10:55 AM

Learnings From the Lampalizumab Chroma and Spectri Phase 3 Trials: Effect of Baseline Characteristics on Geographic Atrophy Progression

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OBJECTIVE This analysis evaluated the predictive effect of baseline lesion characteristics on geographic atrophy progression in the first 48 weeks of the lampalizumab Chroma and Spectri phase 3 trials.

PURPOSE Chroma and Spectri, phase 3 trials that evaluated lampalizumab for geographic atrophy (GA) due to age-related macular degeneration (AMD), provide a large cohort with bilateral GA and detailed anatomical and functional outcomes. This analysis evaluated week (wk) 48 outcomes by baseline (BL) lesion characteristics, including factors previously found to be potential predictors of GA progression rate.

METHODS Chroma (N=906, NCT02247479) and Spectri (N=975, NCT02247531) were double-masked, multicenter, randomized clinical trials that enrolled participants (pts) ≥50 years with bilateral GA from AMD and no current/prior choroidal neovascularization in either eye. Pts received lampalizumab 10 mg every 4 wks (LQ4),

sham Q4, lampalizumab 10 mg every 6 wks (LQ6), or sham Q6. Sham arms were pooled. The primary outcome was mean change in GA area from BL to wk48 on fundus autofluorescence images; exploratory analyses evaluated this within prespecified clinical subgroups. Pooled Chroma and Spectri results are shown. Effect of BL characteristics on natural history of GA was further evaluated in the sham arm.

RESULTS The trials enrolled sham: 626, LQ4: 628, and LQ6: 627 pts, with overall adjusted mean (SE) changes in GA area from BL at wk48 of 1.98 (0.04), 2.06 (0.04), and 2.05 (0.04) mm^2. Analysis by prespecified clinical subgroups did not show any treatment benefit for lampalizumab vs sham, but suggests factors predictive of lesion growth. Sham arm pts had a mean GA increase (mm^2/48 wks) by **age** : <75 years, 1.88 (0.08), 75–84 years, 2.00 (0.06), ≥85 years, 2.11 (0.10); **sex:** female, 2.08 (0.06), male, 1.85 (0.07); **tobacco use**: never, 1.88 (0.06), ever, 2.07 (0.06); **BCVA:** <64 letters, 1.94 (0.07), ≥64 letters, 2.02 (0.05); **low-luminance deficit:** <30 letters, 1.80 (0.06), ≥30 letters, 2.20 (0.06); **BL GA area:** <4 disc areas (DA), 1.81 (0.05); ≥4 DA, 2.46 (0.08); **BL lesion configuration**: multifocal, 2.06 (0.05), unifocal, 1.71 (0.08); and **BL lesion location:** non-subfoveal, 2.29 (0.07), subfoveal, 1.72 (0.05). Additional exploratory analysis from sham pts only will be presented.

CONCLUSION Understanding BL risk factors associated with higher GA progression may help inform patients of disease prognosis and is critical for the design of clinical trials to assess future therapies. Chroma and Spectri provide the most comprehensive dataset on bilateral GA to date, and learnings from these trials can further the understanding of this vision-threatening condition.

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

11:03 AM

Common Age-Related Macular Degeneration Genetic Risk Variants and Geographic Atrophy Lesion Growth in the Chroma and Spectri Phase 3 Lampalizumab Trials

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- Lee Honiberg, PhD

OBJECTIVE To test the effect of single-nucleotide polymorphisms associated with increased risk of advanced age-related macular degeneration on geographic atrophy lesion growth in two large phase 3 trials.

PURPOSE The Fritsche et al 2016 genome-wide association study (GWAS) defines common single nucleotide polymorphisms (SNPs) associated with risk of developing advanced age-related macular degeneration (AMD), including geographic atrophy (GA). We tested the effect of common GWAS-associated complement and ARMS2/HTRA1 SNPs on GA area growth in sham arms of the phase 3 Chroma and Spectri lampalizumab trials.

