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Phase 2 Clinical Trial To Evaluate The Efficacy Of Phentolamine Ophthalmic Solution And Low-Dose Pilocarpine For The Treatment Of Presbyopia

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Dr. Pepose's financial disclosures:

- Acufocus
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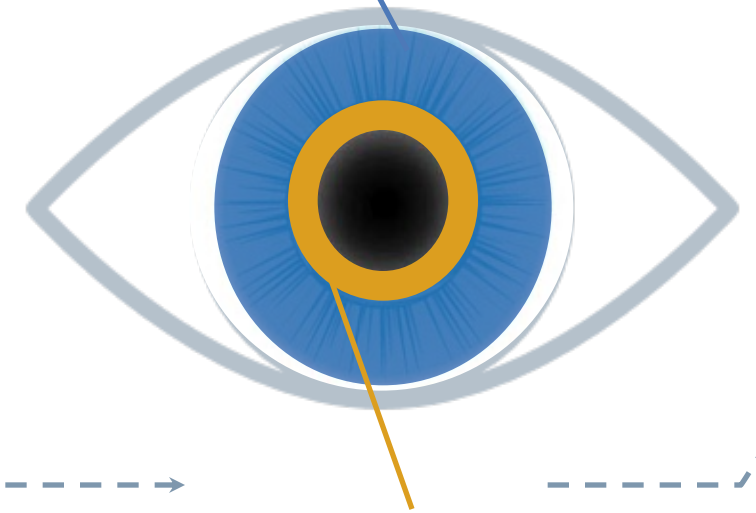
- Sun Pharma
- TearLab
- Thea Pharm

Phentolamine Ophth. Solution (POS) + Low-Dose Pilocarpine (LDP) Combination

Moderate Use Of Iris Dilator And Iris Sphincter Muscles To Improve Near Vision

0.75% POS

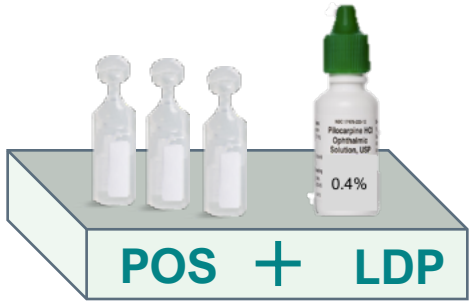
Iris Dilator Muscle Inhibition



0.4% LDP

Iris Sphincter Muscle Activation

- **Alpha1/2 antagonist approved decades ago 505(b)(2)**
- **Novel MOA on iris dilator with 24+ hour durability with moderate 1+mm pupil reduction**
- **No daytime redness with chronic evening dosing of POS**
- **Well-tolerated with no systemic effects**
- **Stable, preservative-free, single use vial**



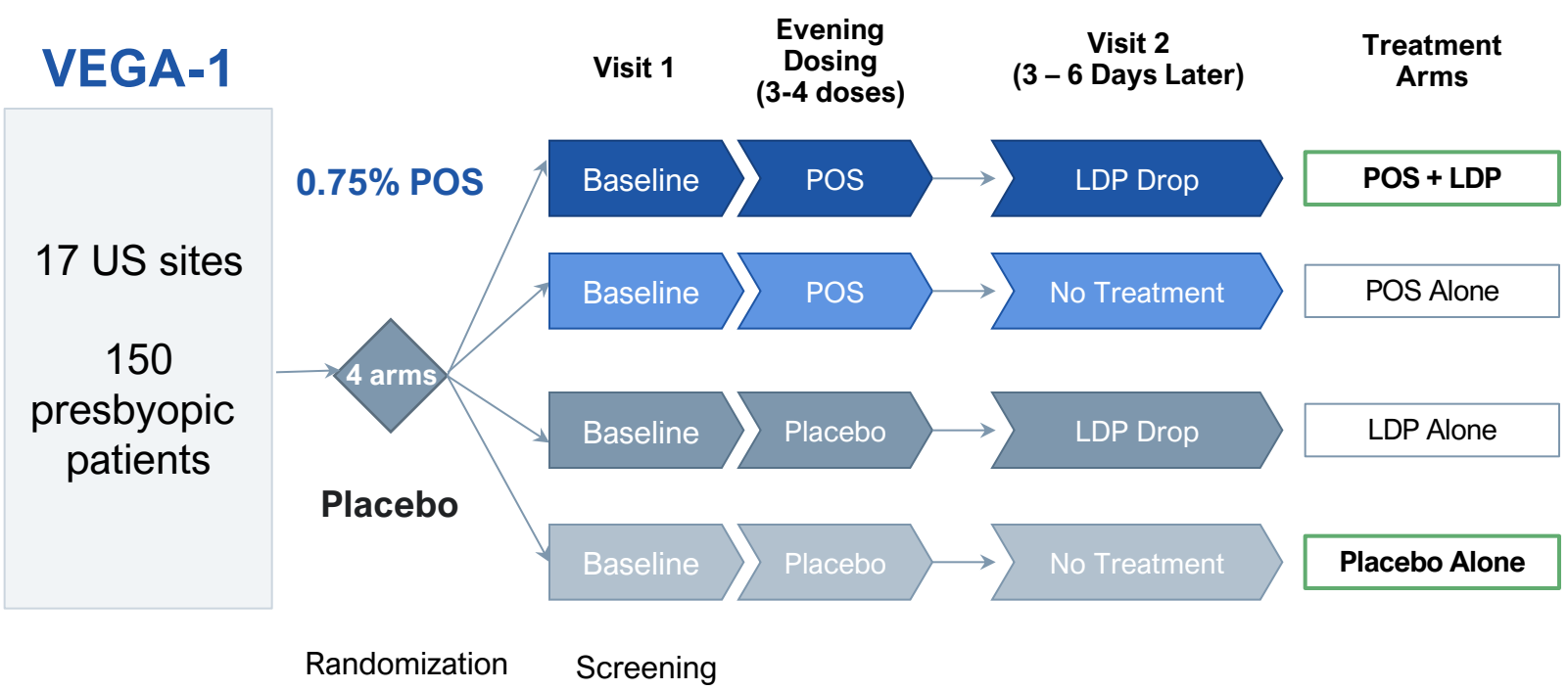
1.5 to 2.5 mm PD reduction moves toward the pin-hole (1.6 to 2.5 mm, up to <3 mm)

