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Safety and Activity of a Single, Intravitreal Injection of Human Retinal Progenitor Cells for Treatment of Retinitis Pigmentosa (RP)

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OBJECTIVE The objective of this first-in-man clinical study was to assess the safety and activity of human retinal progenitor cells (hRPC) in adults with retinitis pigmentosa.

PURPOSE RP is an incurable blinding disease caused by death of first rod, then cone, photoreceptors in the retina. Preclinical studies demonstrated that transplantation of retinal progenitor cells into the eye can significantly slow photoreceptor loss. The purpose of this study was to assess the safety and potential efficacy of a single intravitreal injection of hRPC for treatment of retinitis pigmentosa

METHODS A phase 1/2a prospective multicenter open-label study (NCT02320812) evaluated 28 patients (ages 18 -73 years) with RP in two vision cohorts: best-corrected visual acuity (BCVA) in the treated eye was between 20/200 and “hand motions” in the first cohort and 20/63-20/200 in the second. Patients received a single 50 microliter intravitreal injection of 0.5, 1.0, 2.0 or 3.0 million hRPC. Safety and efficacy were evaluated at scheduled intervals through 12 months post-treatment. Safety was demonstrated at each dose level in cohort 1 subjects before proceeding to a higher dose level in the same cohort and before cohort 2 subjects could be enrolled at the same dose level.

RESULTS Treatment-related adverse events were reported in 21 subjects (75.0%) and were mostly mild to moderate and transient. Although the study was not powered or designed to assess efficacy, BCVA and other parameters were monitored over 12 months. Vision of hand motions or counting fingers were scored as zero letters correct for purposes of analysis. Mean change in BCVA from pre-treatment to month 12 (treated eye minus untreated eye) was 3.64 letters for all study subjects, 1.38 letters for the 0.5M dose group, 1.00 letter for the 1.0M dose group, 4.83 letters for the 2.0M dose group and 9.00 letters for 3.0M hRPC. When subjects without measurable BCVA at baseline (n = 8) were excluded the difference in mean change in BCVA (treated eye - untreated eye) at 12 months was 1.83 letters for the 0.5M dose group, 0.17 letters for the 1.0M dose group, 7.50 letters for the 2.0M dose group and 11.25 letters for 3.0M hRPC.

CONCLUSION Intravitreal injection of hRPC was safe and well-tolerated at doses up to 3 million cells. The change in BCVA between treated and untreated eyes was positive at all dose levels, with suggestion of a dose response at the higher dose levels. A phase 2b masked, controlled study designed to confirm efficacy using BCVA and other potentially more sensitive endpoints is currently ongoing.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

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Year 1 Time to Mobility Test Completion in a Voretigene Neparvovec-rzyl Trial in Subjects With *RPE65* Mutation–Associated Inherited Retinal Disease

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OBJECTIVE To determine time to Multi-Luminance Mobility Test (MLMT) completion in subjects receiving voretigene neparvovec-rzyl (VN) with *RPE65* mutation–associated inherited retinal disease (IRD).

PURPOSE One year after receiving VN in a phase 3 trial, subjects with *RPE65* mutation–associated IRD showed improved ambulatory navigation, light sensitivity, and visual field compared with controls. We report year 1 time to completion data from the MLMT, which measures the ability to navigate in various light levels.

METHODS Subjects were randomized 2:1 to enter the intervention (receiving bilateral, subretinal injections of VN; n=20) or control group (n=9), stratified for age and MLMT performance at screening, and tested for accuracy and speed on MLMT at 7 standardized illumination levels (1 to 400 lux). The lowest level subjects could pass MLMT was determined at baseline. Endpoints included time to MLMT completion: averaged over lux levels; at the lowest common lux level (lowest lux level for which a

subject had time observations at all 5 visits from baseline to year 1); at the lowest passing baseline lux level (across time points); and at the highest failing baseline lux level (across time points).

RESULTS Changes from baseline to year 1 in MLMT time to completion were analyzed using analysis of variance with change from baseline as the response variable and treatment group as a covariate. Time to complete the MLMT for subjects receiving VN was significantly shorter compared with control subjects for all analyses except the lowest passing baseline lux level, not adjusting for multiplicity ($P<0.05$; Table 1). The mean treatment difference (95% CI) for the time to complete the MLMT (in seconds) was: −49.5 (−77.9, −21.2) when averaging across lux levels; −101.0 (−200.2, −1.8) when using the lowest common lux level over time; −14.8 (−41.6, 12.1) when using the lowest passing baseline lux level; and −98.4 (−192.9, −4.0) when using the highest failing baseline lux level.

CONCLUSION Subjects with biallelic *RPE65* mutation–associated IRD who received VN gene replacement experienced significant reductions in MLMT time to completion at 1 year versus subjects in the control group.