METHODS Chroma (NCT02247479) and Spectri (NCT02247531) were double-masked, multicenter, randomized clinical trials that evaluated lampalizumab 10 mg vs sham for GA. Participants were ≥50 years with bilateral GA and no current or prior choroidal

neovascularization in either eye. SNPs in CFH (rs1329428), ARMS2/HTRA1 (rs10490924), C2/CFB (rs429608), C3 (rs2230199), and CFI (rs4698775, rs10033900) were genotyped by validated Taqman assays. Change from baseline (BL) to week 48 in GA area on fundus autofluorescence was compared across genotype groups (0, 1, or 2 risk alleles) in pooled sham arms by a mixed effects repeated measures model adjusted for BL lesion size, location, multifocality, sex, and BCVA.

RESULTS Risk SNPs, assessed in 626 sham-treated participants, were present at frequencies as expected for advanced AMD. GA growth rates across genotypes are summarized in the Table. The 95% CIs between genotype groups at each of the 6 SNPs largely overlap, and no meaningful differences were observed in growth rates for any of the genotype subgroups.

CONCLUSION In the Chroma and Spectri population with established GA, lesion growth to 48 weeks was not affected by common SNPs associated with risk of developing advanced AMD, including either complement-related SNPs or the ARMS2/HTRA1 SNP, the strongest genetic risk factor for advanced AMD. Thus other unidentified genetic or non-genetic factors may contribute to variability in rate of GA lesion progression.

	Genotype		
	0 Risk Alleles	**1 Risk Allele**	**2 Risk Alleles**
CFH (rs1329428)	2.35 (1.91, 2.79); n=23	1.99 (1.83, 2.15); n=165	1.95 (1.84, 2.05); n=377
C2/CFB (rs429608)	1.58 (0.73, 2.44); n=6	2.07 (1.84, 2.29); n=87	1.97 (1.87, 2.06); n=472
C3 (rs2230199)	1.97 (1.86, 2.09); n=305	1.98 (1.84, 2.12); n=210	1.93 (1.61, 2.24); n=44
CFI (rs10033900)	1.75 (1.56, 1.94); n=120	2.00 (1.88, 2.12); n=289	2.11 (1.94, 2.27); n=150
CFI (rs4698775)	1.91 (1.77, 2.04); n=227	2.01 (1.88, 2.14); n=260	2.07 (1.84, 2.31); n=78
ARMS2/HTRA1 (rs10490924)	1.83 (1.67, 1.99); n=172	2.02 (1.89, 2.14); n=268	2.09 (1.90, 2.28); n=119

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

11:16 AM

APL-2, a Complement C3 Inhibitor, Slows the Growth of Geographic Atrophy Secondary to AMD: 18-Month Results of a Phase 2 Trial (FILLY)

- Nathan C. Steinle, MD
- Prema Abraham, MD

OBJECTIVE To determine whether treatment with APL-2, a complement C3 inhibitor, has the potential to improve outcomes in patients with geographic atrophy secondary to AMD.

PURPOSE To evaluate the safety and efficacy of APL-2 (pegcetacoplan, 15mg), a complement C3 inhibitor, administered intravitreally for 12 months, with follow-up for an additional 6 months, in subjects with geographic atrophy (GA) secondary to AMD.

METHODS In this prospective, randomized, sham-controlled trial, patients with GA area measuring 2.5-17.5 mm^2 and best-corrected visual acuity (BCVA) of 24 letters or better (20/320 Snellen equivalent) were eligible. There were no exclusions based on fellow eye disease. 246 subjects were randomized (2:2:1:1) to four arms; APL-2 monthly, APL-2 every other month (EOM), sham monthly, and sham EOM. Total treatment period was 12 months with additional assessments at 15 and 18 months. The 12-month primary

efficacy outcome was the difference in mean change from baseline in square-root GA area based on fundus autofluorescence. Secondary endpoints included change in BCVA & incidence of conversion to wet AMD.

