Efficacy and Safety of the Melanocortin Agonist PL9643 in a Phase 2 Study of Subjects With Dry Eye Disease

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Disclosures

- **Kenneth Kenyon** was an independent contractor at Ora Inc throughout the duration of the study.
- **George Ousler** and **Michael Watson** were employees of Ora Inc throughout the duration of the study.
- **Gail Torkildsen** received financial support from Mitotech, Kowa, Aldeyra, Topivert, Brim, Palatin, Oyster Point, Allergan, Aerie, Aurinia, Regentree, Novaliq, Hanall, and Ora Inc. Patrick Vollmer has nothing to disclose.
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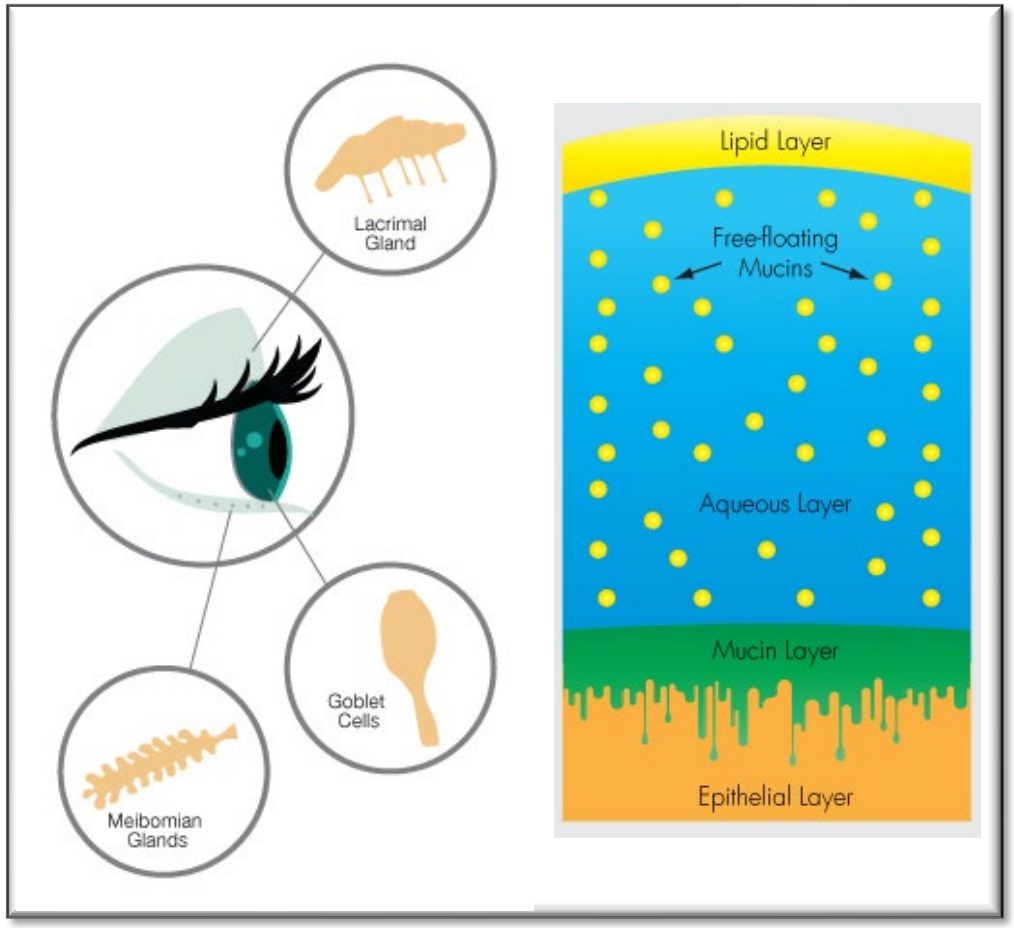
Background

- Dry eye disease
  - Multifactorial inflammatory and aqueous tear deficient disorder affecting the cornea and conjunctiva[1,2]
  - Characterized by ocular irritation and potential visual impairment[1,2]
- Existing dry eye therapies are often regarded as inadequate by many physicians and patients due to poor response, adverse effects (AEs), poor ocular tolerability, and prolonged interval preceding therapeutic activity[3,4]



