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Melanocortin Agonist PL9643 Significantly Improves Ocular Signs and Symptoms of Moderate to Severe Dry Eye Disease, Including Tear Film Break Up Time

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Purpose

- 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 include several melanocyte-stimulating hormones (α, ß, and γ-MSH) and adrenocorticotropin hormone[6-8]
  - These hormones bind to melanocortin receptors (MCRs) to exert their effect
- Melanocortins have a wide range of anti-inflammatory properties[6,9,10]
  - Inhibition of leukocyte activation by suppressing proinflammatory cytokine production[9,11]
  - Protection of tissues from the inflammatory response[10,12,13]
- Melanocortin agonists may represent a new therapeutic avenue to treat inflammatory ocular diseases[14-16]
- α-MSH has been shown to promote anti-apoptotic activity, promote healing of epithelial corneal lesion, and reduce ocular irritation in rats[17,18]

PL9643

- PL9643 is synthetic MCR pan-agonist (not active at MC2R) currently being investigated for anti-inflammatory ocular indications, including DED

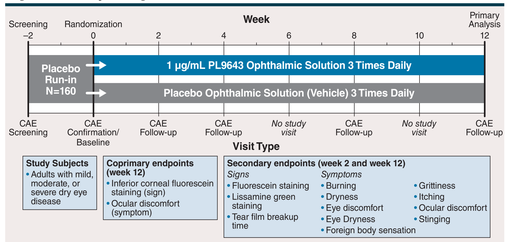
Objective

- The efficacy and tolerability of PL9643 was examined in a subpopulation of subjects with moderate to severe DED as part of a phase 2 study

Methods

- This was a 12-week, phase 2, multicenter, 1:1 randomized, double-masked, placebo-controlled study of subjects with DED (NCT 04268069)
- Subjects received placebo solution during a 2-week run-in period and were randomized to either placebo or PL9643 topical ophthalmic solution 3 times daily for 12 weeks (**Figure 1**)

Figure 1. Study Design



CAE, controlled adverse environment.

- Study enrolled adults with mild, moderate, or severe DED
- A subpopulation of subjects (n=53) with moderate to severe DED was analyzed
  - Subjects had duration of DED ≥5 years, inferior corneal staining >1, and eye discomfort on a visual analog scale (VAS) ≥25 (on a scale of 0–100)
- Controlled adverse environment (CAE®) model was used to exacerbate signs/symptoms of dry eye[19]
- Endpoints included tear film break up time, changes in inferior corneal fluorescein and Lissamine green staining, and ocular discomfort after 2 and 12 weeks
  - Ocular discomfort was measured by Ora Calibra® scales[20,21]
- Other endpoints were changes in additional signs and symptoms of DED
- The VAS assessed burning/stinging, itching, foreign body sensation, eye discomfort, blurred vision, eye dryness, photophobia, and pain
- Safety was assessed by recording AEs throughout the study
- Ora Calibra Drop Comfort Scale and Questionnaire®[22] assessed the tolerability of the topical solution at baseline
- *All treatment differences are shown as least squares mean ± standard error*

Results

Overall (Safety) Population

- 160 subjects were randomized, 80 in the PL9643 group, and 80 in the placebo group
- 156 subjects (97.5%) completed the study: 79 (98.8%) in the PL9643 group, and 77 (96.3%) in the placebo group
- 4 subjects (2.5%) discontinued from the study: 1 (1.3%) in the PL9643 group and 3 (3.8%) in the placebo group
- 1 subject in the PL9643 group discontinued owing to a serious AE of chronic lymphocytic leukemia

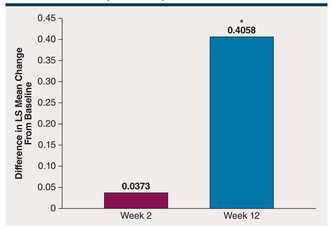
Moderate and Severe DED Population

- Baseline demographics of the subjects with moderate and severe DED (n=53) were balanced across the 2 groups. Median age was 69 (range 51–84) years for placebo group, and 69.5 (range 51–80) years for PL9643 group

Tear Film Breakup Time

- In the moderate or severe dry eye population, PL9643 treatment demonstrated a significant improvement over placebo at week 12 for tear film breakup time with a treatment difference vs placebo of +0.4058±0.1584 (P<0.05) (**Figure 2**).

