.3
Range	33–71	27–68	33–71
Total Mac Vol,* mm^3			
Mean (SD)	6.29 (0.51)	5.79 (0.47)	6.01 (0.56)
Median	6.06	5.86	6.05
Range	5.66–7.2	4.97–6.35	4.78–7.28
Area of GA lesion,† mm^2			
Mean (SD)	9.84 (8.41)	11.41 (7.56)	7.23 (5.29)
Median	4.81	11.05	5.72
Range	1.04–25.28	0.48–22.61	1.21–21.0
ERG, μV			
Mean (SD)	95.25 (1.36)	83.48 (1.80)	72.98 (1.92)
Median	91.96	94.19	95.35
Range	65.3–140.5	22.7–200.9	19.2–218.1
Visual field sensitivity, dB			
Mean (SD)	1504.9 (336.7)	1217.2 (390.3)	1407.8 (487.5)
Median	1472.0	1123.0	1470.5
Range	1003–1974	747–2060	434–2359

*The overall P value is 0.175. $P = 0.298$ (High vs. Sham), $P = 0.064$ (Low vs. Sham) and $P = 0.268$ (High vs. Low).
†The overall P value is 0.506. $P = 0.3078$ (High vs. Sham), $P = 0.3202$ (Low vs. Sham) and $P = 0.8320$ (High vs. Low).

Table 2. Adverse events at 12 mo

Adverse events/eye disorders	Sham ($n = 12$)	Low dose ($n = 12$)	High dose ($n = 27$)
IOP increase*	3 (25%)	2 (16.7%)	2 (7.4%)
Eye hemorrhage†	1 (8.3%)	1 (8.3%)	2 (7.4%)
Photopsia	0 (0.0%)	1 (8.3%)	2 (7.4%)
Miosis	0 (0.0%)	1 (8.3%)	1 (3.7%)
Cataract‡	0 (0.0%)	0 (0.0%)	1 (3.7%)
CNV	1 (8.3%)	0 (0.0%)	0 (0.0%)
Wound leaks or erosion	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endophthalmitis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Implant extrusion	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retinal detachment	0 (0.0%)	0 (0.0%)	0 (0.0%)

*IOP increase (24–31 mmHg) usually lasted a few days to a few weeks and returned to normal at the next scheduled visit without medical intervention.
†Related to the surgical wound and recovered with no sequelae within 10 d.
‡Worsening of a preexisting cataract (mild).

To determine whether the observed increase in macular volume was due to pathologic changes of the retina, the frequency and incidence of cystoid macular edema (CME), epiretinal membrane (ERM), vitreomacular traction (VMT), choroidal neovascularization (CNV) at baseline and 12 mo were evaluated for each treatment groups. There was no increase in incidence and frequency in any of the pathologic changes associated with the high and low CNTF groups compared with the sham group (Table 3). In addition, when eyes with any of the above pathologies were excluded, the remaining high- and low-dose CNTF groups still had a significant increase in total macular volume compared with baseline at all time points (months 4, 6, and 12).

Visual acuity changes. When patients were grouped according to their baseline best corrected visual acuity (BCVA), there was a trend toward greater decline in BCVA in patients with better baseline vision in the combined low-dose/sham group, whereas BCVA in the high-dose group remained stable regardless of the baseline vision (Table 4). There is no BCVA change in either the high-dose group (-0.2 ± 8.4) or the low-dose/sham group (-1.0 ± 13.5) for patients with baseline BCVA at 20/200 or better (including all study patients). Although stable in BCVA in high-dose treated groups, a trend of greater level of BCVA worsening is associated with low-dose/sham groups at better baseline vision. For the subgroups of patients with baseline BCVA at 20/100 or better, 20/80 or better, and 20/63 or better, there is no change in BCVA in the high-dose groups (0.1 ± 6.7, 1.5 ± 5.6, and 0.8 ± 5.4, respectively). In comparison, the low-dose/sham groups showed an increasing decline of vision (-4.4 ± 12.9, -6.0 ± 14, and -9.7 ± 13, respectively). In the subgroup analysis of the mean BCVA change of those with baseline BCVA at 20/63 or better, the difference is also statistically significant ($P = 0.0313$) (Table 4).

