B0286

Presented at:

Association for Research in Vision and Ophthalmology

April 23–27, 2023 • New Orleans, LA

Effectiveness of PL9643 in Treating the Signs and Symptoms of Moderate to Severe Dry Eye Disease: Results From 2 Independent Clinical Trials

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Introduction

- Dry eye disease (DED) is a multifactorial inflammatory and aqueous tear deficient disorder affecting the cornea and conjunctiva, characterized by ocular irritation and potential visual impairment[1,2]
- Current dry eye therapies are often regarded as inadequate by many physicians and patients owing to poor response, adverse events (AEs), poor ocular tolerability, and prolonged interval preceding therapeutic activity[3-5]

Melanocortins

- Melanocortins are a family of hormone agonists that bind to melanocortin receptors (MCRs) and include several melanocyte-stimulating hormones (α-, ß-, and γ-MSH) and adrenocorticotropin hormone[6-8]
- The melanocortin pathway plays an important role in resolving inflammation, promoting tissue healing processes, and maintaining immunological homeostasis[6,9]
- Melanocortin agonists may represent a new therapeutic avenue to treat inflammatory ocular diseases[10-14]

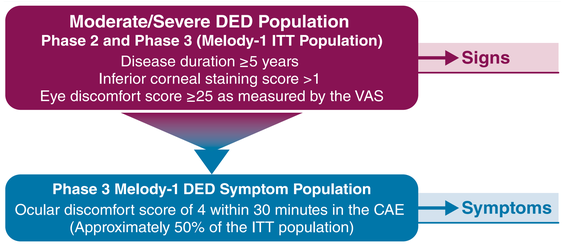
PL9643

- PL9643 is a synthetic MCR pan-agonist (not active at MC2R) with anti-inflammatory ocular activity that is being investigated in the phase 3, Melody-1 clinical trial as a treatment for DED

Phase 2 DED study (PL9643-201)[15]

- A phase 2, multicenter, randomized, placebo-controlled, double-masked 12-week study that evaluated the efficacy and safety of PL9643 in patients with DED (n=80, NCT 04268069)
- In patients with moderate or severe DED (n=53, defined as duration of DED ≥5 years, inferior corneal staining >1, and eye discomfort on the visual analog scale [VAS] ≥25) PL9643 treatment demonstrated nominally significant ($P<0.05$) or trending ($P<0.1$) improvement over placebo in mean change from baseline at week 12/day 85 in several sign and symptom endpoints including
  - Fluorescein staining in inferior, superior, corneal sum, and total sum regions
  - Lissamine green staining in nasal, temporal, conjunctival sum, and total sum region
  - Tear film breakup time
  - Conjunctival redness
- 80 patients received PL9643 for 12 weeks. There were no ocular AEs related to PL9643 and no patients discontinued use of the study drug because of tolerability issues
- Efficacy across multiple sign and symptom endpoints in patients with moderate to severe DED, and the low number of ocular AEs, were encouraging and led to the phase 3 (Melody-1) study (**Figure 1**)

Figure 1. Analysis Populations

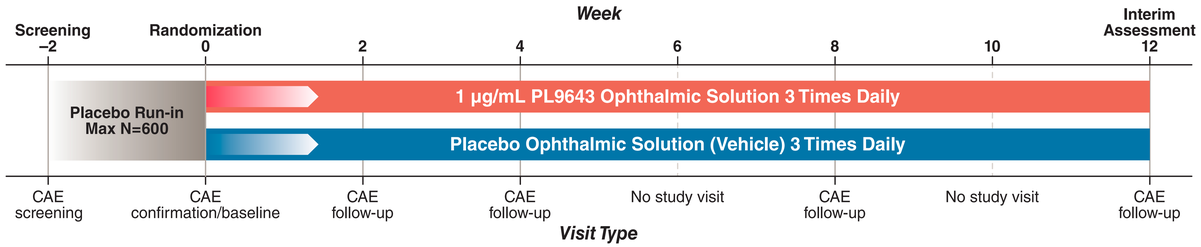


CAE, controlled adverse environment; DED, dry eye disease; ITT, intent-to-treat; VAS, visual analog score.

Methods

- Melody-1 (NCT 05201170) is a 12-week, multicenter, 1:1 randomized, double-masked, vehicle-controlled adaptive design study in up to 600 patients to evaluate the efficacy and safety of PL9643 in patients with moderate to severe DED (**Figure 2**)
- The first 120 randomized patients to complete 12-weeks of double-blind treatment were designated as the lead-in population, and their data were part of an interim analysis (IA)
  - The objective of the IA was to identify the clinical signs and symptom endpoints that meet the clinical, regulatory, and statistical requirements for success to be used in analyzing the full trial population which will consist of up to 600 patients
- The Ora controlled adverse environment® (CAE) challenge model controls the environment for relative humidity, airflow, and visual tasking and was used to standardize the evaluation of signs and symptoms of DED[16]
- Placebo/vehicle used in the phase 2 study and the lead-in patients from Melody-1 was an active control with the same composition as artificial tears, which provides temporary relief of DED symptoms
- Clinical signs were analyzed using the IA intent-to-treat (ITT) population (n=120)
- Ocular surface damage was assessed by fluorescein and lissamine green staining by region (central, superior, inferior, nasal, temporal, corneal sum, conjunctival sum, and total staining) scored on a 5-point scale (0=none, 4=severe), using the Ora Calibra® Corneal and Conjunctival Staining Scale. Corneal sum was the sum of the central, superior, and inferior regions (range 0–12). Conjunctival sum was the sum of the nasal and temporal regions (range 0–8). Total eye score was the sum of all 5 regions (range 0–20)
- Clinical symptoms were analyzed in the IA DED Symptom subpopulation (n=70) which was 58% of the ITT population

Figure 2. MELODY-1 Study Design



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

Co-Primary Sign Endpoint (Week 12)
Inferior corneal fluorescein staining

Co-Primary Symptom Endpoint (Week 12)
Ocular pain

Key Secondary Endpoints (Week 12)
- Conjunctival sum lissamine green staining
- Total sum lissamine green staining
- Tear film break-up time

Other Secondary Endpoints Include
Burning, foreign body sensation, eye dryness, eye discomfort, ocular discomfort

CAE, controlled adverse environment, DED, dry eye disease; VAS, visual analog scale.

