Evaluation of Baseline Characteristics on Lesion Progression in a Large Phase 2 Clinical Trial for Geographic Atrophy (FILLY Study)

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OBJECTIVE The goal of this study is to evaluate the impact of select baseline characteristics on progression of geographic atrophy in eyes receiving treatment with APL-2 or sham.

PURPOSE To evaluate the impact of select baseline characteristics on progression of geographic atrophy (GA) in eyes receiving treatment with APL-2 or sham.

METHODS The FILLY trial was a 246-patient Phase 2 multicenter, randomized, single-masked, sham-controlled clinical trial of APL-2 in patients with GA. Intravitreal injections of APL-2 were administered in the study eye monthly or every other month (EOM) for 12 months. The primary efficacy endpoint was the change in GA lesion size from baseline to Month 12 as compared to sham. The effect of select baseline characteristics (gender, baseline GA lesion size and lesion type [unifocal or multifocal]) on mean change in GA lesion size at Month 12) was analyzed. Only patients with observed data at Month 12 were included.

RESULTS The FILLY phase 2 study met its primary endpoint. The overall mean change in GA lesion size (mm^2) at 12 months from baseline was 1.46 (SD 0.98, 95% CI 1.21-1.70, $p< 0.05$) in the monthly APL-2 (n=67), 1.63 (SD 1.61, 95% CI 1.20-2.05, $p= 0.067$) in bi-monthly APL-2 (n=58), and 2.19 (SD 1.50, 95% CI 1.82-2.55) in the sham (n=67) groups, respectively. Changes in lesion size by select baseline factors are summarized in Table 1.

CONCLUSION Benefit of treatment with APL-2 was observed across all selected subgroups of baseline factors. Treatment with APL-2 trended to be more effective in controlling GA progression with increasing baseline lesion size in a non-linear manner. The impact of active treatment was observed irrespective of lesion type.

Table 1

Baseline Factor	Treatment Group	N	Baseline GA Lesion Size, mm^2	Mean Change in GA Lesion Size at M12, mm^2 (SD)	95% CI
Gender					
Female	APL-2 M	44	8.22	1.48 (0.95)	(1.18-1.76)
	APL-2 EOM	37	9.18	1.63 (1.78)	(1.03-2.22)
	Sham	43	8.99	2.48 (1.63)	(1.97-2.97)
Male	APL-2 M	23	7.5	1.42 (1.07)	(0.96-1.88)
	APL-2 EOM	21	7.6	1.64 (1.27)	(1.06-2.22)
	Sham	24	7.24	1.67 (1.09)	(1.20-2.12)
Lesion Size (mm^2)					
< 4.5	APL-2 M	14	3.48	1.15 (0.81)	(0.68-1.62)
	APL-2 EOM	13	3.07	1.08 (1.40)	(0.23-1.92)
	Sham	15	3.53	1.44 (0.70)	(1.05-1.82)
≥ 4.5 - < 7.5	APL-2 M	22	5.85	1.19 (0.91)	(0.78-1.58)
	APL-2 EOM	15	5.65	1.45 (0.99)	(0.90-1.99)
	Sham	19	5.96	1.83 (1.33)	(1.18-2.46)
≥ 7.5 - < 10.5	APL-2 M	13	8.83	2.19 (1.02)	(1.57-2.80)
	APL-2 EOM	9	9.11	2.91 (2.73)	(0.81-5.00)
	Sham	10	8.87	2.68 (1.37)	(1.70-3.66)
≥ 10.5	APL-2 M	18	13.43	1.50 (0.96)	(1.02-1.98)
	APL-2 EOM	21	13.93	1.56 (1.25)	(0.98-2.12)
	Sham	23	13.27	2.75 (1.81)	(1.96-3.53)
Lesion Type					
Unifocal	APL-2 M	19	7.75	1.61 (1.02)	(1.11-2.10)
	APL-2 EOM	22	9.98	1.17 (0.88)	(0.77-1.55)
	Sham	24	8.19	2.32 (1.52)	(1.67-2.95)
Multifocal	APL-2 M	48	8.06	1.40 (0.97)	(1.11-1.68)
	APL-2 EOM	36	7.77	1.92 (1.88)	(1.28-2.55)
	Sham	42	8.33	2.11 (1.52)	(1.63-2.57)

M: Monthly; EOM: Every Other Month

Table 1.