- **Cholinergic agonist approved decades ago 505(b)(2)**
- **Known MOA on sphincter muscle with more potent miotic effects at approved doses (1%, 2%, 4%)**
- **Chronic daily dosing of LDP in daytime**
- **Low concentration avoids known tolerability issues:**
  - **headache and browache**
  - **redness**
  - **accommodative spasm causing loss of distance vision especially at night**

Source: POS (Nyxol®) data from 8 completed trials; Pilocarpine Product label

Presbyopia VEGA-1 Phase 2 Design

Randomized, Double-Masked, Placebo-Controlled Multi-Center One-Week Trial



Eligibility Criteria

- Males or females ≥ 40 and ≤ 64years of age
- BCDVA of 0.0 LogMAR(20/20 Snellen equivalent) or better in each eye under photopic conditions
- DCNVA of 0.4 LogMAR (20/50 Snellen equivalent) or worse under photopic conditions in each eye & binocularly

Endpoints

Primary: % of subjects with ≥ 3 lines of improvement in distance-corrected near visual acuity comparing POS + LDP vs placebo alone at 1 hour

Secondary:

- % of subjects with ≥ 2 and ≥ 3 lines gained at time points from 30 min to 6 hours in photopic and mesopic lighting comparing POS + LDP vs placebo, POS alone, and LDP alone
- No loss of distance vision
- Pupil diameter at time points
- Safety and tolerability (redness)

Demographics and Baseline Characteristics

Treatment And Placebo Arms Were Balanced In the VEGA-1 Phase 2 Clinical Trial

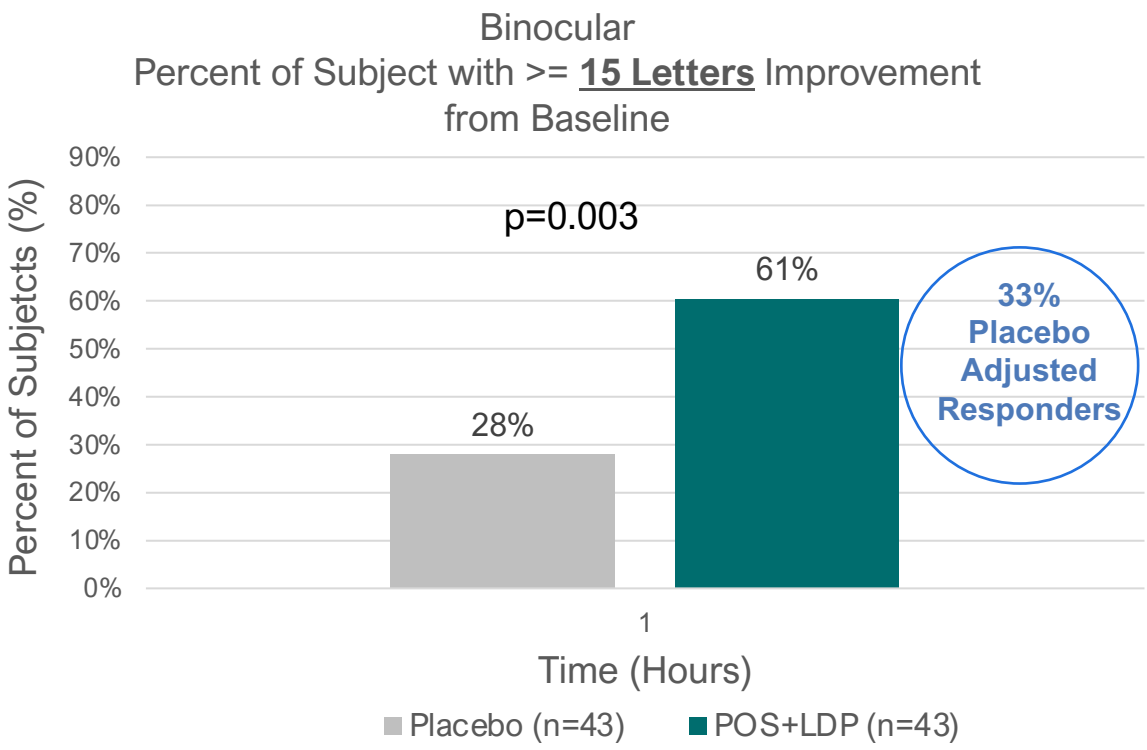
	Placebo Alone N=43	POS Alone N=30	LDP Alone N=31	POS+LDP N=43	Total N=147
Age (years): Median (Range)	52 (42-62)	54 (41-60)	52 (44-64)	53 (43-63)	53 (41-64)
Sex: Male n (%) **Female** n (%)	15 (35%) 28 (65%)	7 (23%) 23 (77%)	13 (42%) 18 (58%)	5 (12%) 38 (88%)	40 (27%) 107 (73%)
Race: White n (%) **Other*** n (%)	37 (86%) 6 (14%)	26 (87%) 1 (3%)	28 (90%) 3 (10%)	40 (93%) 3 (7%)	131 (89%) 15 (11%)
Dark Iris Color: n (%)	18 (42%)	12 (40%)	12 (39%)	18 (42%)	60 (41%)
Light Iris Color: n (%)	25 (58%)	18 (60%)	19 (61%)	25.1 (58%)	87 (59%)
Photopic DCNVA Mean Letters read-Binocular *(Snellen Equiv.)* *70 letters = 20/20*	46 (20/63)	45 (20/63)	48 (20/63)	46 (20/63)	46 (20/63)
Photopic BCDVA Mean Letters read-Binocular *(Snellen Equiv.)* *55 letters = 20/20*	62 (20/15)	61 (20/15)	60 (20/15)	61 (20/15)	61 (20/15)
Photopic Pupil Diameter Mean (mm)	4.3	4.5	4.3	4.3	4.3
Mesopic Pupil Diameter Mean (mm)	5.1	5.0	5.0	5.1	5.1
IOP (mmHg)	13.5	14.8	13.9	14.4	14.1