Table 1. Bilateral Mobility Test Time to Completion, Summary of Analyses (mITT)

	Intervention (n=20)			Control (n=9)			Year 1	
Time to complete (sec)	Baseline	Year 1	Change	Baseline	Year 1	Change	Difference (95% CI) (Intervention-Control)	*P* Value
Averaged over lux levels[a]								
N	20	20	20	9	9	9		
Mean (SD)	101.1 (41.7)	49.0 (35.6)	-52.1 (38.1)	81.8 (20.8)	79.3 (20.3)	-2.6 (23.5)	-49.5 (-77.9, -21.2)	0.001
Range (min, max)	38, 179	16, 147	-145, 5	57, 124	54, 120	-32, 26		
Quartiles (25^{th}, med, 75^{th})	63, 91, 134	22, 33, 75	-67, -44, -29	66, 81, 91	64, 79, 92	-27, -9, 20		
Improved, n (%)			19 (95)			5 (56)		
Lowest common lux level								
N	17	17	17	9	9	9		
Mean (SD)	184.6 (127.7)	50.9 (48.6)	-133.6 (131.1)	131.2 (43.8)	98.6 (65.1)	-32.7 (79.9)	-101.0 (-200.2, -1.8)	0.046
Range (min, max)	67, 573	15, 196	-541, 19	64, 195	31, 253	-143, 86		
Quartiles (25^{th}, med, 75^{th})	120, 139, 184	20, 32, 69	-166, -111, -59	94, 140, 167	58, 84, 112	-91, -30, 25		
Improved, n (%)			16 (94)			6 (67)		
Lowest passing baseline lux level								
N	19	19	19	9	9	9		
Mean (SD)	60.7 (19.2)	29.7 (15.1)	-31.0 (20.1)	79.8 (38.4)	63.6 (32.1)	-16.2 (49.7)	-14.8 (-41.6, 12.1)	0.27
Range (min, max)	33, 102	16, 69	-79, -2	40, 141	26, 126	-91, 62		
Quartiles (25^{th}, med, 75^{th})	43, 62, 68	19, 24, 32	-44, -34, -13	52, 64, 119	44, 59, 88	-37, -26, 2		
Improved, n (%)			19 (100)			6 (67)		
Highest failing baseline lux level								
N	19	19	19	9	9	9		
Mean (SD)	161.4 (132.8)	34.4 (17.5)	-127.0 (128.9)	124.8 (55.1)	96.2 (71.2)	-28.6 (67.4)	-98.4 (-192.9, -4.0)	0.042
Range (min, max)	40, 573	16, 70	-541, 1	44, 195	26, 253	-143, 86		
Quartiles (25^{th}, med, 75^{th})	74, 134, 191	20, 31, 44	-144, -87, -54	87, 112, 174	57, 84, 112	-36, -23, -12		
Improved, n (%)			18 (95)			7 (78)		

mITT, modified intent to treat; SD, standard deviation; sec, seconds.
P value is from an analysis of variance with change from baseline as the response variable and treatment group as a covariate.
[a]All measures per person, per visit were averaged and then analyzed.

HUMAN RESEARCH This study involves human research.

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3-Year Update for the Phase 3 Voretigene Neparvovec-rzyl Study in Biallelic *RPE65* Mutation–Associated Inherited Retinal Disease

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OBJECTIVE To provide an update of the durability of this potentially one-time intervention.

PURPOSE To present data from a phase 3 trial conducted in subjects with biallelic *RPE65* mutation–associated IRD to determine whether improvements observed in functional vision, light sensitivity, and visual field 1 and 2 years after administration of VN are maintained at 3 years after administration.

METHODS Twenty-nine subjects with biallelic *RPE65* mutation–associated IRD were randomized to either intervention (I; bilateral subretinal VN) or control/intervention (C; VN after 1 year of observation). The primary endpoint was bilateral multi-luminance mobility test (MLMT) at 7 standardized illumination levels. Additional endpoints were full-field light sensitivity threshold (FST) testing, visual acuity (VA), and Goldmann kinetic visual field (GVF). Safety endpoints were adverse event reporting, physical and ophthalmic examinations, and laboratory testing.

RESULTS MLMT mean (SD) bilateral change score was 1.8 levels (1.0) for I subjects (n=20) at 3 years and 2.1 levels (1.6) for C subjects (n=9) at 2 years, with >68% of subjects passing MLMT at the lowest light level measured at 3 years (I subjects) and 2 years (C subjects). Mean change in white light FST averaged over both eyes was -2.04 $\log_{10}$ (cd.s/m^2) (1.43) at 3 years for I subjects (n=19) and -2.69 $\log_{10}$ (cd.s/m^2) (1.41) at 2 years for C subjects (n=9). Mean improvements in FST were >150-fold in light sensitivity measured at 3 years (I subjects) and 2 years (C subjects). Mean change (SD) in VA averaged over both eyes was consistent through 3 years for I subjects and 2 years for C subjects. Mean change (SD) in sum total degrees on GVF III4e, averaged over both eyes, was +282 (257) for I subjects at 3 years (n=18) and +183 (310) in C subjects at 2 years (n=9). The safety profile was consistent with vitrectomy and the subretinal injection procedure.

CONCLUSION VN therapy demonstrated a favorable benefit-risk profile with improved functional vision and visual function in subjects with biallelic *RPE65* mutation–associated IRD for at least 3 years following administration in I subjects. Improvements in MLMT, FST, and GVF in C subjects were consistent with those in I subjects. The safety profile was consistent with the administration procedure.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board