HUMAN RESEARCH Yes: Approved by institutional review board

Surgical Implantation of a Biosynthetic RPE Monolayer for Advanced Dry Age-Related Macular Degeneration (AMD): Experience From a Phase 1/2A Study

- Amir H. Kashani, MD , PhD
- Jeremy Uang
- Jane S. Lebkowski, PhD
- Debbie Mitra, PhD
- Dennis Clegg, PhD
- David R. Hinton, MD
- Mark S. Humayun, MD, PhD

OBJECTIVE Is it feasible and safe to surgically implant a confluent monolayer of human embryonic stem cell-derived RPE into the area of geographic atrophy in patients with advanced, dry AMD?

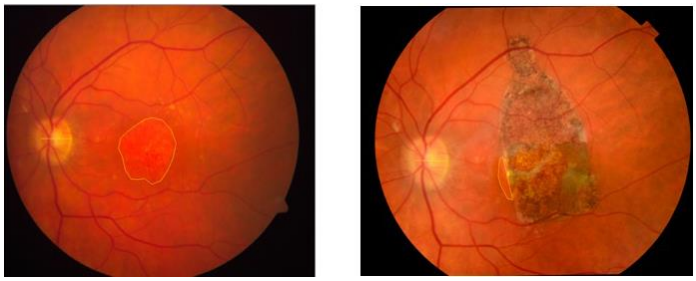
PURPOSE To report the anatomic and surgical results from a phase I/2a clinical trial testing the safety and efficacy of an investigational human embryonic stem cell (hESC) derived RPE monolayer on an ultrathin synthetic substrate to treat severe vision loss from geographic atrophy (GA) in advanced dry AMD. The implant is called California Project to Cure Blindness RPE 1 (CPCB-RPE1).

METHODS A single-arm, open label, prospective, non-randomized, Phase 1/2a study was conducted using a single outpatient surgical intervention on the worse-seeing eye (20/200 or worse) of subjects with advanced dry AMD with GA involving the fovea. Surgery involved the subretinal implantation of a single CPCB-RPE1 (3.5x6.25mm) implant using commercially available 23 gauge vitrectomy equipment, a custom surgical forceps, and operating microscope with or without intraoperative OCT (iOCT) guidance. Surgical recordings and operative notes

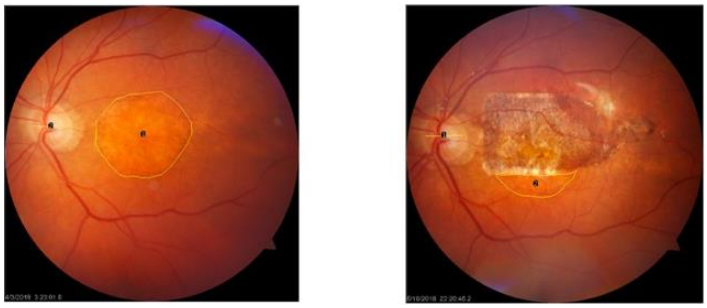
were used to quantify duration of the surgery. Fundus photographs and OCT were used to determine implant location and GA coverage.

RESULTS Sixteen subjects were recruited with mean age of 78 ± 5 (SD) years. Mean duration of the surgery was 194±98 min and improved from 249±115 to 139±16 min for the first eight and last eight surgeries, respectively (P<0.0001). iOCT was used to guide and confirm subretinal implant placement in 9 cases. Subretinal placement was confirmed in all 16 subjects using postoperative SD-OCT. Mean GA area at baseline was 16.7±11.1mm^2 and was reduced to 5.3±6.6mm^2 after CPCB-RPE1 implantation. Overall, CPCB-RPE1 implants covered 76±21% of the baseline GA area. In 4 subjects, >90% of the GA area was covered. No unanticipated serious adverse events related to the implant or surgery were reported.