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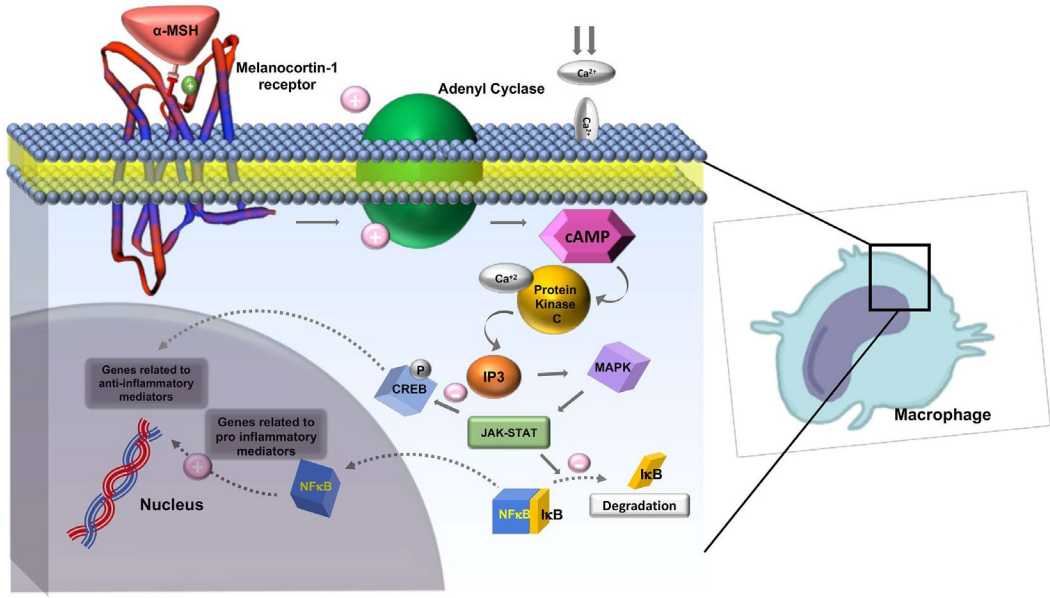
Background

- Melanocortins have a wide range of anti-inflammatory properties[1-3]
  - Inhibition of leukocyte activation
  - Protection of tissues from the inflammatory response
- Therefore, melanocortin agonists may represent a novel therapeutic avenue to treat inflammatory ocular diseases[4,5]
- PL9643, a melanocortin receptor pan-agonist (not active at MC2r), is currently being investigated for anti-inflammatory ocular indications, including dry eye disease



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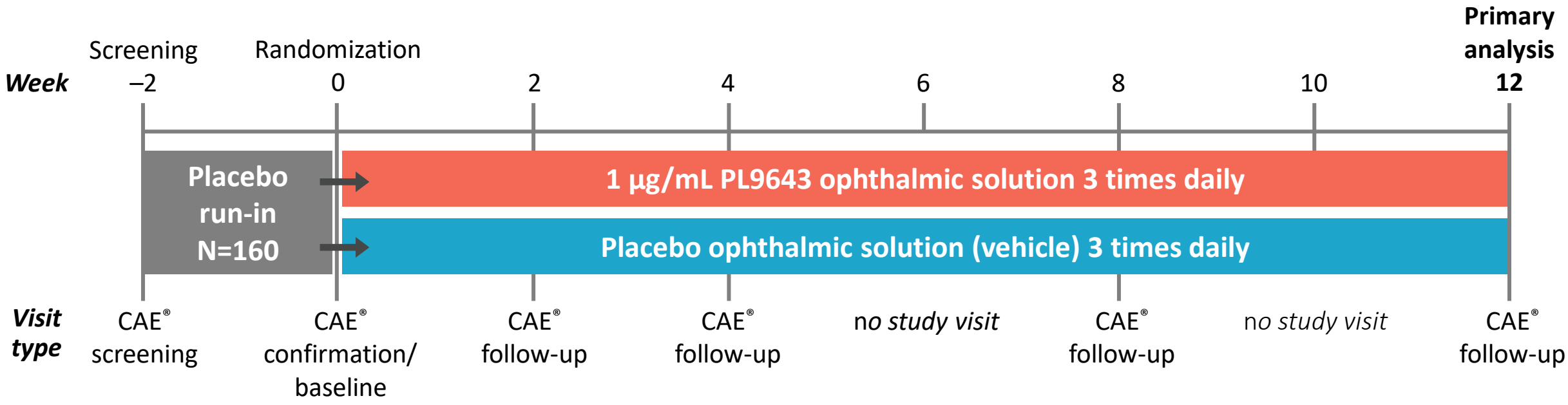
Objective

- This phase 2 study evaluated the efficacy and tolerability of PL9643 in adults with dry eye disease

Study Design

12-week Phase 2, multicenter, 1:1 randomized, double-masked, placebo-controlled study



Study Subjects

- Adults with mild, moderate, or severe dry eye disease

Co-primary endpoints (Week 12)

- Inferior corneal fluorescein staining (sign)
- Ocular discomfort (symptom)

Secondary endpoints (Week 2 and Week 12)

Signs

- Fluorescein staining
- Lissamine green staining
- Tear film break-up time

Symptoms

- Burning
- Dryness
- Eye discomfort
- Eye dryness
- Foreign body sensation
- Grittiness
- Itching
- Ocular discomfort
- Stinging

CAE®, controlled adverse environment.