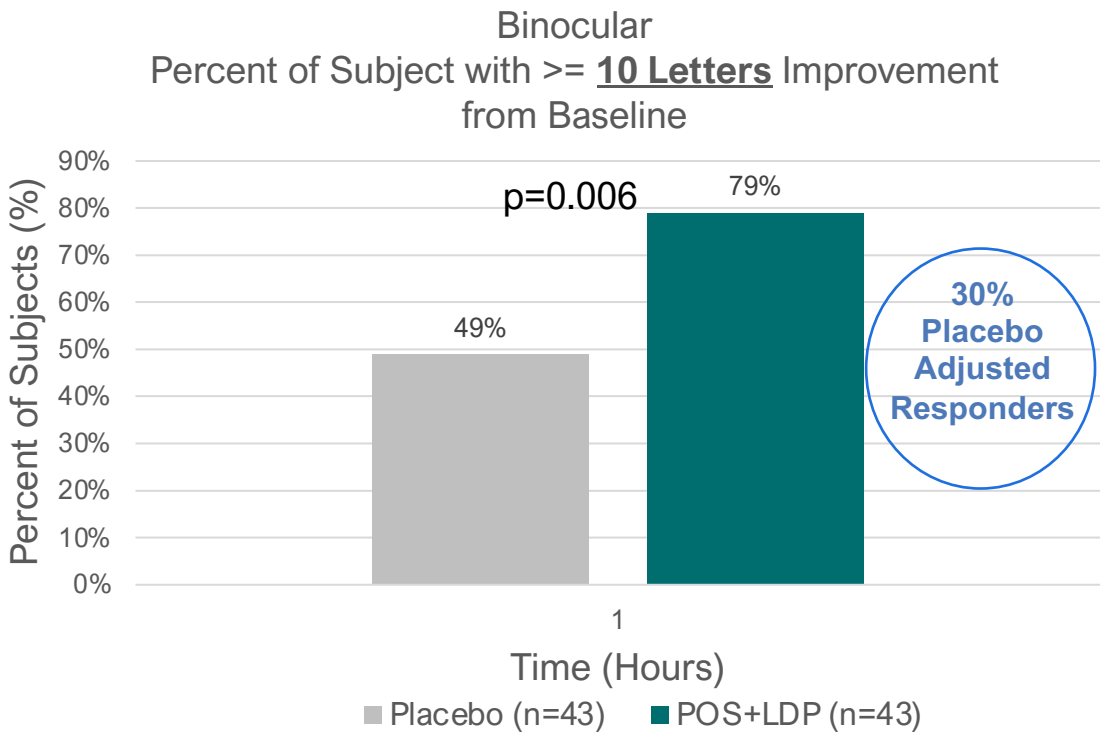
Source: VEGA-1 TLR Table 14.1.2.2 Demographics and Baseline Characteristics (PP Population). Snellen Conversion Chart.

Primary Endpoint: % Of Subjects ≥ 15 Letter Gain In Photopic DCNVA At 1 Hour

Primary Endpoint Was Met For POS + LDP Gaining ≥ 15 Letters Near Vision In PP Population