DED Symptom (Hyper-Responder) Population

Includes those patients whose ocular discomfort worsens to 4 using the Ora Calibra® Ocular Discomfort scale (0=none to 4=worst) within 30 minutes in the CAE

- VAS ocular pain was scored by patients rating their ocular pain on a 100-mm horizontal line to indicate the level of discomfort; 0=no discomfort, 100=maximal discomfort

Results

Clinical Signs

- Clinical sign data were determined from the IA ITT population (n=120)
- At 12 weeks total and conjunctival sum lissamine green staining, and central and inferior fluorescein staining for the PL9643 group was superior to that of vehicle (treatment differences least squares [LS] meawns of –0.79 to –0.22 vs vehicle) (**Figure 3**)
- PL9643 was also superior to vehicle for tear film breakup time with an LS mean treatment difference of 0.38 seconds
- The effect size for all of these signs was ~0.3
  - Effect size was calculated as the difference (PL9643–vehicle) divided by the common SD

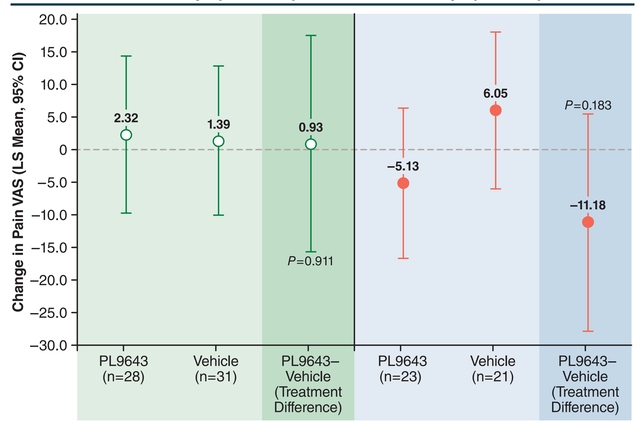
Figure 3. Clinical Signs: Treatment Differences for Fluorescein and Lissamine Green Staining and Tear Film Breakup at Week 12 (IA ITT Population, n=120)

Treatment difference values are PL9643–vehicle, displayed as LS mean change +95% CI (Pre-CAE week 12)–(Pre-CAE baseline). For lissamine green and fluorescein staining a negative treatment difference represents improvement. For tear film breakup time a positive treatment difference represents improvement. CAE, controlled adverse environment; IA, interim assessment; ITT, intent-to-treat; LS, least squares.

Clinical Symptom: Ocular Pain

- Clinical symptom data were determined from the IA DED Symptom population
- The PL9643 IA DED Symptom population was enriched in response to PL9643 compared to the non-DED Symptom responder population as measured by the pain VAS (**Figure 4**)
- At week 12 in the DED Symptom population, PL9643 showed a clinically significant difference of –11.8 over vehicle in VAS pain

Figure 4. Clinical Symptoms: Change in Ocular Pain VAS Scores vs Baseline at Week 12 For Non-DED Symptom Responder and IA DED Symptom Populations



Change in VAS scores is (Post-CAE minus Pre-CAE at week 12)–(Post-CAE minus Pre-CAE at baseline). A negative treatment difference represents an improvement (less pain). CAE, controlled adverse environment; DED, dry eye disease; IA, interim assessment; VAS, visual analog scale.

Safety

- Based on the IA ITT population, where 60 patients received PL9643 for 12 weeks, there were no ocular AEs related to PL9643 and no patients discontinued use of the study drug because of tolerability issues

Conclusions

- PL9643 has a novel mechanism of action and potentially protects the ocular surface from the damaging effects of inflammation and help resolve ongoing inflammation
- Based on the positive results from both phase 2 and phase 3 study IA, and the successful utilization of the Ora CAE challenge DED Symptom subpopulation, the PL9643 Melody-1 phase 3 clinical trial is continuing to enroll patients with the DED Symptom population specified for the analysis of dry eye symptoms
- PL9643 demonstrated effectiveness across multiple clinical signs and reduced symptomatic ocular pain indicating that PL9643 is having a positive affect across multiple regions of the eye, offering a potentially differentiating efficacy profile from currently available treatments for DED
- The safety results from the phase 2 and initial phase 3 studies present no ocular AEs related to PL9643 and no patients discontinued use of the study drug because of tolerability issues
- Considering other products, the magnitude of the absolute difference between PL9643 and vehicle exceeds what has been reported for other approved products for several clinical sign and symptom endpoints
- PL9643 may fill a number of important unmet patient needs in front of the eye conditions, including DED, by providing a safe and tolerable treatment option

Acknowledgments The authors and Palatin give special acknowledgment to Bruce Stouch, PhD, for his significant statistical support. Writing and editorial assistance was provided by Robin Smith, PhD, of The Curry Rockefeller Group, LLC (Tarrytown, NY, USA), which was funded by Palatin Technologies, Inc.

Support Palatin Technologies, Inc.

Disclosures **George Ousler** is an employee of Ora Inc. **Robert Jordan** and **Carl Spana** are employees of Palatin Technologies, Inc.

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