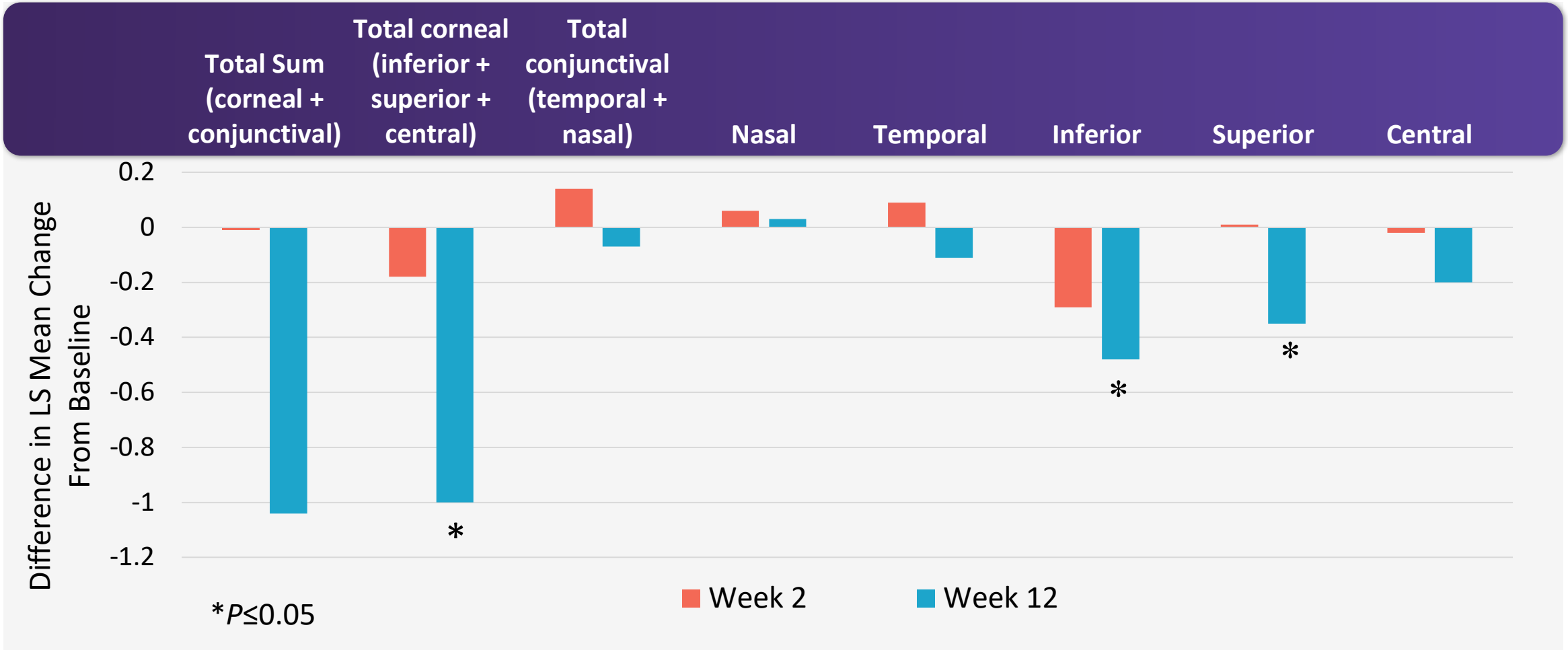
Results: Co-Primary and Secondary Endpoints

- Co-primary endpoints of inferior corneal fluorescein staining (sign) and ocular discomfort (symptom) after 12 weeks
  - Overall ITT population of mild, moderate, or severe dry eye disease (N=160): **no significant difference**
  - Subjects with moderate or severe disease (n=61): **improvements in both endpoints were observed (sign endpoint was significant)**
- Several signs and symptoms secondary endpoints were significant