Visual acuity stabilization. The high dose of NT-501 showed a trend toward stabilization of BCVA at 12 mo; 96.3% ($P = 0.078$) of treated-patients lost fewer than three lines of visual acuity (15 letters), versus 75% of the patients in the sham-treatment group (Fig. 2*A*). In a subgroup analysis of those with baseline BCVA at 20/63 or better, 5 of 9 (55.6%) in the combined low-dose/sham group lost <15 letters, whereas 10 of 10 (100%) in the high-dose group lost <15 letters, and this difference was statistically significant ($P = 0.033$) (Fig. 2*B*).

Geographic atrophy (GA) lesion. No statistically significant difference in progression of GA lesion size were observed at 12 mo for either the high-dose (2.03 ± 1.04 mm^2) or low-dose (2.19 ± 1.87 mm^2) groups compared with the sham group (2.42 ± 1.95 mm^2) (Table 3).

Electroretinogram (ERG). White flash amplitude (single flash), white, light adapted 31 Hz flicker amplitude and implicit time were

Table 3. Summary of changes from baseline at 4, 6, and 12 mo

End point		Sham (n = 12)	Low dose (n = 11)	High dose (n = 26)	P value
Change in total macular volume, mm^3					
Month 4	Mean	0 ± 0.14	0.26 ± 0.16	0.43 ± 0.25	<0.001
	Range	−0.18 to 0.26	0.03 to 0.48	−0.04 to 1	
Month 6	Mean	−0.01 ± 0.19	0.24 ± 0.18	0.45 ± 0.29	<0.001
	Range	−0.28 to 0.26	−0.01 to 0.61	−0.2 to 0.93	
Month 12	Mean	−0.07 ± 0.15	0.22 ± 0.24	0.48 ± 0.22	<0.001
	Range	−0.31 to 0.13	−0.12 to 0.68	0.08 to 0.91	
Change in cystoid macular edema at month 12*					
	Total	11	9	25	
	No	4 (36.36%)	6 (66.67%)	15 (60%)	
	Yes	7 (63.64%)	3 (33.33%)	10 (40%)	
Change in area of geographic atrophy, mm^2					
Month 12	Mean	2.42 ± 1.95	2.19 ± 1.87	2.03 ± 1.04	0.788
	Range	0.3 to 6.36	−0.03 to 5.91	0.5 to 3.86	
Change in electroretinogram (geometric means), μV					
Month 12	Mean	1.09 ± 1.66	0.97 ± 1.79	1.16 ± 1.78	0.766
	Range	0.4 to 2.0	0.2 to 1.8	0.4 to 4.1	
Change in Humphrey visual field sensitivity, dB					
Month 12	Mean	75.0 ± 135.9	−136.0 ± 279.3	59.1 ± 373.1	0.893
	Range	−154 to 281	−589 to 176	−756 to 846	

*Only eyes without CME at baseline were included in this analysis.

evaluated. No significant changes in ERG were observed at 12 mo compared with the baseline in any of the treatment groups (Table 3).

Humphrey visual field. Humphrey visual field (HVF 10–2) sensitivity was evaluated. No significant changes in Humphrey visual field sensitivity were observed (Table 3).

Discussion

This study was a pilot, proof-of-concept phase 2 study of NT-501. We found that CNTF treatment resulted in a dose-dependent increase in retinal thickness as early as 4 mo after implant and this increase was maintained through 12 mo ($P < 0.001$). This anatomical change was associated with visual function stabilization, as measured by mean BCVA change. The high-dose treated eyes maintained stable vision regardless of baseline BCVA. However, a trend of greater vision loss is associated with low-dose/sham treated eyes in subgroups with better baseline vision (Table 4). Among eyes with starting BCVA 20/63 or better, the difference of mean BCVA change between the high-dose group and the low-dose/sham group was >10.5 letters favoring the high-dose group ($P < 0.0313$). A trend of vision stabilization is also demonstrated by 15-letter loss, in the high-dose treated group compared with sham and low-dose groups at 12 mo (Fig. 2*A*). Among eyes with starting BCVA 20/63 or better, the difference of vision stabilization as measured by 15-letter loss between the high-dose group and the low-dose/sham group was statistically significant favoring the high-dose group ($P < 0.033$) (Fig. 2*B*). Both the NT-501 implant and the implant procedure were well-tolerated; no serious adverse events associated with the implant or implantation procedure were reported. Furthermore, there was no change in ERG and visual field sensitivity in the treated eyes compared with the baseline. The explanted devices showed healthy cells and stable CNTF output up to 12 mo.

