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Efficacy and Safety of PL9643 in Dry Eye Disease: Results From a Phase 3, Randomized, Vehicle-Controlled Study

Presented at:

Association for Research in Vision and Ophthalmology 2025 Annual Meeting

May 4-8, 2025 • Salt Lake City, UT

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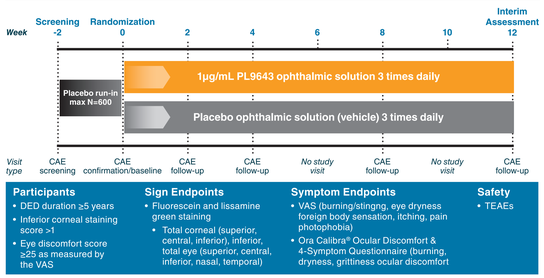
Introduction

- Dry eye disease (DED) is a multifactorial disorder that disrupts tear film homeostasis, leading to inflammation and damage of the ocular surface[1]
  - The prevalence of DED ranges from 5%-50%, with greater prevalence observed in females and older adults[1,2]
- The melanocortin system plays an important role in response to stress, resolution of inflammation, and tissue repair[3-5]
- Melanocortin receptors (MCR) are found on multiple structures of the anterior segment of the eye[6]
  - In preclinical studies using DED disease models, melanocortin agonists have shown great promise as a potential treatment for DED[5]
- PL9643 (Palatin Technologies) is a melanocortin pan-agonist of MC1R, MC3R, MC4R, and MC5R that is in development as a treatment for DED[7,8]
  - PL9643 is most selective for MC1R and has more selectivity for MC5R than α-melanocortin-stimulating hormone
- The objective of the current study was to compare the safety and efficacy of PL9643 with the vehicle for the treatment of signs and symptoms associated with dry eye

Methods

- This was a phase 3, multi-center, double-masked, randomized, vehicle-controlled study that evaluated the efficacy and safety of PL9643 in patients with dry eye (NCT05201170)[9]
- The study consisted of 6 visits over a 14-week period, which was partitioned into a 2-week run-in period followed by a 12-week treatment period (**Figure 1**)
  - Eligibility was determined at visits 1 and 2 (run-in period); those who qualified at visit 2 were randomized to receive either PL9643 or vehicle (eye drops, 3 times daily) in a double-masked fashion for 12 weeks with visits at weeks 2, 4, 8, and 12
  - At each study visit, participants were exposed for 90 minutes to a Controlled Adverse Environment® (CAE), which exacerbates dry-eye signs and symptoms

Figure 1. Study Design



Participants
- DED duration ≥5 years
- Inferior corneal staining score >1
- Eye discomfort score ≥25 as measured by the VAS

Sign Endpoints
- Fluorescein and lissamine green staining
  - Total corneal (superior, central, inferior), inferior, total eye (superior, central, inferior, nasal, temporal)

Symptom Endpoints
- VAS (burning/stinging, eye dryness foreign body sensation, itching, pain photophobia)
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire (burning, dryness, grittiness ocular discomfort

Safety
- TEAEs

CAE, controlled adverse environment; DED, dry eye disease; TEAE, treatment-emergent adverse event; VAS, visual analog scale.

- Fluorescein and lissamine green staining as measured by the Ora Calibra® Corneal and Conjunctival Staining Scale (corneal and conjunctival staining scale) were used to evaluate clinical signs
  - This scale is partitioned into 3 corneal (inferior, superior, and central) and 2 conjunctival (temporal and nasal) zones; each zone is scored from 0 (no staining) to 4 (severe, confluent staining)[7]
- A visual analog scale (VAS), the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire (discomfort and symptom questionnaire), and the Ora Calibra® Ocular Discomfort Scale (ocular discomfort scale) were used to evaluate clinical symptoms (eg, pain and burning)
  - VAS symptoms are scored on a 100-mm horizontal line, with 0 representing no discomfort and 100 representing maximal discomfort
  - A composite score of the 7 VAS symptoms (sum of differences from baseline for each participant) was calculated at each time point
  - Each symptom on the discomfort and symptom questionnaire is scored from 0 (no discomfort) to 5 (severe discomfort)
  - The ocular discomfort scale is scored from 0 (no discomfort) to 4 (constant discomfort)[7]
- Safety endpoints included treatment-emergent adverse events (TEAEs)