Results: Baseline Demographics

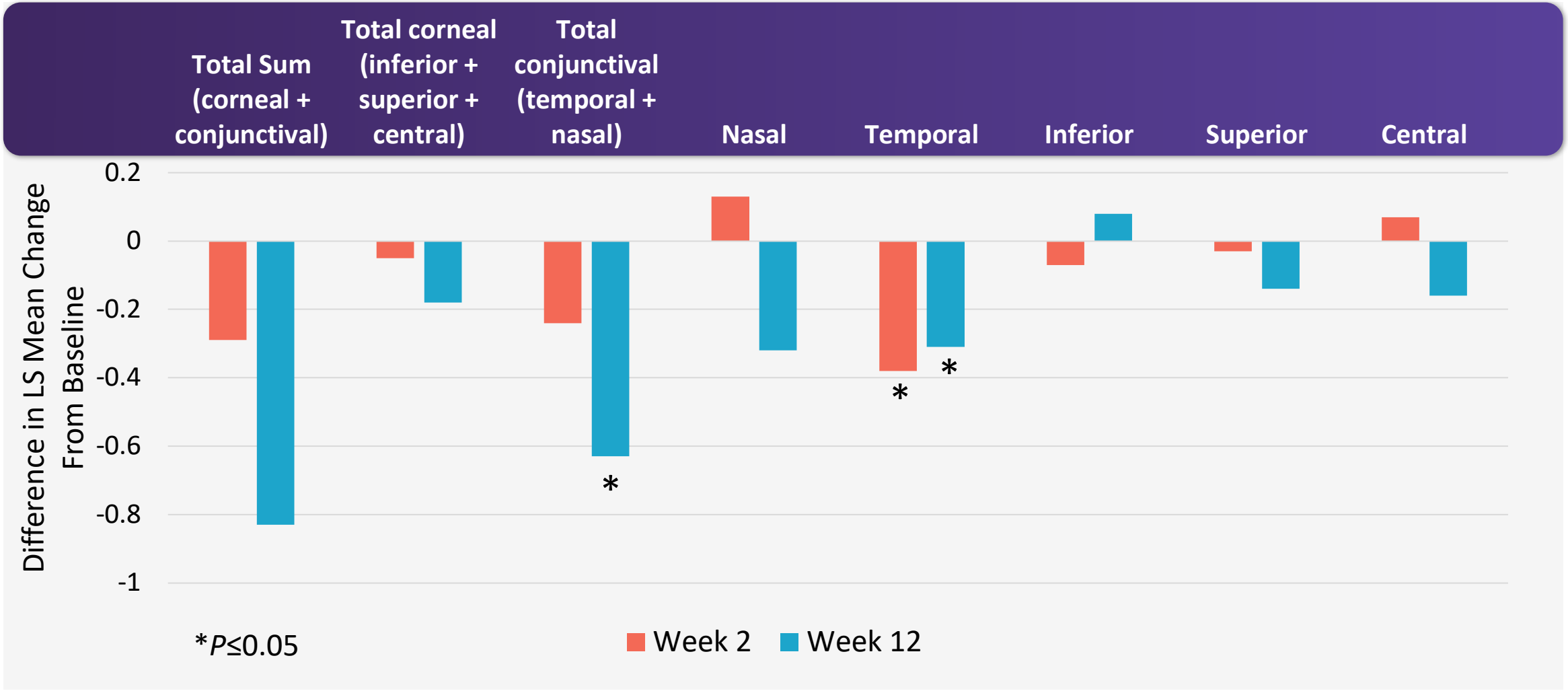
- Baseline demographics of the moderate or severe subset were balanced across the groups
  - Median age was 69 years (range, 51–84) for the placebo group and 69.5 (range, 51–80) for the PL9643 group
  - 71% and 70% of subjects, respectively, were female

Differences between PL9643 and placebo (least squares mean change from baseline) in fluorescein staining in the subset of subjects with moderate or severe disease