Although the GA area for different treatment groups at baseline differed slightly among groups, this difference was not statistically significant (Table 1). The three treatment groups did not show a statistically significant difference in their rate of progression in the GA area (Table 3). However, the trend favors the treated groups. The progression of GA area in the sham group was 2.42 ± 1.95 mm^2, compared with the CNTF-treated groups, with GA progression at 2.19 ± 1.87 mm^2 (low-dose group) and 2.03 ± 1.04 mm^2 (high-dose group). Because of the relative small sample size and short study duration, it was not a surprise that there was not a significant difference in area of GA progression at 1 y. It is important to note that the progression rate in this study is consistent with that reported in a long-term natural history study (22). It is also important to note that the GA area change represents RPE lesion progression and

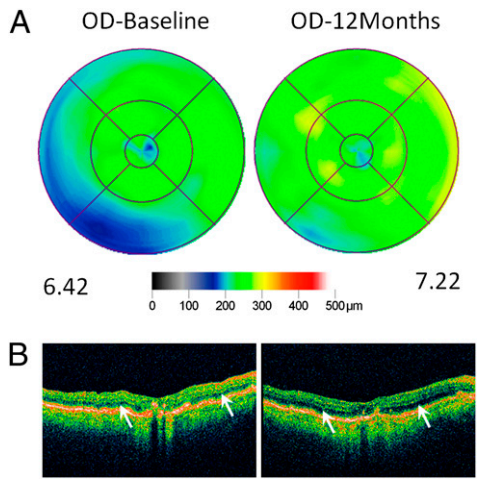

Fig. 1. Effect of high-dose CNTF on the increase of retinal thickness of the right eye of an 85-y-old GA patient. (*A*) Optical coherence tomography (OCT) volume scans at baseline (*Left*; 6.42 mm^3) and 12 mo (*Right*; 7.22 mm^3). (*B*) Individual OCT images of the macula at baseline (*Left*) and 12 mo (*Right*). The dark areas indicated by arrows show the outer nuclear layer. The images were both obtained as 7 mm long scans offset 5 degrees from the horizontal, beginning at the midpoint of the temporal aspect of the optic nerve. Because these custom scans are oriented with respect to the midpoint of the temporal aspect of the optic nerve, rather than with the presumed foveal center, registration and foveal centration difficulties inherent with time domain Stratus OCT are minimized. Accordingly, these images were obtained from similar, if not identical retinal locations. The variation in choroidal shadowing is not related to differing retinal scan locations; rather, it represents differences in thickness of the overlying layers after treatment with NT-501 and, possibly, to differences in overall image saturation. The qualitative widening of the outer layer complex was observed consistently among subjects.

Table 4. BCVA changes from baseline at 12 months

Baseline BCVA	High dose	Sham/low dose	*P* value
20/200 or better	−0.2 ± 8.4 (*n* = 27)	−1.0 ± 13.5 (*n* = 24)	0.8087
20/100 or better	0.1 ± 6.7 (*n* = 19)	−4.4 ± 12.9 (*n* = 15)	0.1966
20/80 or better	1.5 ± 5.6 (*n* = 12)	−6.0 ± 14.0 (*n* = 12)	0.0998
20/63 or better	0.8 ± 5.4 (*n* = 10)	−9.7 ± 13.0 (*n* = 9)	0.0313

the primary target of CNTF is photoreceptors; therefore, CNTF does not have a direct impact on RPE cells. Any potential effect of CNTF on the GA lesion would be indirect and mediated through its effect on photoreceptors.