Results

- Of the 1244 participants screened, 575 were randomized either to the PL9643 (n=287) or vehicle group (n=288) (safety population)
  - The initial 120 participants enrolled (PL9643 [n=59], vehicle [n=61]) were analyzed separately to identify the most promising clinical signs and symptoms[10]
  - The remaining 455 participants (PL9643, n=228; vehicle, n=227) comprised the intent-to-treat (ITT) population used for the efficacy analysis

Demographics

- Of the 575 participants enrolled (mean [SD] age, 61.5 [12.99] years), 390 were female (67.8%), and 257 (44.7%) were 65 years of age or older
  - In the ITT population, the vehicle group had more females (72.7% vs 63.2%) and participants ≥65 years old (49.8% vs 39.9%) than the PL9643 group

Efficacy Analyses

Clinical Symptoms

- In the ITT population, PL9643 demonstrated broad efficacy across multiple symptoms and signs
  - The co-primary endpoint of pain met statistical significance ($P<0.025$) over vehicle, specifically in female participants and participants aged ≥65 years
  - Additionally, 5 other secondary symptoms met statistical significance over vehicle ($P<0.05$)
- In female participants and participants aged ≥65 years, significant improvements in favor of PL9643 were observed at week 12 for various symptom endpoints, such as burning/stinging, eye discomfort, eye dryness, foreign body sensation, itching, pain, photophobia, burning, dryness, grittiness, and ocular discomfort (**Table 1**)

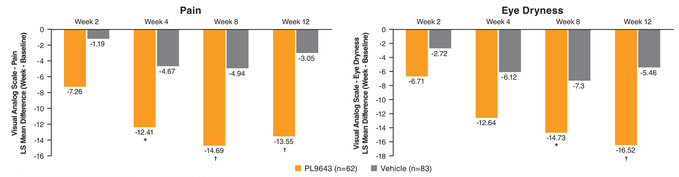
Table 1. Visual Analog Scale and Discomfort and Symptom Questionnaire Scores (Pre-CAE): Change from Baseline to Week 12

Scale Symptom	Mean Difference From Baseline (PL9643 minus Vehicle)	SE	*P*-value
Female, ≥65 years*			
Visual analog scale			
Burning/stinging	-8.93	3.82	<0.05
Eye discomfort	-8.02	3.92	<0.05
Eye dryness	-11.05	3.95	<0.01
Foreign body sensation	-10.45	3.97	<0.01
Pain	-10.51	3.60	<0.01
Photophobia	-13.36	3.90	<0.01
Discomfort and symptom questionnaire			
Burning	-0.57	0.20	<0.01
Dryness	-0.47	0.19	<0.05
Ocular discomfort	-0.51	0.18	<0.01
Grittiness	-0.61	0.21	<0.01
Female			
Visual analog scale			
Burning/stinging	-4.55	2.63	<0.10
Eye dryness	-9.10	2.71	<0.01
Foreign body sensation	-4.95	2.71	<0.10
Itching	-4.89	2.59	<0.10
Pain	-6.62	2.47	<0.01
Photophobia	-8.76	2.68	<0.01
Discomfort and symptom questionnaire			
Burning	-0.32	0.14	<0.05
Dryness	-0.29	0.13	<0.05
Ocular discomfort	-0.25	0.13	<0.10
≥65 years			
Visual analog scale			
Burning/stinging	-6.70	3.48	<0.10
Eye dryness	-6.95	3.63	<0.10
Foreign body sensation	-5.62	3.70	0.13
Pain	-6.23	3.29	<0.10
Photophobia	-7.22	3.58	<0.05
Discomfort and symptom questionnaire			
Burning	-0.45	0.18	<0.05
Dryness	-0.39	0.17	<0.05
Grittiness	-0.46	0.20	<0.05
Ocular discomfort	-0.47	0.17	<0.05

CAE, controlled adverse environment; SE, standard error.
*The US Food and Drug Administration (FDA) has agreed on the female, ≥65 year-old population as the primary analysis population for symptoms for future phase 3 studies in this program.

- A trend in favor of PL9643 was detected in female participants aged ≥65 years from week 2 for pain and week 4 for eye dryness, with statistically significant and progressively larger differences over time (**Figure 2**)

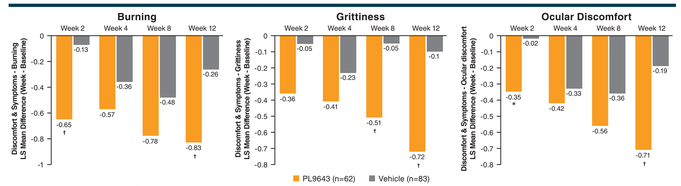
Figure 2. Change in VAS scores (pre-CAE) from baseline in female participants aged ≥65 years



CAE, controlled adverse environment; VAS, visual analog scale.
*P<0.05, †P<0.01; PL9643 vs vehicle.

