#331

A Phase I/II Clinical Study Evaluating the Safety and Efficacy of Bilaterally Dosed Topical Lipoic Acid Choline Ester Eye Drops for the Treatment of Presbyopia

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Purpose

There are no currently approved pharmacological therapies to treat presbyopia, a condition thought to be related to an increased number of disulfide bonds between crystalline lens proteins. This leads to a loss of lens flexibility. Lipoic acid is an antioxidant shown to chemically reduce lens disulfide bonds. This results in greater cytosol displacement during accommodation and increased dynamic lens refractive power. This first-in-man, Phase I/II study (NCT02516306) was designed to evaluate the topical bilateral use of a lipoic acid choline ester formulation (EV06 Ophthalmic Solution,1.5%) on distance corrected near visual acuity (DCNVA) in a sample of presbyopic subjects.

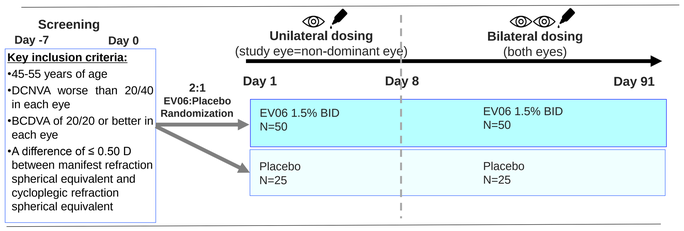
Methods

Objective:

- To evaluate Safety & Efficacy of EV06 Ophthalmic Solution in Improving Distance Corrected Near Visual Acuity (DCNVA) in Subjects with Presbyopia

Study Design:

- Prospective, randomized, double-masked, placebo-controlled multicenter Phase I/II study
- 75 subjects with hyperopia, myopia, or emmetropia and a diagnosis of presbyopia randomized 2:1 (EV06 or Placebo) BID
- Study visits, Days -7, 0, 1, 8, 15, 31, 61, 91
- 4 US Sites



Study Outcomes:

Safety

- BCDVA
- Pupil Diameter
- IOP
- Slit-lamp findings
- Adverse Events

Exploratory Efficacy

-Mean change in DCNVA

-Proportion of subjects with gain of ≥ 10 letters in DCNVA

Study Demographics:

	Placebo Control	Active EV06
Number of Subjects	**25**	**50**
Age (years)± SD	**51.4 (± 3.0)**	**50.1 (± 3.2)**
Gender		
Female	80%	66%
Male	20%	33%
Race		
White	72%	70%
Black	28%	30%
Ethnicity		
Hispanic/Latino	20%	32%
Not Hispanic/Latino	80%	68%
Refractive Status		
Myopes	24%	18%
Emmetropes	68%	68%
Hyperopes	8%	14%
Baseline DCNVA (Mean LogMAR ± SD)		
Study Eye	0.500 (± 0.10)	0.507 (± 0.11)
Bilateral (OU)	0.408 (± 0.12)	0.397 (± 0.10)

Results:

EV06 (UNR844) Is Safe and Well-Tolerated

- **No Subjects Discontinued for Adverse Events, Safety Concerns, or Tolerability**
- **No Serious Treatment-Related AEs; No Sight-Threatening AEs**
- **No Change in IOP**
- **Comfortable Upon Instillation**
  - **EV06 Comfort Rating 3.0 vs Placebo Comfort Rating 2.7**

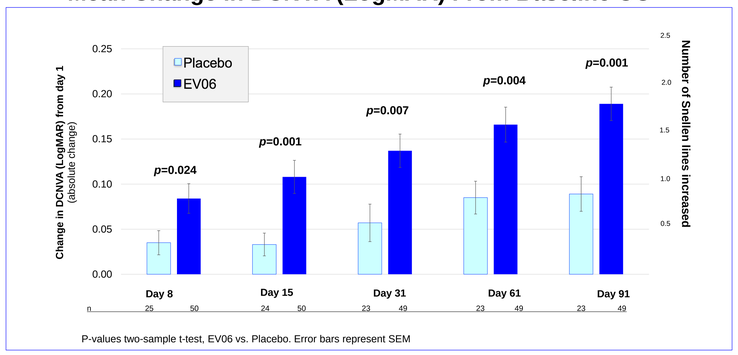
  (Scale 0 – 10; "0" = Very Comfortable; "10" = Uncomfortable)
- **No Change in Best Corrected Distance Visual Acuity (BCDVA)**
- **No Changes in Manifest Refraction Spherical Equivalent or Cycloplegic Refraction**
- **No Change in Pupil Diameter**

Adverse Events

	Placebo Control	Active EV06
Number of Subjects	25	50
Any Subject Discontinuations	2 (8%)	1 (2%)
Any Treatment-Related Serious Adverse Events	0	0
Ocular related TEAE*	3 (12%)	8 (16%)
Asthenopia	0%	4%
Conjunctival hyperaemia	8%	0%
Eye irritation	0%	4%
Eye pruritus	0%	4%
Foreign body sensation	0%	4%
Installation irritation	0%	4%
Installation pain	4%	6%
Non-Ocular related TEAE*	1 (4%)	8 (16%)
Dysgeusia	0%	14%
Headache	0%	4%
Somnolence	4%	0%