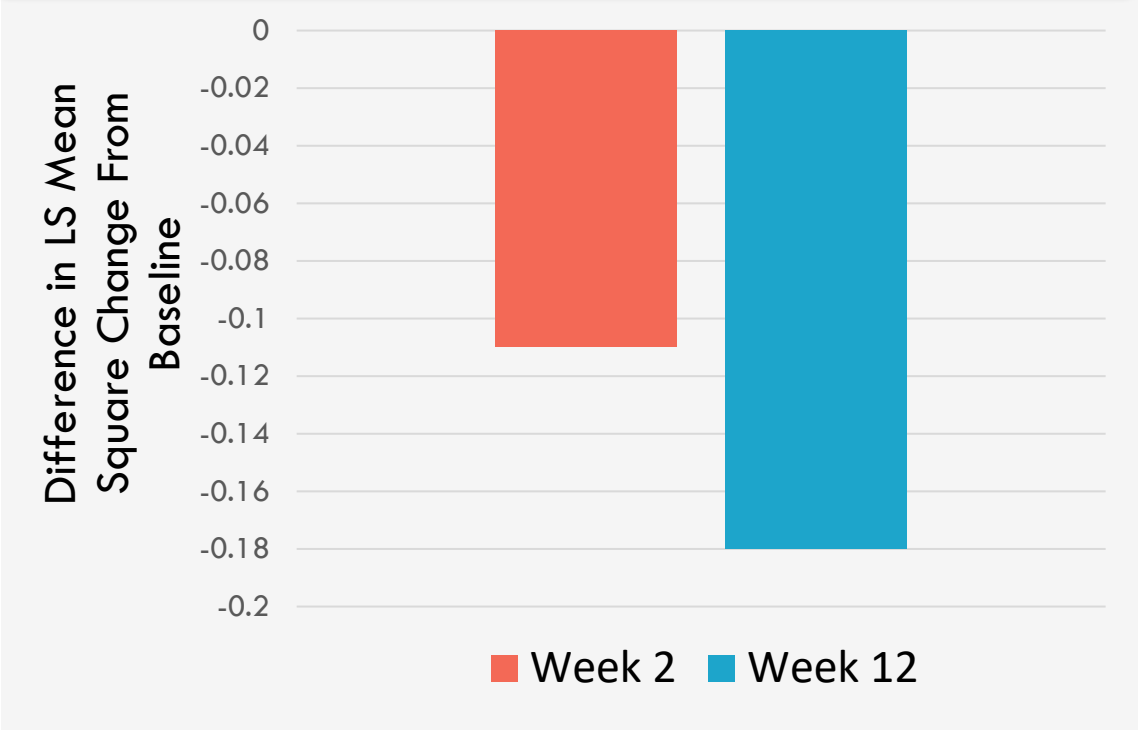
- For subjects in the moderate or severe subgroup, significant improvement was observed for the PL9643 group compared with the placebo group for the primary endpoint of inferior corneal fluorescein staining (LS mean difference [SEM], –0.5 [0.2], $P<0.05$)

Differences between PL9643 and placebo (least squares mean change from baseline) in Lissamine™ green staining in the subset of subjects with moderate or severe disease

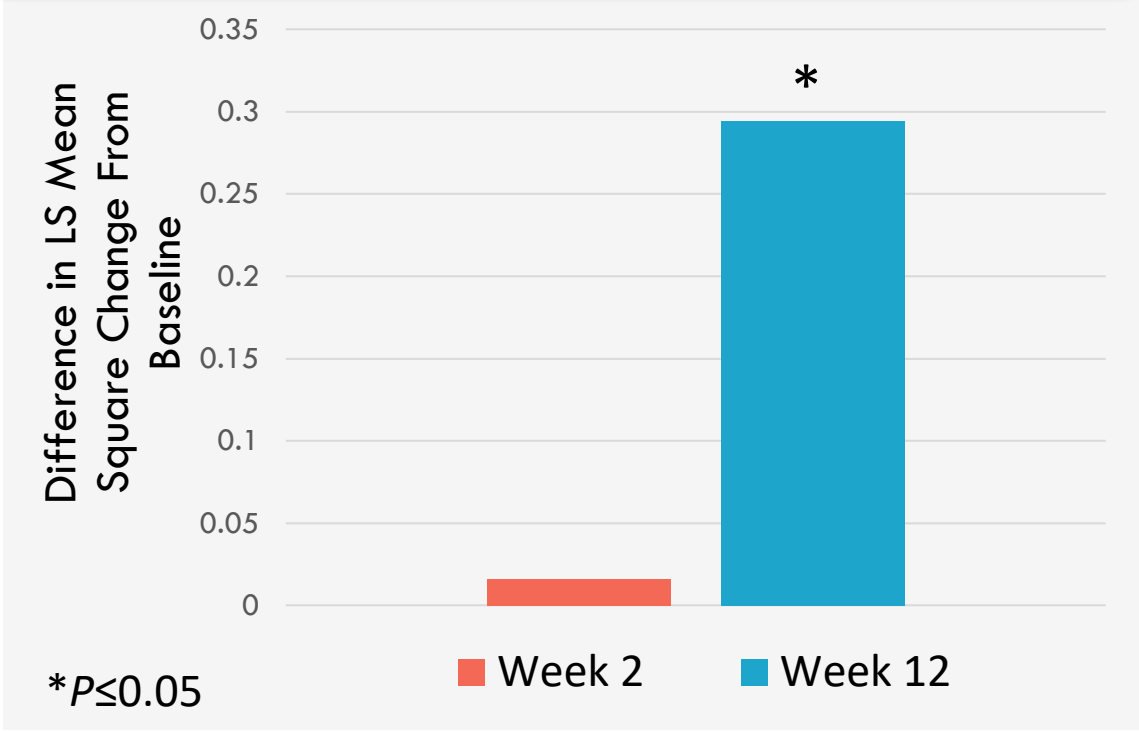


Differences between PL9643 and placebo (least squares mean change from baseline) in conjunctival redness and tear film break-up time in the subset of subjects with moderate or severe disease