CONCLUSION Surgical implantation of CPCB-RPE1 within the area of GA in subjects with severe vision loss from advanced dry AMD is feasible and well-tolerated in an outpatient setting. Intraoperative OCT is not necessary but may be useful in guiding CPCB-RPE1 placement.



Preoperative (left) and postoperative day 28 (right) fundus photographs of a subject with geographic atrophy (GA) demonstrate ~89% coverage of the area of GA with an implant consisting of human embryonic stem cell derived RPE on a synthetic substrate. Outlined area indicates approximate margins of GA.



Preoperative (left) and postoperative day 28 (right) fundus photographs of a subject with geographic atrophy (GA) demonstrate ~81% coverage of the area of GA with an implant consisting of human embryonic stem cell derived RPE on a synthetic substrate. Outlined area indicates approximate margins of GA.

HUMAN RESEARCH Yes: Approved by institutional review board

Prophylaxis Intravitreal Aflibercept Against Conversion to Neovascular Age-Related Macular Degeneration in High Risk Eyes (PRO-CON): 24-Month

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- David M. Brown, MD
- Sumit P. Shah, MD, FACS
- Sabin Dang, MD
- Nadia K. Waheed, MD, MPH

OBJECTIVE To evaluate 2 mg intravitreal aflibercept as prophylaxis against the conversion to neovascular age-related macular degeneration in high-risk eyes at 24 months.

PURPOSE To evaluate intravitreal aflibercept injection (IAI) 2 mg as prophylaxis against the conversion to neovascular age-related macular degeneration (nAMD) in high-risk eyes at 24 months.

METHODS Prospective, single-masked study evaluating IAI versus sham as prophylaxis treatment against conversion to nAMD in patients with intermediate AMD in one eye (study eye), defined as presence of >10 intermediate sized drusen (≥ 63 and <125 µm), >1 large druse (≥125 µm), and/or retinal pigmentary changes with nAMD in the fellow eye. Patients were randomized 1:1 to receive either IAI or sham quarterly for 24 months. The primary endpoint is proportion of patients converting to nAMD at Month 24 characterized by development of choroidal neovascularization (CNV) assessed by leakage on FA and fluid on SD-OCT by an independent masked reading center. Planned interim analysis was performed at Month 12.

RESULTS Of the 128 patients enrolled in the study, 116 completed the Month 12 visit. Baseline best-corrected visual acuity (BCVA) was 78.4 and 79.2 letters in the IAI and sham groups

respectively. By Month 12, 4/63 (6.3%) and 6/64 (9.4%) eyes in the IAI and sham groups, respectively, converted to nAMD. The rate of conversion between the two groups was not significant (p=0.50). In patients with non-exudative CNVs at any point prior to the Month 12 visit as determined by OCT-Angiography, 2/7 (25%) and 3/10 (30%) eyes in the IAI and sham groups, respectively, converted to nAMD (p=0.18 for rate of conversion). No new safety events were identified.

CONCLUSION Interim analysis at Month 12 did not demonstrate a benefit of IAI as a prophylactic treatment against conversion to nAMD in high risk eyes. Primary results at Month 24 will be presented that will help determine the benefit of prophylactic IAI in the management of these patients.

HUMAN RESEARCH Yes: Approved by institutional review board

Safety and Efficacy of Risuteganib in Intermediate Nonexudative Age-Related Macular Degeneration: First Time Results From a Phase 2 Study

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- David S. Boyer, MD
- Jeffrey S. Heier, MD
- Julia Kornfield, PhD
- Baruch D. Kuppermann, MD, PhD
- Hugo Quiroz-Mercado, MD
- Lisa Karageozian, MBA
- Vicken Karageozian
- Melvin Sarayba, MD
- Janine Aubel, BS, MBA

OBJECTIVE To evaluate the safety and efficacy of risuteganib in patients with intermediate non-exudative age-related macular degeneration.

PURPOSE Non-exudative (dry) age-related macular degeneration (dAMD) results from oxidative stress in retinal pigment epithelial (RPE) cells eventually leading to RPE and photoreceptor degeneration. Risuteganib is a novel anti-integrin that downregulates the oxidative stress response in the retina. This study evaluates safety & efficacy of risuteganib for treatment of dAMD.