VEGA-1 Phase 2 Trial





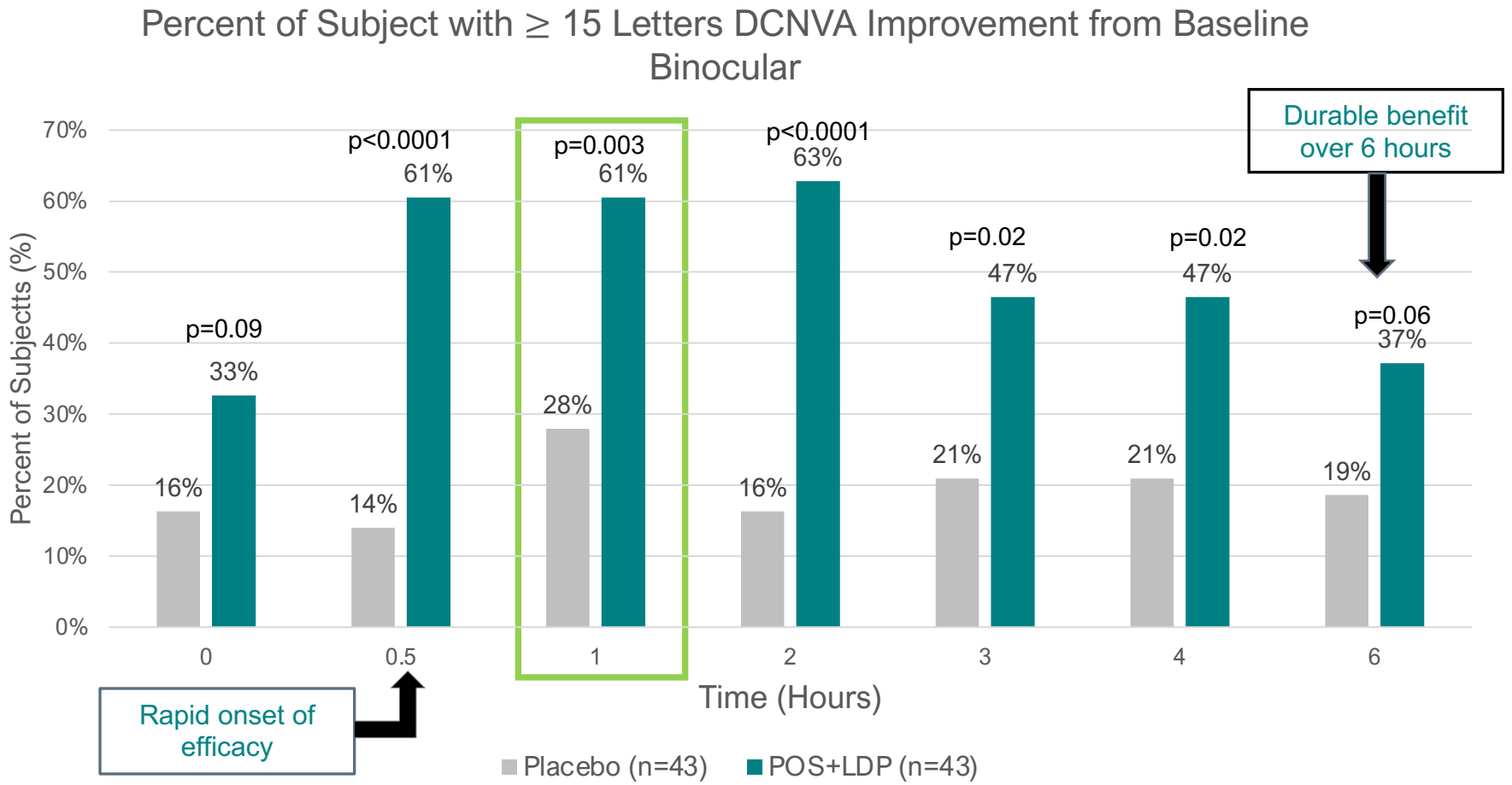
Note: PP population differs from mITT by only one subject; results were essentially identical.

Source: VEGA-1 TLR *Table 14.2.1.2 %of Subjects With Improvement From Baseline in Photopic DCNVA by Time Point (PP Population). 15 letters is 3 lines and 10 letters is 2 lines.*

Secondary Endpoint: % Of Subjects ≥ 15 Letter Gain At All Timepoints

POS + LDP Had Strong Response With ≥ 15 Letter Gain From 30 Min To 6 Hours

VEGA-1 Phase 2 Trial



Similar Efficacy was Observed In:

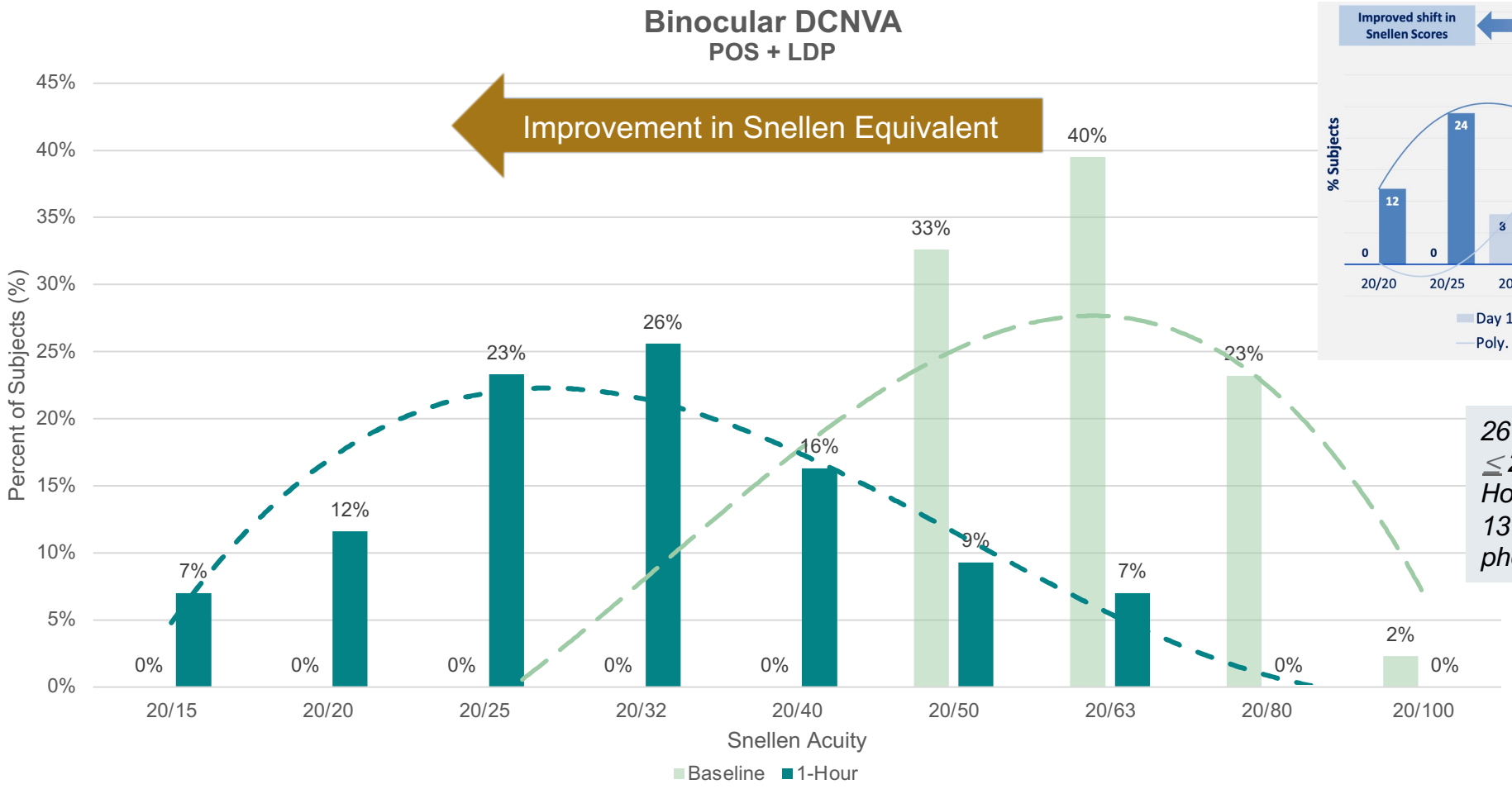
- ✓ Study Eye and Fellow Eye
- ✓ Light and Dark Irides

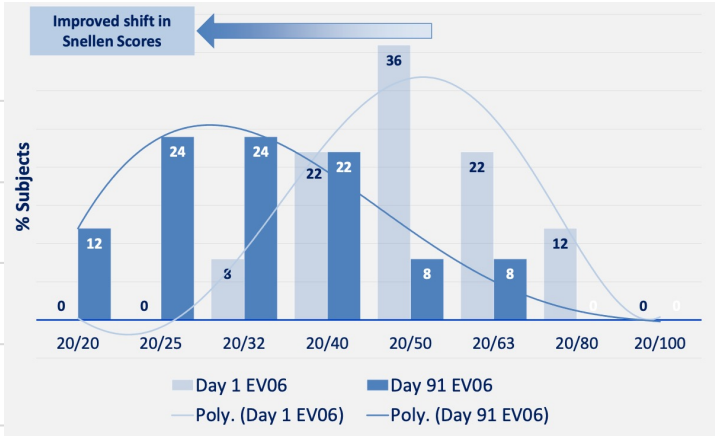
Source: VEGA-1 TLR Table 14.2.1.2 Percent of Subjects with Improvement From Baseline in Photopic DCNVA by Time Point (PP Population). 15 letters is 3 lines.

Secondary Endpoint: Snellen Equiv. DCNVA Baseline vs. 1 Hour Post POS+LDP

POS+LDP Had A Dramatic Effect On Near Vision With A Clear Improvement Shift

VEGA-1 Phase 2 Trial





26% Placebo Adjusted Response ≤20/40 for POS+LDP Combo at 1 Hour (p=0.02) Compared to AGN 13% Placebo Adjusted (p= 0.02) photopic DCNVA

Source: VEGA-1 TLR Table 14.2.24.1 Percent of Subjects with Photopic DCNVA by Time Point (PP Population); Novartis/Encore Materials, ASCRS 2021 Allergan Abstracts