Conjunctival Redness



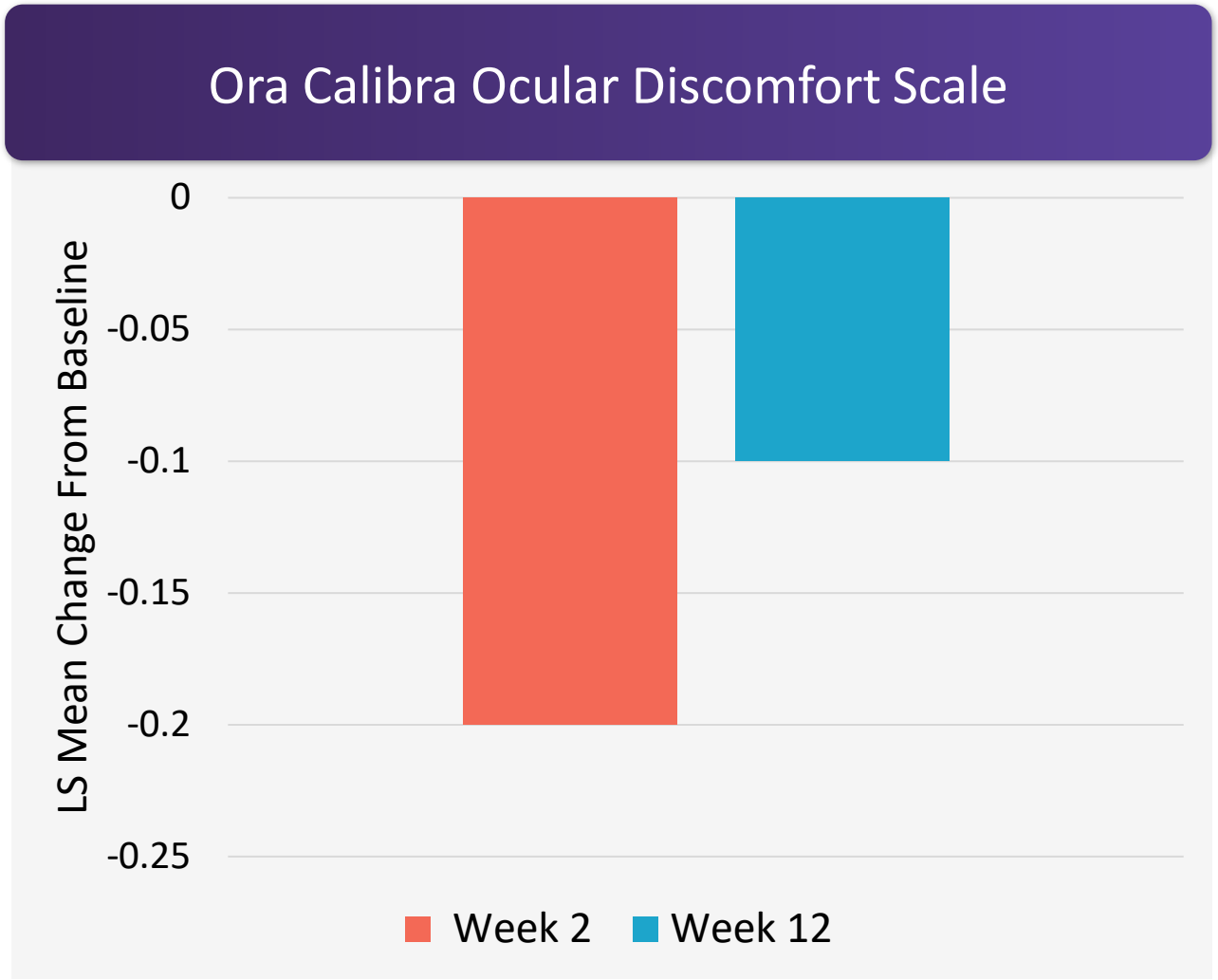
Tear Film Break-up Time



TFBUT, tear film break-up time.

- Signs of conjunctival redness showed numeric improvements (as demonstrated by negative change from baseline) and tear film break-up time showed significant improvement at 12 weeks