METHODS Prospective, randomized, double-masked, placebo-controlled Phase 2 study evaluating eyes with intermediate dAMD, best-corrected visual acuity (BCVA) between 20/40-20/200 and preserved foveal outer retina and RPE. Patients were randomized to receive either intravitreal 1.0mg risuteganib or sham injection at baseline (BSL). At week 16, patients in the

risuteganib group received a 2nd dose and those in the sham group could cross over and receive a single dose of risuteganib. The primary endpoint is change in BCVA of the risuteganib group (BSL-week 28) compared to sham (BSL-week 12). Other endpoints include change in low luminance BCVA, color vision, and microperimetry.

RESULTS Forty-five patients from seven sites in the United States were enrolled in the study between August 2017 and July 2018. The mean age of patients at time of enrollment was 76.2 years. Of these, 76% (34/45) of the patients were female. The mean baseline BCVA was 61 letters. Primary endpoint data through week 28 will be presented.

CONCLUSION Risuteganib is a novel integrin inhibitor with a potential role for the treatment of intermediate dry AMD. The safety and efficacy data from the Phase 2 study will be presented.

HUMAN RESEARCH Yes: Approved by institutional review board

Mitochondria-Targeted Drug Elamipretide for Treatment of Vision Loss in Dry AMD With Noncentral Geographic Atrophy: Results of Phase 1 RECLAIM Study

- Scott W. Cousins, MD
- Michael J. Allingham, MD, PhD
- Priyatham (Prithu) S. Mettu, MD

OBJECTIVE Is subcutaneous administration of mitochondrial-targeted elamipretide safe, well tolerated, and potentially beneficial to vision, in patients with dry AMD and noncentral geographic atrophy?

PURPOSE To report the results from the noncentral geographic atrophy (NCGA) subgroup of the ReCLAIM Study, an open-label, phase 1 clinical trial to evaluate safety, tolerability, and efficacy of elamipretide, a mitochondria-targeted drug.

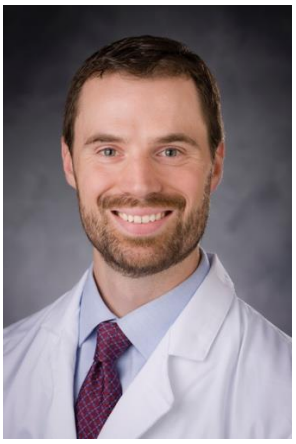
METHODS Open-label phase 1 clinical trial of daily subcutaneous elamipretide (40 mg) for 24 weeks in individuals with dry AMD. For pre-defined NCGA subgroup, NCGA was defined as well demarcated areas of hypo-autofluorescence (AF) on fundus AF with cumulative area ≥ 1.27 mm^2 (~0.5 disc areas (DA)) and ≤ 10.16 mm^2 (~4 DA), sparing foveola. One eye of each participant was eligible if ETDRS best-corrected visual acuity (BCVA) was ≥ 55 letters with low luminance VA (LLVA) deficit > 5 letters. LLVA was measured as ETDRS BCVA through log 2 neutral density filter, and LLVA deficit was defined as [BCVA] – [LLVA]. Safety and clinical assessments occurred every 4 weeks, with outcomes assessed at week 24.

RESULTS Elamipretide was safe and well tolerated with no treatment-related serious adverse events. Among participants in NCGA subgroup (n=19, mean age 76.0, 57.9% female), mean BCVA at baseline was 73.7 ± 9.5 letters, with mean increase of 4.6 ± 5.1 letters (p=0.003) at week 24. Mean baseline LLVA was 43.9 ± 19.8 letters, with mean increase of 5.4 ± 7.9 letters (p=0.019). Mean best-corrected reading acuity under standard lighting conditions (BCRA) at baseline was logMAR 0.15 ± 0.23, with mean change in BCRA of -0.02 ± 0.13 (p=0.55). Mean low luminance reading acuity through log 2 neutral density filter (LLRA) at baseline was logMAR 1.28 ± 1.07, with mean increase in LLRA of 0.52 ± 0.75 (p=0.017), equivalent to ~ 5-line gain. Mean change in NCGA area (SQ RT) was 0.13 mm over 24-week study period. Patient-reported outcomes on low luminance and VFQ-39 questionnaires demonstrated statistically significant improvement in daily quality of-life measures, especially in low luminance visual function.