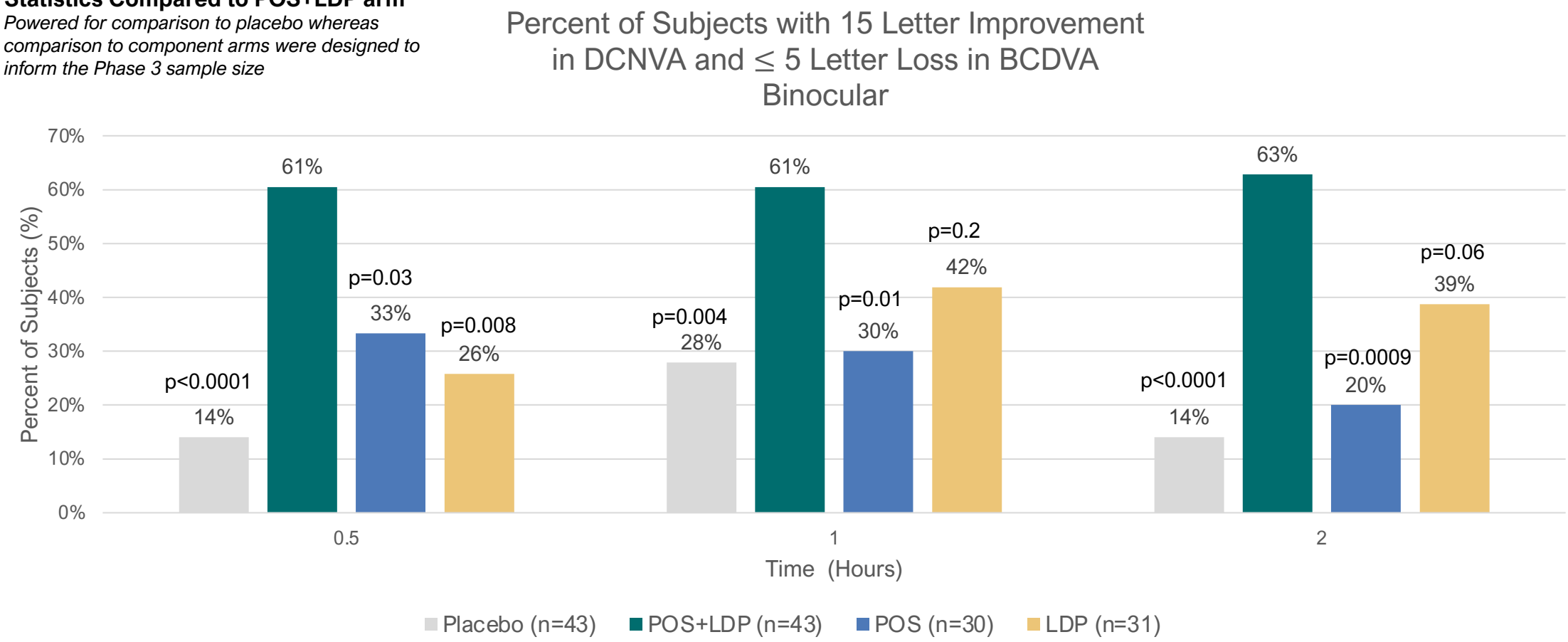
Secondary Endpoint: % of Subjects ≥ 15 Letter Gain In Near & ≤ 5 Letter Loss In Distance

Phase 3 Approval Endpoint Also Showed Early Onset & Durable Near Vision Gain Without Loss Of Distance

VEGA-1 Phase 2 Trial

Statistics Compared to POS+LDP arm

Powered for comparison to placebo whereas comparison to component arms were designed to inform the Phase 3 sample size



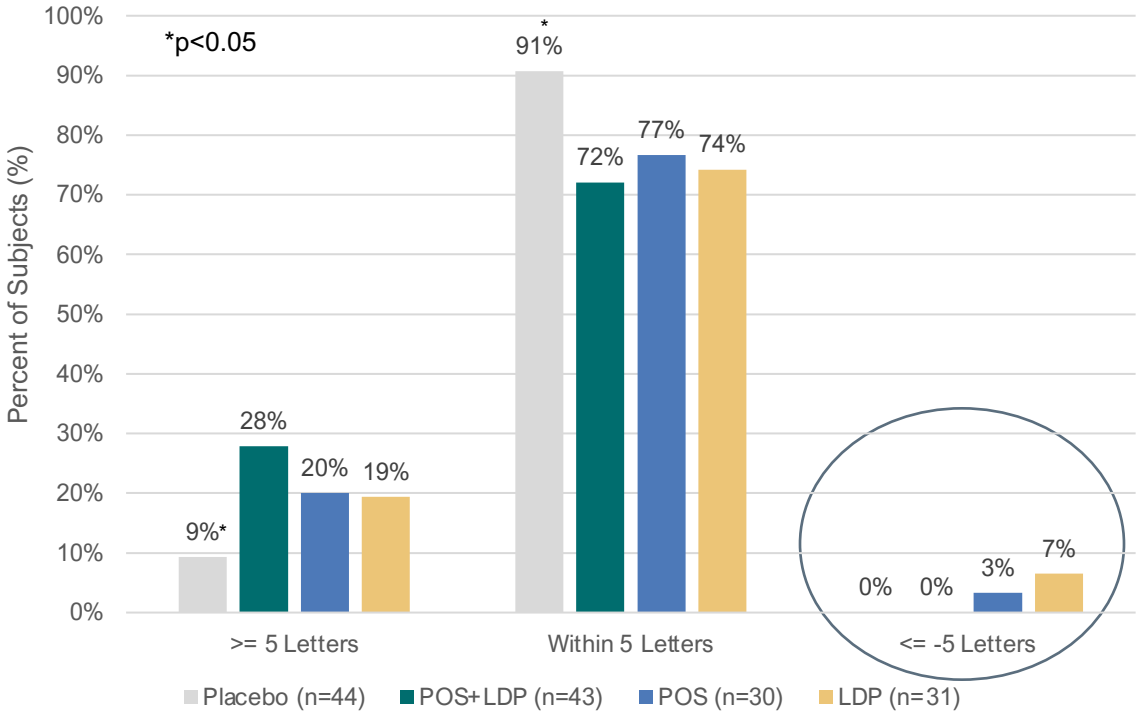
Source: VEGA-1 TLR Table 14.2.2.2 Percent of Subjects with >= 15 Letters of Improvement in Photopic DCNVA and < 5 Letters of Loss in Photopic Binocular BCDVA by Time Point (PP Population)