Figure 2. Tear Film Breakup Time Treatment Difference PL9643 vs Placebo (Moderate to Severe DED Population)

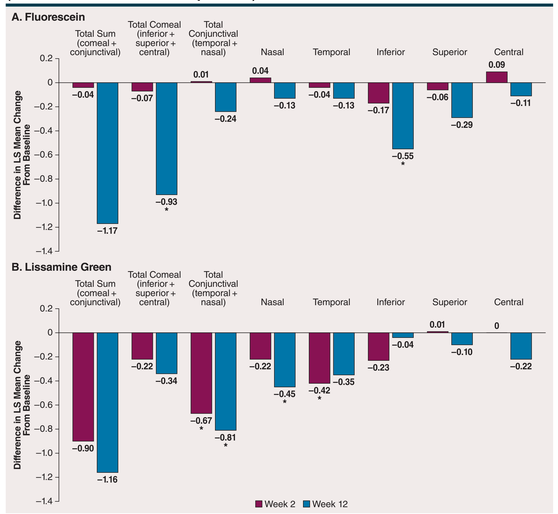


CAE, controlled adverse environment; DED, dry eye disease; LS, least squares. Note: Difference was change post-CAE. *P≤0.05 vs placebo via analysis of covariance.

Corneal and Conjunctival Fluorescein Staining (Figure 3A)

- PL9643 treatment demonstrated a significant improvement over placebo (P<0.05) at week 12 for fluorescein staining for
  - Inferior corneal staining: treatment difference −0.55±0.202
  - Total corneal staining (inferior, superior, and central): treatment difference −0.93±0.398

Figure 3. Corneal and Conjunctival Staining Treatment Difference vs Placebo (Moderate to Severe DED Population)



CAE, controlled adverse environment; LS, least squares. Note: Difference was change from pre-CAE to post-CAE. Fluorescein and Lissamine Green staining was measured with the Ora Calibra Corneal and Conjunctival Staining Scale®. *P≤0.05 vs placebo via analysis of covariance.

Corneal and Conjunctival Lissamine Green Staining (Figure 3B)

- PL9643 treatment demonstrated significant improvement (P<0.05) over placebo for Lissamine green staining

At week 12

- Nasal staining: treatment difference −0.45±0.173
- Total conjunctival staining (temporal and nasal): treatment difference −0.81±0.285

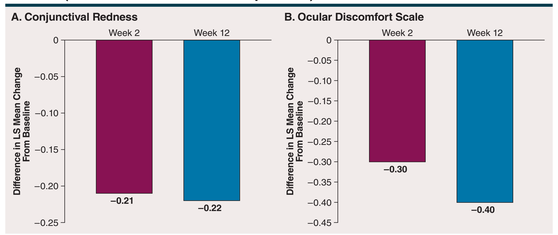
At week 2

- Total conjunctival sum staining (temporal and nasal): treatment difference −0.67±0.285
- Temporal staining: treatment difference −0.42±0.175

Conjunctival Redness and Ocular Discomfort (Symptoms)

- PL9643 treatment showed numeric, but nonsignificant improvement over placebo at weeks 2 and 12 for conjunctival redness (week 12 treatment difference, −0.22±0.133; P=0.1001) (**Figure 4A**)
- Ocular discomfort as measured by the Ora Calibra Ocular Discomfort Scale® demonstrated numeric, but non-significant improvement vs placebo at weeks 2 and 12 (week 12 treatment difference, −0.4±0.27; P=0.1302) (**Figure 4B**)
- Using the Ora Calibra Ocular Discomfort and 4-Symptom Questionnaire® (**Figure 5A**), PL9643 treatment demonstrated significant improvement over placebo at week 2 in ocular discomfort (treatment difference, −0.4±0.19; P<0.05)
  - All other symptoms measured by the questionnaire (dryness, stinging and grittiness) showed numeric superior, but nonsignificant PL9643 treatment difference compared with placebo throughout the duration of the study, except for grittiness at week 12

Figure 4. Conjunctival Redness and Ocular Discomfort Treatment Difference vs Placebo (Moderate to Severe DED Population)