RESULTS Baseline characteristics were well balanced across groups. The primary outcome was assessed using a pre-specified modified intent-to-treat population (N=243). At 12 months, using least squares mean change from baseline in square root lesion area, monthly APL-2 (N=84) slowed GA growth by 29% (p=0.008) and EOM APL-2 (N=78) slowed GA growth by 20% (p=0.067) versus the pooled sham group (N=80). The effect increased in the second six months of treatment, during which monthly and EOM APL-2 slowed GA growth by 47% (p<0.001) and 33% (p=0.01) respectively vs sham. No differences in BCVA outcomes were observed between groups. There was a dose-dependent difference in onset of investigator-determined study eye conversion to wet AMD: 15 eyes in monthly APL-2, 6 in EOM APL-2, and 1 in sham. These eyes discontinued APL-2 treatment, and overall visual and anatomic outcomes were not negatively impacted. Most other adverse events were attributable to the intravitreal injection procedure.

CONCLUSION At 12 months, intravitreal APL-2 slowed GA growth and this treatment effect was more pronounced in the second six months of therapy. APL-2 was associated with an increase in study eye conversion to wet AMD, though overall visual and anatomic outcomes were not negatively impacted.

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

11:24 AM

Subretinal Implantation of a Bioengineered Embryonic Stem Cell-Derived Retinal Pigment Epithelium Monolayer in Dry Age-Related Macular Degeneration

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- Chih-Min Lin, PhD

OBJECTIVE To assess the safety of subretinal implantation of a bioengineered embryonic stem cell-derived retinal pigment epithelium (hESC-RPE) monolayer for advanced dry age-related macular degeneration (AMD)

PURPOSE Non-neovascular AMD (NNAMD) can result in severe vision loss secondary to loss of RPE and geographic atrophy (GA). There is no treatment for GA or the resulting vision loss. We report the interim results from phase 1/2a study to assess the safety and potential efficacy of a bioengineered hESC-RPE monolayer implant in preventing or reversing vision loss among subjects with NNAMD and GA.

METHODS A prospective, phase 1/2a study to assess the safety and efficacy of a bioengineered subretinal implant in subjects with advanced NNAMD and GA. Other sight threatening disease were excluded. Key inclusion criteria were NNAMD with GA, pseudophakic status, and best-corrected visual acuity of < 20/80. A single implant was surgically delivered (via a vitrectomy based approach) to the area of GA in the more affected eye. The implant is a polarized monolayer of hESC-RPE on an ultrathin, synthetic parylene substrate designed to mimic Bruchâ€™s membrane. The primary outcome was safety at 1 year. Secondary endpoints include visual acuity, fixation testing and optical coherence tomography (OCT).

RESULTS We report an interim analysis of the phase 1 cohort (up to 10 subjects) that have been enrolled for 120-365 days. Baseline imaging and clinical examination confirmed that each subject had a large area of GA exhibiting decreased pigmentation involving the fovea. Baseline OCT demonstrated no evidence of RPE and minimal or no evidence of an outer nuclear layer in the area of GA. Four of five initial subjects received the implant which treated a significant region of GA or the complete region of GA in all cases. OCT demonstrated an appropriately placed CPCB-RPE1 implant in the subretinal space of GA in all cases. There was one expected ocular severe adverse event (severe subretinal and intraretinal hemorrhage) that was asymptomatic and resolved without significant vision loss. There were two unrelated and unanticipated general adverse event (prolapsed rectum and 20lb weight loss) requiring hospitalization. Both of these were treated successfully.

CONCLUSION These interim results suggest this composite implant is safe at least for 120 days and up to 1 year. Additional results will be reported as they become available at the time of the meeting.

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

11:37 AM

Direct-to-Consumer Marketing by U.S. “Cell Therapy” Clinics for Retinal Conditions

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OBJECTIVE To assess the scope of direct-to-consumer marketing of "cell therapy" for retinal diseases by "cell therapy" clinics.

PURPOSE “Cell therapy” treatments for retinal diseases are increasingly available to patients via online direct-to-consumer advertisement in the U.S.. There are reports of blinding complications after such treatments at “cell therapy” clinics. We performed a cross-sectional clinical study to investigate “cell therapy” clinics across the U.S. that advertise and offer treatments for retinal diseases online.