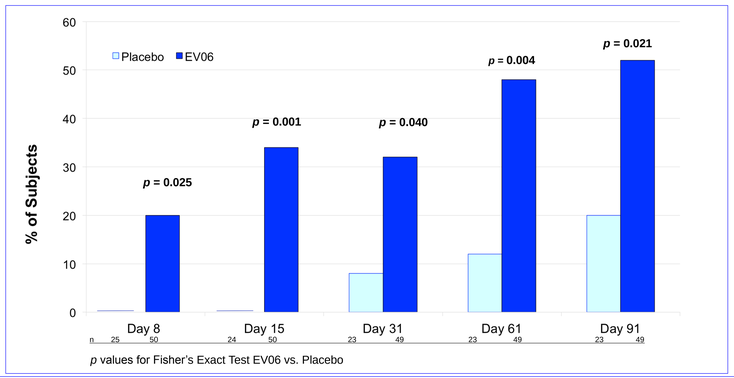
* Related Treatment Emergent Adverse Events with an incidence of 4% or greater

EV06 (UNR844) Showed Improved Bilateral Near Vision Over Time
Mean Change in DCNVA (LogMAR) From Baseline OU



P-values two-sample t-test, EV06 vs. Placebo. Error bars represent SEM

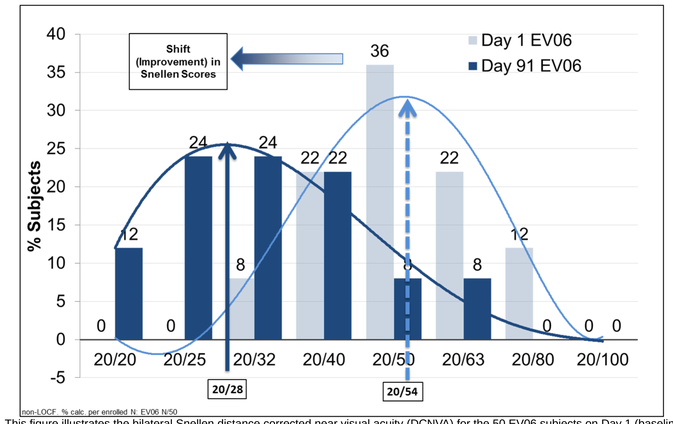
EV06 (UNR844) Improved Percent of Subjects with Gains in Bilateral Near Vision
Percentage of Subjects Showing a Gain of ≥10 letters in DCNVA (OU)



p values for Fisher's Exact Test EV06 vs. Placebo

Results:

EV06 (UNR844) Showed Improved Bilateral Near Vision Over Time
DCNVA Snellen Scores (OU) Baseline vs Day 91: A population shift



This figure illustrates the bilateral Snellen distance corrected near visual acuity (DCNVA) for the 50 EV06 subjects on Day 1 (baseline) compared to Day 91 (final visit). The results indicate that there was a clinically significant shift in the DCNVA in this cohort of subjects. The mean Snellen values of 20/28 (Day 91) and 20/54 (Day 1) are approximations.

EV06 (UNR844) Improved Near Vision
ETDRS Lines Changed (DCNVA, OU), Baseline vs Day 91

	Placebo Control*		Active EV06*		
Subjects with:	**n = 23**		**n = 49**		
Improvement in DCNVA	**n**	**%**	**n**	**%**	
1 line (≥ 0.10 LogMAR)	12	52%	41	84%	***p=0.009***
2 lines (≥ 0.20 LogMAR)	5	22%	26	53%	***p=0.021***
3 lines (≥ 0.30 LogMAR)	0	0%	11	22%	***p=0.013***
4 lines (≥ 0.40 LogMAR)	0	0%	6	12%	*p=0.167*
Any Loss in DCNVA (≥ 0.10)	1	4%	1	2%	*p=0.540*
No Change in DCNVA (-0.09 to 0.09)	10	44%	7	14%	***p=0.015***
*non-LOCF, % calc based on n per day	p values for Fisher's Exact Test EV06 vs. Placebo				

Summary and Conclusions

EV06 (UNR844) Ophthalmic Solution, 1.5% improved near vision as measured by clinically and statistically significant improvements in DCNVA compared to Placebo measured by LogMAR and Snellen line changes.

- Statistically significant improvements in DCNVA were observed in each eye (unilateral vision) following topical ocular use of EV06 (UNR844). Improvements in DCNVA were most pronounced when subjects employed bilateral (OU) vision.
- 84% of subjects completed the study with 20/40 bilateral vision or greater treated with EV06 (UNR844) versus 52% in Placebo.
- 53% of subjects completed the study with ≥ 0.2 LogMAR change in bilateral vision treated with EV06 (UNR844) versus 22% in Placebo.

Treatment with EV06 (UNR844) Ophthalmic Solution, 1.5%, BID for three months was not associated with an increase in Adverse Events, slit-lamp findings, fundus findings or IOP compared to Placebo.

There were no changes in pupil diameter, BCDVA, Manifest Refraction or Cycloplegic Refraction in the EV06 (UNR844) group compared to Placebo.

- This study was funded by Encore Vision Inc, a privately held eye care company at the time the study was planned, conducted and analyzed. Encore Vision was acquired by Novartis in January 2017.
- EV06 is now identified as UNR844 by Novartis.