CONCLUSION Elamipretide, a mitochondria-targeted drug, is safe and well tolerated in patients with dry AMD and may improve visual acuity in patients with NCGA. A Phase 2b, placebo-controlled clinical trial is being organized.

HUMAN RESEARCH Yes: Approved by institutional review board

Elamipretide, a Mitochondrial-Targeted Drug, for the Treatment of Vision Loss in Dry AMD with High Risk Drusen: Results of the Phase 1 ReCLAIM Study



- Michael J. Allingham, MD, PhD
- Priyatham (Prithu) S Mettu, MD
- Scott W. Cousins, MD

OBJECTIVE Is subcutaneous administration of mitochondrial-targeted elamipretide safe, well tolerated, and potentially beneficial to vision, in patients with dry AMD and high-risk drusen?

PURPOSE To report the results from the high-risk drusen (HRD) subgroup of the ReCLAIM Study, an open-label, phase 1 clinical trial to evaluate safety, tolerability, and efficacy of elamipretide, a mitochondria-targeted drug.

METHODS Open-label phase 1 clinical trial of daily subcutaneous elamipretide (40 mg) for 24 weeks in individuals with dry AMD. For the pre-defined HRD subgroup, HRD was defined as presence of at least 1 large (≥ 125 µm) druse or multiple medium-size (63-124 µm) drusen. Eyes with geographic atrophy were excluded from the HRD subgroup. A single eye of each participant was eligible if ETDRS best-corrected visual acuity (BCVA) was ≥ 55 letters with low luminance VA (LLVA) deficit > 5 letters. LLVA was measured as ETDRS BCVA through a log 2 neutral density filter and LLVA deficit was defined as [BCVA] – [LLVA]. Safety and clinical assessments occurred every 4 weeks, with outcomes assessed at week 24.

RESULTS Elamipretide was safe and well tolerated with no treatment-related serious adverse events. Among participants in the HRD subgroup (n=21, age 70.9, 61.9% female), mean BCVA at

baseline was 79.6 ± 7.3 letters, with mean increase of 3.6 ± 6.4 letters (p=0.03) at week 24. Mean baseline LLVA was 63.7 ± 9.8 letters, with mean increase of 5.6 ± 7.8 letters (p=0.006). Mean best-corrected reading acuity under standard lighting conditions (BCRA) (tested using MN read acuity chart) at baseline was logMAR 0.01 ± 0.17, with mean increase of -0.11 ± 0.15 (p=0.005), equivalent to an approximately 1-line gain. Mean low luminance reading acuity through log 2 neutral density filter (LLRA) was logMAR 0.38 ± 0.22 at baseline, with mean increase of -0.28 ± 0.17 (p<0.001), equivalent to an approximately 3-line gain.

CONCLUSION Elamipretide, a mitochondrial-targeted drug, is safe and well-tolerated in patients with dry AMD and may improve vision in patients with intermediate (dry) AMD manifest as HRD. A phase 2b, placebo-controlled clinical trial is being organized.

HUMAN RESEARCH Yes: Approved by institutional review board

Frequency of Age-Related Macular Degeneration Risk Alleles Y402H and A69S in a Direct-to-Consumer Genetic Database

- Theodore Leng, MD, MS
- Hoang Nhan, PhD
- Jianan Zhan
- Jamaica Perry, PhD
- Esther Kim, Phar, MD

OBJECTIVE To report the Y402H and A69S allele frequencies associated with age-related macular degeneration among individuals using an at-home genetic test.

PURPOSE The CFH Y402H (rs1061170) and ARMS2 A69S (rs10490924) genetic variants are the most common variants associated with an increased risk of developing AMD. Y402H and A69S variants are likely responsible for approximately 43% and 36% of AMD in older adults, respectively. Understanding the frequency of these alleles in the general US population can better inform population health approaches.