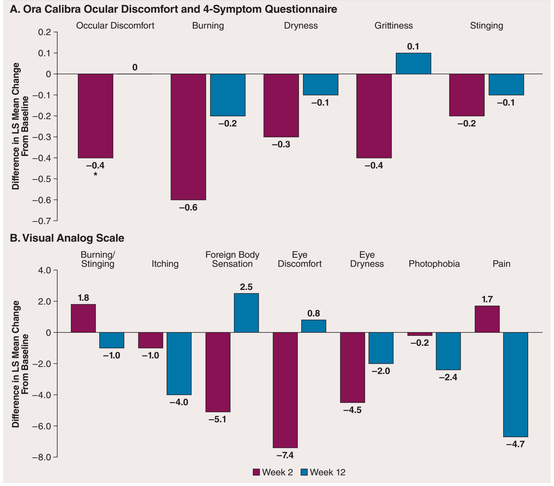


DED, dry eye disease; LS, least squares. Conjunctival redness was measured by the Ora Calibra Conjunctival Redness Scale®, ocular discomfort by the Ora Calibra Ocular Discomfort Scale®.

VAS

- PL9643 treatment showed non-significant improvement over placebo in change from baseline at week 2 for the VAS symptoms of itching (−1), foreign body sensation (−5.1), eye discomfort (−7.4), eye dryness (−4.5), and photophobia (−0.2) (**Figure 5B**)
  - Treatment effect of PL9643 was maintained throughout the study for symptoms of itching, eye dryness, and photophobia from week 2 to week 12
  - Other non-significant improvements over placebo at week 12 were observed for burning/stinging (−1.0), and pain (−2.4)

Figure 5. Ora Calibra Ocular Discomfort and 4-Symptom Questionnaire and Visual Analog Scale Treatment Difference vs Placebo (Moderate to Severe DED Population)



CAE, controlled adverse environment; DED, dry eye disease, LS, least squares. Note: Difference was change pre-CAE. *P≤0.05 vs placebo via analysis of covariance.

Safety and Tolerability (Safety Population)

- In the overall safety population (mild, moderate and severe dry eye) there were more AEs and more treatment-emergent AEs (TEAEs) in the placebo group than in the PL9643 group (AEs, 31 [38.8%] vs 19 [23.8%], respectively; TEAEs, 23 [28.8%] vs 16 [20.0%])
- There were no discontinuations owing to PL9643 and no deaths were reported for either group
  - 1 ocular TEAE of chalazion was reported in the PL9643 group and there were no reports of pain owing to instillation of PL9643 drops
- 3 (1.9%) subjects reported 3 serious TEAEs: 1 (1.3%) subject in the PL9643 group and 2 (2.5%) subjects in the placebo group.
  - The 2 serious TEAEs in the placebo group were classified as severe (chronic lymphocytic leukemia, deep vein thrombosis) and the serious TEAE in the single subject in the PL9643 group was reported as moderate (lung adenocarcinoma)
- No serious TEAEs were considered related to the study drug. No effects on visual acuity, slit-lamp biomicroscopy, intraocular pressure, or dilated fundoscopy were observed
- Responses to the drop comfort questionnaire were comparable for the PL9643 and placebo groups, and there were no reported AEs of pain on instillation.

Summary and Conclusions

- In subjects with moderate or severe DED (duration of dry eye ≥5 years, inferior corneal staining >1, and eye discomfort on the VAS ≥25), PL9643 treatment led to significant improvement in tear film breakup time at week 12 and other subjective and objective benefits at 2 weeks, which were maintained for 12 weeks vs placebo
- Significant improvement (P<0.05) over placebo was demonstrated in
  - Inferior and corneal sum fluorescein staining at week 12
  - Conjunctival temporal Lissamine green staining at week 2 and Lissamine green nasal staining at week 12,
  - Conjunctival sum Lissamine green staining at weeks 2 and 12.
  - Ocular discomfort (Ora Calibra Ocular Discomfort and 4-Symptom Questionnaire) at week 2
  - PL9643 treatment demonstrated numeric improvement only, in conjunctival redness and in various VAS symptoms at weeks 2 and 12
- PL9643 had a safety profile comparable to placebo
- Positive efficacy results across multiple signs and symptoms in subjects with moderate to severe DED, the low number of ocular AEs, and no tolerability issues, suggest that PL9643 could be a valuable novel therapeutic option for treating DED and support its continued development

Support Palatin Technologies, Inc.

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