- Significantly greater effects with PL9643 were observed from baseline to week 2 for burning and ocular discomfort (**Figure 3**); some improvement was noted for grittiness
  - Similarly, improvement with PL9643 increased over time

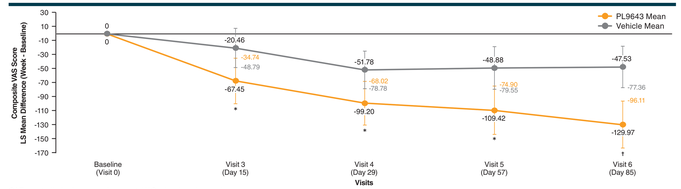
Figure 3. Change in discomfort and symptom questionnaire scores (pre-CAE) from baseline in female participants aged ≥65 years



CAE, controlled adverse environment.
*P<0.05, †P<0.01; PL9643 vs vehicle.

- The composite score of change in VAS symptoms in female participants aged ≥65 years was significantly different at week 2 between PL9643 and vehicle groups, with greater improvement in symptoms with PL9643 treatment (**Figure 4**)
  - The magnitude of improvement in symptoms with PL9643 increased over time
  - In contrast, vehicle-treated participants showed minimal improvement that plateaued early

Figure 4. Change in composite VAS score (pre-CAE) from baseline in female participants aged ≥65 years

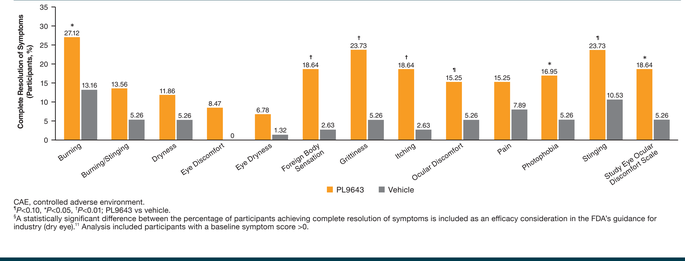


CAE, controlled adverse environment; VAS, visual analog scale.
*P<0.05, †P<0.01; PL9643 vs vehicle.
Error bars represent 95% confidence interval.

Resolution of Clinical Symptoms

- A numerically greater percentage of female participants aged ≥65 years treated with PL9643 achieved complete resolution of symptoms than those treated with vehicle (**Figure 5**)
  - Statistically significant differences in complete resolution of symptoms with PL9643 (vs vehicle) were detected in 6 of 13 symptom endpoints ($P<0.05$), with a trend noted for 2 other symptom endpoints ($P<0.10$)
  - Across all 13 symptom endpoints, a greater percentage of patients in the PL9643 group achieved complete symptom resolution compared to those receiving placebo
  - Symptom clearing with PL9643 was evident as early as 2 weeks, with an increasing number of symptoms reaching statistical significance from week 4 through week 12 — consistent with the resolution of inflammation, the mechanism of action of melanocortin agonists

Figure 5. Percentage of female participants aged ≥65 years who had complete resolution of symptoms§ (pre-CAE) at week 12

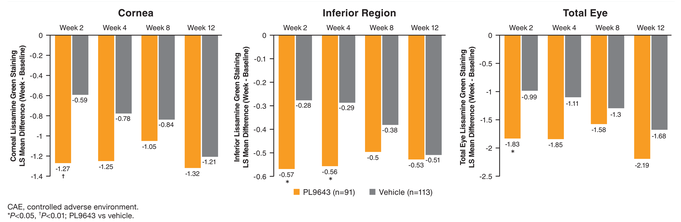


CAE, controlled adverse environment.
*P<0.10, †P<0.05, ‡P<0.01; PL9643 vs vehicle.
§A statistically significant difference between the percentage of participants achieving complete resolution of symptoms is included as an efficacy consideration in the FDA's guidance for industry (dry eye).[11] Analysis included participants with a baseline symptom score >0.