CNTF had a significant biological effect in increasing total macular volume (Table 3). The initial increase was seen as early as 4 mo and continued through 12 mo. The relative change in macular volume from baseline was highly statistically significantly greater in the high-dose treated group compared with the low-dose treated group and sham-treated group. The increased total macular volume may be related to an increased retinal cell number, increased cell volume, retinal toxicity, or a combination of these factors. There was no evidence for a toxic effect, as shown by lack of difference in cystoid macular edema (Table 3) or epiretinal membrane in CNTF-treated eyes compared with sham-treated eyes and by a strong trend of emerging visual acuity benefit at 12 mo. Furthermore, the increased width of the outer layer complex (21), as observed on OCT cross-sections, was very similar to that observed in preclinical studies (17, 23). We cannot rule out changes in the width of other retinal layers in addition to the outer hyporeflective layer to account for the increased total macular volume. Although it would have been preferable to specifically segment each of the retinal layers, including the outer layer complex, the resolution of the time domain scans did not permit accurate segmentation from which quantitative measurements could be obtained. Any future clinical trials with NT-501 should use spectral domain OCT, which would allow quantitation of specific retinal layer thickness. Together, these data suggest that the increased retinal thickness reflects increased photoreceptor metabolic activity or an increased number of photoreceptors. Consistent with these findings, CNTF was recently shown to prolong cone photoreceptor survival and regenerate cone outer segments in a rat model of retinal degeneration (24). In this study, the CNTF cone rescue was most effective during early stage of the disease when the loss of cones was incomplete. Once complete cone loss had occurred during late stage of disease, CNTF could no longer bring the cone receptors back, suggesting the importance of early treatment (24). Consistent with observations in the animal studies, using adaptive optics scanning laser ophthalmoscopy (AOSLO), Talcott et al. (25) recently reported cone preservation in CNTF-treated eyes compared with the sham-treated fellow eyes in patients with retinitis pigmentosa and Usher Syndrome Type 2.

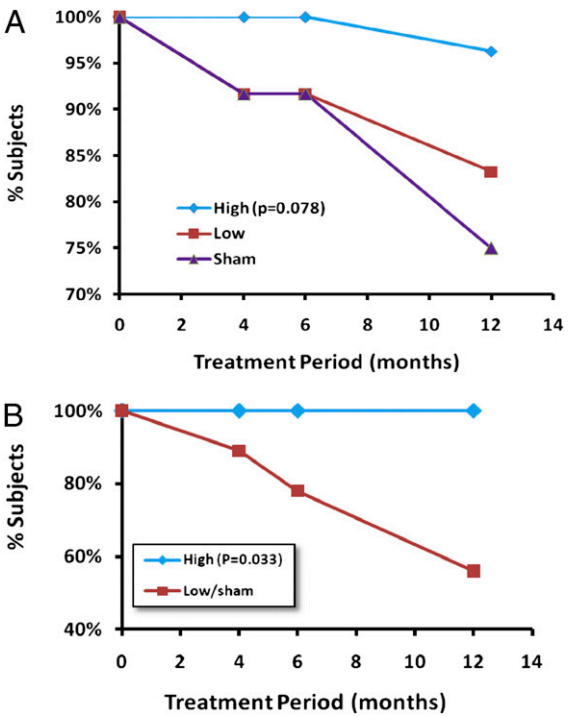

Fig. 2. Effect of intraocular CNTF on visual acuity stabilization. (*A*) Percentage of subjects losing <15 letters from baseline over 12 mo. (*B*) Significant effect of CNTF on visual acuity stabilization in the high-dose group with baseline BCVA at 20/63 or better.

Although no statistically significant improvement in visual acuity was observed across all treatment groups at 12 mo after implant, the CNTF implant appeared to preserve vision. For mean BCVA change, high-dose treated eyes maintained stable vision regardless of baseline BCVA. However, there is a greater vision loss associated with low-dose/sham groups with better baseline BCVA groups. When BCVA decrease (15-letter loss) from the baseline is considered, the trend is also favoring the treatment groups ($P = 0.078$). The statistically significant OCT results combined with the favorable observation in BCVA preservation demonstrate an encouraging trend toward a beneficial treatment effect for CNTF. This trend reaches maximal effect when the high-dose group is compared with that of the low-dose/sham group with baseline BCVA at 20/63 or better ($P < 0.033$). Visual acuity loss as a function of baseline visual acuity was also observed in a natural history study of geographic atrophy (5, 22). In these studies, a higher rate of acuity loss was associated with better baseline BCVA (>20/50) with 41% of subjects losing greater than three lines of vision at 2 y and 70% at 4 y.

The protective effect of CNTF has been shown in 12 animal models of retinal degeneration in four different species. This study demonstrated that CNTF may be beneficial in preserving vision in patients with geographic atrophy. The encapsulated cell technology implant is particularly suited for the long-term delivery of CNTF directly to the retina to treat this sight-threatening disease. Future clinical studies in a larger patient population should be considered (ClinicalTrials.gov no. NCT00277134).

Materials and Methods

Study Design. A total of 51 patients were enrolled at eight sites in the United States in a 1-y, prospective, randomized, double-masked, sham-controlled study of the safety and efficacy of intraocular NT-501 in patients with GA associated with dry age-related macular degeneration. Approvals were received from the National Institutes of Health Recombinant DNA Advisory Committee, the Food and Drug Administration, and from the institutional review board and institutional biosafety committee at each site before enrollment. Subjects signed written informed consent before determination of their full eligibility.