Secondary Endpoint: Change In Photopic/Mesopic BCDVA At 1 Hour

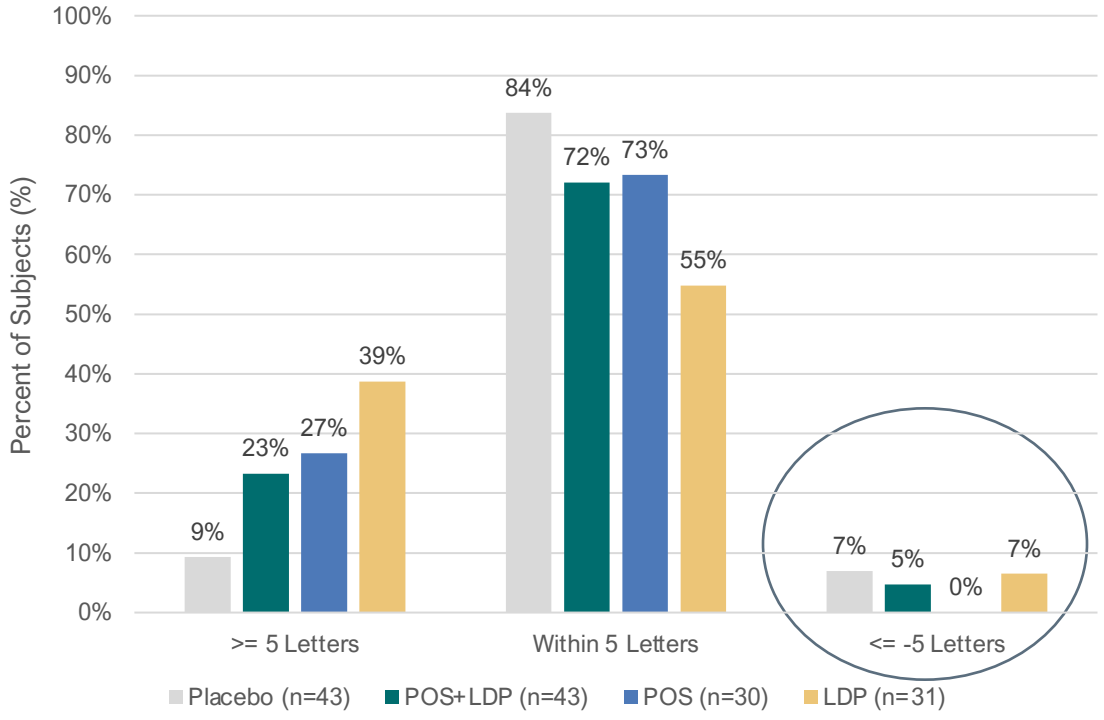
Treatment With POS And/Or LDP Did Not Reduce BCDVA And Had A Modest Beneficial Effect

VEGA-1 Phase 2 Trial

Percent of Subjects With Improvement or Loss From Baseline in Photopic BCDVA at 1 hour



Percent of Subjects With Improvement or Loss From Baseline in Mesopic BCDVA at 1 hour