METHODS identify and analyze U.S. businesses marketing “cell therapy” for retinal conditions. We included U.S.-based companies that participate in direct-to-consumer online marketing, have websites that can be data-mined with content analysis, and advertise therapy for ocular conditions. We recorded and analyzed clinic locations, source of cells used, route of administration, marketed ocular conditions, and cost of treatment. Businesses that had offices in the U.S. but performed the procedure in various countries were noted and recorded, but were excluded from the analysis.

RESULTS We found 37 companies that advertise “cell therapy” for retina conditions. California contained the most clinics (20), followed by Florida (11), and Illinois (9).

Sources of cells included autologous adipose derived stem cells (SCs, 33; 89.1%) and bone marrow-derived stem cells (9; 24.3%), placental SCs (2; 5.4%), amniotic SCs (2; 5.4%), peripheral blood-derived SCs (2; 5.4%), and umbilical cord SCs (2; 5.4%). We found 8 (21.6%) companies that offered the use of multiple cell types. The remaining 29 (78.3%) made use of a single source. The most common marketed ocular condition was macular degeneration (34). The most common routes of administration were intravenous (21) and "targeted injections" (16), while others included more ocular specific routes such as intravitreal injections (2), retrobulbar injections (2), retrofundal injection (1), and eye drops (1). The cost of the interventions ranged from $4,000 to $10,500.

CONCLUSION It is evident that "cell therapy" for retinal conditions is readily available via direct-to-consumer marketing. The cells are harvested from numerous sources and administered in different ways. This study demonstrates there is a large number of "cell therapies" offered at "cell therapy" clinics across the U.S. for a variety of retinal conditions.

11:42 AM

Progression of Visual Function Endpoints in Early and Intermediate Age-Related Macular Degeneration

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- Lejla Vajzovic, MD
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- Ulrich FO Luhmann, PhD

OBJECTIVE The objective of our study was to examine longitudinal changes in visual function metrics over 12 months in subjects with early and intermediate age-related macular degeneration (AMD).

PURPOSE There is a significant unmet need to develop treatments for earlier stages of AMD before irreversible visual loss has occurred. To achieve this, reliable functional clinical trial endpoints are required. Our study evaluated the most comprehensive set of visual function measures in early-intermediate AMD patients to determine the parameters that can serve as robust endpoints for clinical trials.

METHODS Prospective, observational cohort study of 101 subjects with AREDS stage 2 (N=33), stage 3 (N=47), and age-matched, normal controls (N=21). At baseline, 6 and 12 months, subjects underwent a dilated retinal examination with best-corrected visual acuity (BCVA), mesopic microperimetry with eye tracking (MAIA), dark adaptometry (DA; AdaptDx), low luminance visual acuity (LLVA) testing (standard with log2.0 neutral density filter and computerized), cone contrast test (CCT), and mobile technology (myVisionTrack; mVT). Low luminance deficit (LLD) was calculated as the

difference in letters read for BCVA and LLVA. Group comparisons were performed using two-sided significance tests.

RESULTS 82 subjects completed both the 6-and 12-month follow-up visits. The intermediate AMD group showed a significant impairment in standard LLVA, standard LLD, and CCT red as compared to the normal group at 12 months. Microperimetry metrics (percent reduced threshold and average threshold), CCT green and blue, and rod intercept on DA remained significantly different between all three groups at 1 year, similar to baseline visits (all $p<0.05$). At 12 months, standard calculated LLD became significantly greater among early and intermediate AMD compared to controls. The intermediate AMD group also had a significant loss of retinal sensitivity on microperimetry average threshold relative to those with early AMD or controls. The mVT shape discrimination hyperacuity test differentiated between normal and early as well as early and intermediate AMD group at 12 months. Both AMD groups had greater mVT score variance than the control group at 12 months.

CONCLUSION Our study suggests that calculated standard LLD and microperimetry average threshold may be useful functional measures of disease progression and clinical trial endpoints in early and intermediate AMD. The mVT mobile hyperacuity test differentiated between normal, early and intermediate AMD at 12 months and paralleled the visual function loss documented on standard in-clinic assessments in AMD.

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