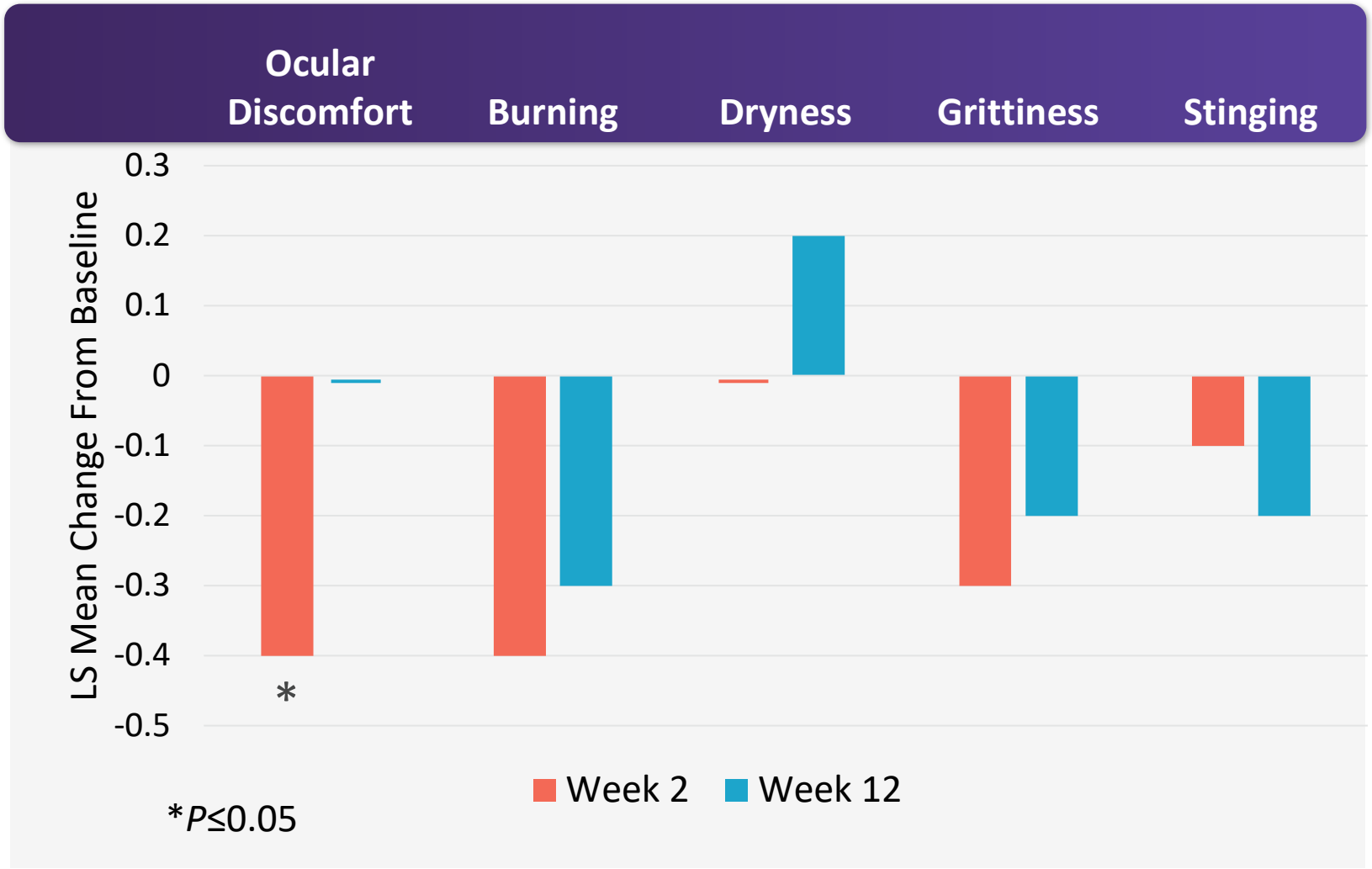
Co-Primary Endpoint (Single Question Scale): Differences between PL9643 and placebo (least squares mean change from baseline) in Ora Calibra® Ocular Discomfort Scale* scores in the subset of subjects with moderate or severe disease



- For ocular discomfort, PL9643 demonstrated numeric improvement over placebo as shown by negative change from baseline

*Measured on 0-4 scale.