The study inclusion criteria were as follows: age at least 50 y with best corrected visual acuity of 20/50–20/200 (Snellen equivalent determined with the use of an EDTRS chart) and presence in the study eye of GA compatible with category 3 or 4:00 AMD as defined by Age Related Eye Disease Study. GA is defined as one or more well-defined, usually more or less circular, patches of partial or complete depigmentation of the RPE (a patch must be at least 175 microns in greatest linear dimensions as determined by grading of fundus photographs). The eligibility of subjects was confirmed by an independent central reading center according to a standardized criteria and trained graders who were masked to subjects' treatment assignment.

The primary efficacy endpoint, change in BCVA, was prespecified at 12 mo after implant. Patients received either a high- or low-dose NT-501 implant or a sham treatment in one eye only. The high dose in this trial was selected based on the dose–response effect of CNTF in the *rcd1* model of retinal degeneration (17). In this model, maximum protection was achieved with the NT-501–6A implant. Because there was an ethical concern for

implanting an empty device, a low-dose device was included in this trial. The intent of the low dose in this trial was to serve as a placebo so it was 50% of the minimum effective dose in the *rcd1* dog model. Because of the small sample size, we combined the low-dose group with the sham group for the analysis.

BCVA was measured by an Electronic Visual Acuity Tester (EVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (26). BCVA was measured six times at three baseline visits. Baseline 1 BCVA was used to qualify subjects, and Baseline 2 and 3 BCVA (average of four measures) was used as baseline BCVA. Three BCVA measurements were taken for each subsequent visit, and the average of the three BCVA values was used to assess the change from baseline.

Retinal thickness and morphology were evaluated by OCT. The fast macular thickness map protocol, a 7-mm 5° horizontal line scan, and 6-mm vertical line scan were obtained with the Stratus OCT and software version 4.0 or higher (Carl Zeiss Meditec). OCT images were collected by certified technicians. The images were evaluated by masked readers at the Duke University OCT Reading Center and analyzed for average thickness at center-point, total macular volume, and average thickness in nine subfields. Pathologic findings, such as cysts, ERM, VMT, and CNV were also recorded and analyzed.

Fundus photos were collected by certified photographers. The protocol required stereo for all fields when performing fundus imaging. The fundus photos were evaluated for GA lesion size by masked graders at the Hoover Rehabilitation Services for Low Vision and Blindness, Greater Baltimore Medical Center. Central vision (Humphrey 10–2) visual field sensitivity tests were performed on the Humphrey Field Analyzer II 700 Series equipped with the 10–2 program. The Central10-2 Program with 4 Dot white stimuli testing target was used for visual field testing. Electroretinography tests were performed as described in "Standard for Clinical Electroretinography (2004 update)" (27).

Study Treatment. The CNTF-secreting, encapsulated cell implants, designated NT-501 (Neurotech USA), are 6 mm long with 1 mm diameter and are constructed of a semipermeable polymer outer membrane. They contain an internal poly-(ethylene terephthalate) yarn scaffold that supports human mammalian cells. The cells were genetically engineered to produce human CNTF. Two separate transfections with this construct yielded two independent cell lines that released CNTF at different output rates. The low-dose implants released 5 ng per day and the high-dose implant released 20 ng per day before implant.

Patients were randomly assigned to receive a high-dose implant, a low-dose implant or sham surgery in one eye at 2:1:1 ratio. The acuity testers were masked to the treatment assignment. The physician who performed the implant surgery was not masked for the implant or sham but was masked to the dose of implant. Other personnel at each study site (except for those assisting with implant), patients, and personnel at the reading centers were masked to the patient treatment assignment.

Statistical Analysis. The efficacy analysis was performed on an intent-to-treat basis among all subjects. Because all subjects completed the study as planned, the last-observation-carried-forward method for missing data was not used. For change in BCVA, ERG, and Visual Field Sensitivity, the within-group and between-group comparisons were based on a paired Student's *t* test. Clinical response rates were compared between groups by using a two-sided Fisher's exact test. For retinal thickness change as measured by OCT, the overall comparison among treatment medians was assessed by using the Kruskal–Wallis test. Pair-wise differences between treatment medians were assessed by using the Wilcoxon rank sum test.

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