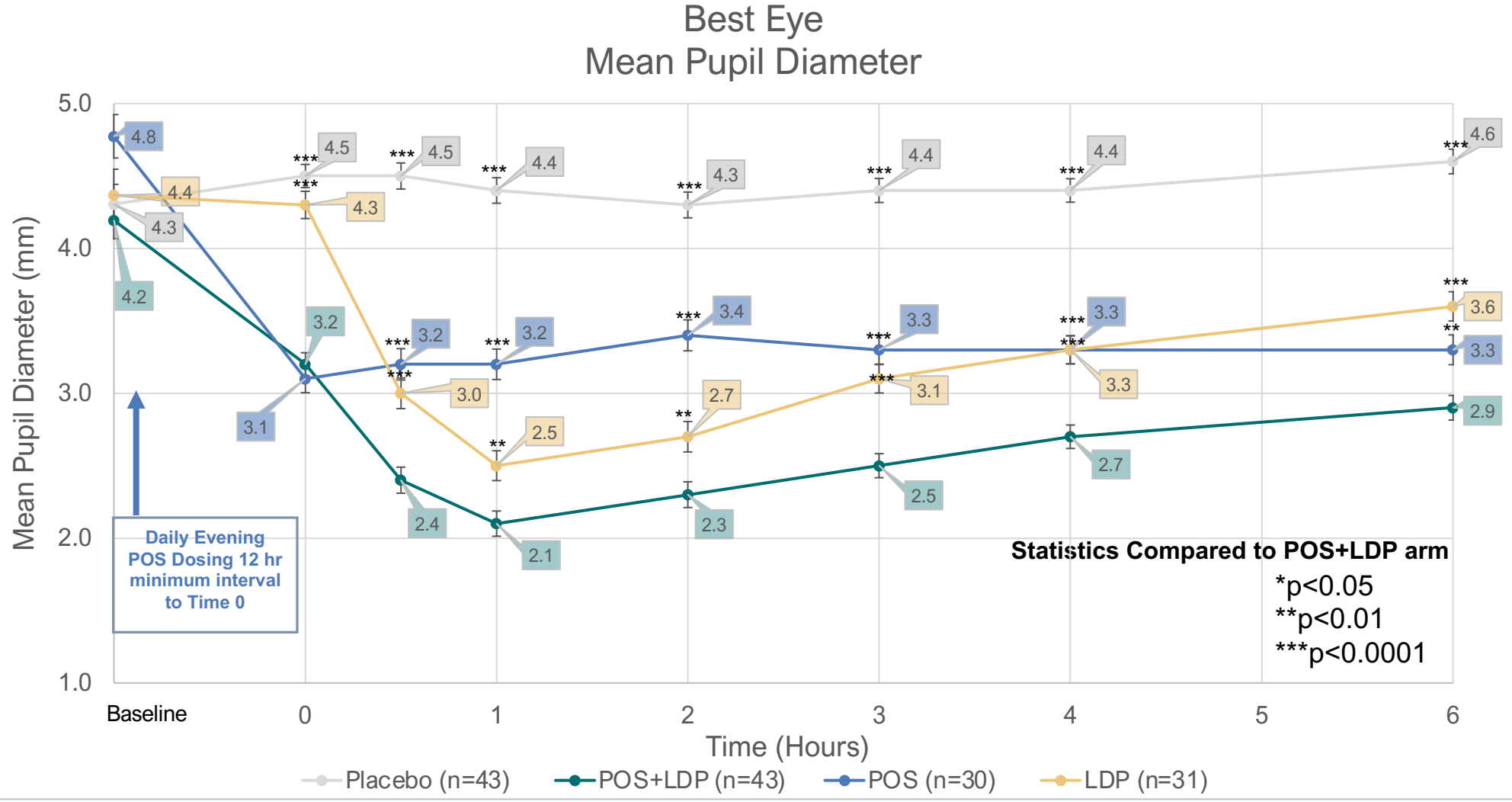


Source: VEGA-1 TLR Table 14.2.8.1 and 14.2.10.1 Percent of Subjects With Improvement or Loss From Baseline in Photopic and Mesopic BCDVA by Time Point (PP)

Secondary Endpoint: Mean Pupil Diameter Over Time

Achieved Pupil Size ~2mm In POS+LDP Consistent With 3-line Improvement In Near Vision

VEGA-1 Phase 2 Trial



Source: VEGA-1 TLR Table 14.2.12.1 Observed Values and Change from Baseline in Photopic Pupil Diameter by Time Point (PP Population)

Secondary Endpoint: Safety Findings

POS+LDP Combination Was Well Tolerated With A Favorable Safety Profile In VEGA-1 Trial

	Placebo Alone n=45	POS Alone n=30	LDP Alone n=31	POS+LDP n=44
Total Treatment Emergent Adverse Events (n)	4	18	13	**50**
TEAEs by Severity (n [%])				
Mild	1 (2.2%)	6 (20%)	6 (19.4%)	**13 (29.5%)**
Moderate	1 (2.2%)	0 (0%)	0 (0%)	**1 (2.3%)**
Severe	0 (0%)	0 (0%)	0 (0%)	**1 (2.3%)**
AEs Occurring in ≥ 5% of subjects (n [%])				
Instillation Site Pain (Mild)	1 (2.2%)	3 (10%)	0 (0%)	**4 (9.1%)**
Instillation Site Erythema (Mild)	0 (0%)	3 (10%)	2 (6.5%)	**5 (11.4%)**
Conjunctival Hyperemia (Mild)	0 (0%)	2 (6.7%)	0 (0%)	**2 (4.5%)**
Eye Disorders (Mild)	1 (2.2%)	2 (6.7%)	4 (12.9%)	**5 (11.4%)**

- No deaths, no serious AEs, and 1 withdrawal due to AEs (on POS alone)
- **0% Headaches or Browaches reported for POS+LDP and POS alone**
- Only 1 subject in LDP alone arm reported mild headache
- Almost all AEs were mild and most common was mild instillation site discomfort
- **Distance visual acuity not adversely affected (as shown earlier)**
- No change in IOP

Conjunctival Hyperemia CCLRU Scale for Reference

Source: VEGA-1 TLR Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events (TEAE) (Safety Population)
Table 14.3.1.3 Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Severity (Safety Population)

Summary Of Positive VEGA-1 Phase 2 Results

POS + LDP Efficacy Data With A Favorable Safety Profile In Presbyopia

- **Met the primary endpoint** with statistical significance for binocular photopic near vision at 1 hour
  - 61% POS+ LDP gained 15 letters (3 lines) or more vs. 28% Placebo (33% Placebo Adjusted)
- **Met the Phase 3 co-primary endpoint** vs. placebo gaining 15 letters (3 lines) near vision with less than 5 letters of distance vision loss
- **Met many key secondary endpoints**
  - Rapid onset at 30 min
  - Durable near vision improvement through at least 6 hours
  - POS+LDP was numerically better than each component through 2-hours
  - A majority of subjects treated with the combination achieved near acuity of 20/30 or better
  - Sustained significant reduction in PD over at least 18 hours due the durability effects of POS
  - Near vision efficacy seen monocularly and binocularly
  - Also, efficacy data in both light and dark iris colors
- **Favorable safety profile for POS + LDP**
  - No serious AEs
  - No systemic AEs were observed in >5% subjects
  - No headaches, no browaches, and no blurry vision AEs were reported
  - Only mild, transient conjunctival hyperemia observed in <5% of subjects
- **Positive Phase 2 results lead to advancing Phase 3 presbyopia program**

Thank you for your attention!

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