Clinical Signs

- In participants aged ≥65 years, PL9643 significantly improved vs vehicle in post-CAE change from baseline to week 2 for corneal, inferior, and total eye fluorescein staining (**Figure 6**)

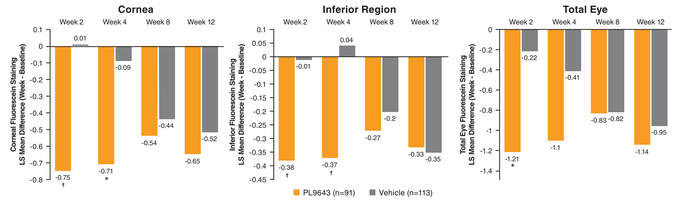
Figure 6. Change in fluorescein staining (post-CAE) from baseline in participants aged ≥65 years



CAE, controlled adverse environment.
*P<0.05, †P<0.01; PL9643 vs vehicle.

- Lissamine green staining results were consistent with the fluorescein staining results, with significant improvements for PL9643 in post-CAE change from baseline to week 2 for corneal, inferior, and total eye regions, and at week 4 for corneal and inferior regions (**Figure 7**)

Figure 7. Change in lissamine green staining (post-CAE) from baseline in participants aged ≥65 years



CAE, controlled adverse environment.
*P<0.05, †P<0.01; PL9643 vs vehicle.

Safety

- PL9643 was well-tolerated, with a TEAE rate similar to vehicle (16.7% and 24.3%, respectively)
- A greater proportion of participants receiving vehicle experienced ocular TEAEs (12.5%) compared with PL9643 (10.1%)
  - The most commonly reported treatment-related ocular TEAE was instillation site pain, reported by 3.1% of participants in the PL9643 group and 4.5% in the vehicle group; all other treatment-related ocular TEAEs occurred in <1% of participants

Conclusion

- There is an unmet need for effective treatments of DED that have a favorable safety and tolerability profile and the ability to provide rapid relief for the multiple DED symptoms patients experience
- The promising results from this initial phase 3 study indicate that PL9643 has a fast onset of efficacy, broad efficacy across multiple signs and symptoms, with multiple symptoms completely resolving, and has excellent tolerability; the profile of PL9643 represents a novel and highly differentiated approach to treating DED
  - Use of PL9643 had a broad effect on treating the symptoms of DED, with significant improvements in a range of clinical symptoms
  - Efficacy was present at 2 weeks; importantly, there was continued improvement over the 12 weeks of the study
  - PL9643 use resulted in significant improvements in clinical signs post-CAE using multiple staining methods across combined eye regions (cornea and total eye), as well as a region prone to the effects of dry eye (inferior), suggesting that PL9643 can protect the surface of the eye
  - PL9643 was associated with a rapid onset, with significant improvements detected in multiple sign and symptom outcomes following 2 weeks of treatment
  - Using a composite score of the 7 VAS symptoms, PL9643 achieved statistically significant results compared with vehicle at 2 weeks and continued improvement through 12 weeks
  - Across all 13 symptom endpoints, a greater percentage of participants in the PL9643 group achieved complete symptom resolution compared to those receiving placebo
  - Six of the 13 symptom endpoints were significant ($P<0.05$) in favor of a higher proportion in the PL9643 arm
  - Symptom clearing with PL9643 was evident as early as 2 weeks, with an increasing number of symptoms reaching statistical significance from week 4 through week 12 — consistent with the resolution of inflammation, the mechanism of action of melanocortin agonists
- PL9643 was well tolerated, with a safety profile similar to or better than vehicle (vehicle similar to artificial tears)
- PL9643 represents a promising new approach to DED treatment, and further phase 3 studies are planned

Acknowledgments The authors thank all study participants. The authors and Palatin give special acknowledgment to Bruce Stouch, PhD, for his significant statistical support and contributions provided for the PL9643 phase 3 clinical study. Medical writing support was provided by Kirk W. Evanson, PhD, from The Curry Rockefeller Group, LLC, a Citrus Health Group company (Chicago, IL), and was funded by Palatin Technologies, Inc. (Cranbury, NJ).

Funding This study was funded by Palatin Technologies, Inc. (Cranbury, NJ).

Disclosures George W. Ousler was an employee of Ora, Inc., throughout the duration of the study. David Louis Wirta has received financial support from Palatin Technologies, Inc. Sherif Mustafa El-Harazi, Guruprasad R. Pattar, and Eric D. Donnenfeld have nothing to declare. Carl Spana, Robert Jordan, and Brian Dodge are employees and own stock in Palatin Technologies, Inc.

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