METHODS Here, we assessed the frequency of Y402H and A69S in an unselected group of genotyped individuals who used direct-to-consumer (DTC) genetic testing (23andMe, Inc. Mountain View, CA). This was a national cross-sectional study. Study participants were genotyped between 2013 and 2017 on custom Illumina genotyping arrays. Eligible subjects were 23andMe customers who consented to participate in research. IRB approval was obtained from Ethical & Independent Review Services.

RESULTS More than 80% of genotyped individuals consented to participate in online research. Of the 1,285,669 participants tested for Y402H, we found an allele frequency of 35.2%. Of the 1,287,821 participants tested for A69S, we found an allele frequency of 22.9%. The most common genotypes (Table 1) were Y402H heterozygotes (27.6%), homozygous non-risk genotype (24.5%), Y402H and A69S compound heterozygotes (15.7%), A69S heterozygote

(14.9%) and Y402H homozygotes (7.5%). Overall, about 75% of genotyped individuals in our cohort carry one or more AMD Y402H and A69S variant(s).

CONCLUSION This is the first description of an unselected cohort with Y402H and A69S alleles identified through DTC genetic testing. DTC genetic testing can identify individuals with high-risk genotypes and may aid in personalized medicine approaches. A large DTC genetic database can also provide further insights into the genetic epidemiology of AMD. Analysis to stratify the allele frequencies are ongoing.

Table 1. AMD Genotype Frequencies in a DTC Genetic Database

# of Y402H variant allele(s)	# of A69S variant allele(s)	percent
0	0	24.5
1	0	27.6
1	1	15.7
0	1	14.9
2	0	7.5
2	1	4.2
0	2	2.5
1	2	2.3
2	2	0.6

HUMAN RESEARCH Yes: Approved by institutional review board

Associations Between Perifoveal Drusen Burden and Genetic Risk in Eyes With Early or Intermediate Age-Related Macular Degeneration

- Johanna M. Seddon, MD, ScM
- Rafael Widjajahakim, MS
- James Dossett, BS
- Bernard Rosner, PhD

OBJECTIVE To determine associations between macular drusen parameters derived from an automatic OCT algorithm, age-related macular degeneration (AMD) stage and genetic variants.

PURPOSE The overall goal is to help identify earlier disease phenotypes and better stratify risk of progression prior to development of advanced AMD and visual loss.

METHODS Eyes with early and intermediate AMD with OCT imaging among participants with genetic data were selected (n=239 eyes). Drusen area and volume measurements were estimated using the Zeiss Cirrus advanced retinal pigment epithelium (RPE) analysis algorithm in a 5mm diameter zone centered on the fovea (perifoveal region). Common variants associated with advanced AMD were evaluated in the genes CFH, ARMS2, CFB, C3, COL8A1, RAD51B, ABCA1, LIPC, and CETP. Associations between drusen measurements and genetic variants were calculated using generalized estimating equations and linear mixed models adjusting for age, sex, smoking, BMI, and education.

RESULTS Mean perifoveal drusen area and volume were significantly associated with grade of AMD, and measurements were higher in eyes with intermediate AMD compared with early AMD. CFH rs 1410996 and ARMS2 A69S were consistently associated with drusen area and

volume ≥ median in the perifoveal region, compared to eyes with no measurable drusen. When analyzed in a linear mixed model, CFH homozygous risk was associated with significantly greater adjusted means of drusen area and volume when compared to the homozygous non-risk genotype (p=0.028; p=0.023, respectively). For ARMS2, both heterozygous and homozygous risk genotyes showed significantly greater adjusted area and volume compared with the non-risk genotype. Results were consistent when one gene was adjusted for the other in a bivariate model, with significant trends for higher means for drusen area and volume measurements with more risk alleles for both CFH rs1410996(P= 0. 004, 0.003, respectively) and ARMS2 A69S (both P trends <0.001).

CONCLUSION CFH and ARMS2 genetic variants, commonly associated with advanced AMD, are independently associated with higher drusen burden in eyes with early and intermediate AMD, as determined by the automatic RPE algorithm using OCT. Further characterization of drusen morphology and other sub-phenotypes may lead to identification of biomarkers that could serve as early anatomic endpoints for clinical trials.

HUMAN RESEARCH Yes: Approved by institutional review board