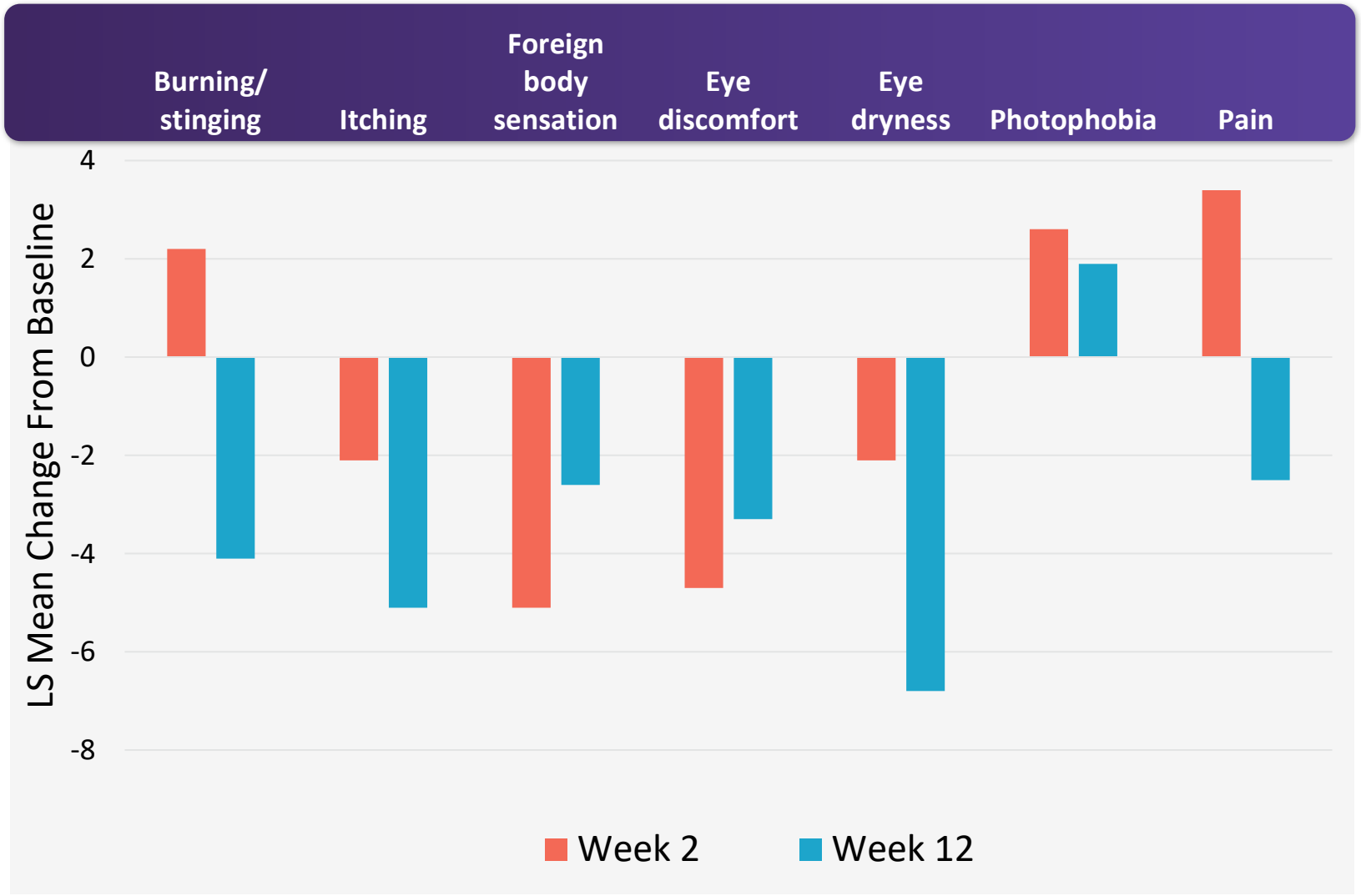
Secondary Endpoint (5-Question Scale): Differences between PL9643 and placebo (least squares mean change from baseline) in the Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire† scores in the subset of subjects with moderate or severe disease



- PL9643 demonstrated significant improvement in ocular discomfort over placebo at Week 2 (as shown by negative change from baseline)

†Measured on 0-5 continuous scale.

Differences between PL9643 and placebo (least squares mean change from baseline) in components of the visual analog scale* in the subset of subjects with moderate or severe disease



- After 2 or 12 weeks, PL9643 demonstrated improvement over placebo (as shown by negative change from baseline) in ocular symptoms

*VAS was measured on 0-100 continuous scale.

Table 1. AEs by severity and relation to treatment

Event	Mild	Moderate	Severe	Total
PL9643	**13**	**3**	**0**	**16**
Non-ocular	12	3	0	15
Not related	10	3	0	13
Possibly related	1	0	0	1
Unlikely related	1	0	0	1
Ocular	1	0	0	1
Not related	1	0	0	1
Placebo	**17**	**4**	**2**	**23**
Non-ocular	9	4	2	15
Not related	9	3	2	14
Possibly related	0	1	0	1
Ocular	8	0	0	8
Not related	4	0	0	4
Possibly related	1	0	0	1
Probably related	1	0	0	1
Definitely related	2	0	0	2
Total	**30**	**7**	**2**	**39**

Safety

- No treatment-related serious AEs or ocular AEs were observed, and no subjects receiving PL9643 reported pain upon instillation of drops
- Fewer AEs occurred among subjects receiving PL9643 compared with placebo

Conclusions

- In subjects with moderate or severe dry eye disease, PL9643 ophthalmic solution led to benefits in signs and symptoms by the first evaluation at 2 weeks, which were maintained for the 12-week study duration
- PL9643 was well tolerated, with no treatment-related ocular AEs and a safety profile comparable to placebo
- These positive results across multiple signs and symptoms support the continued development of PL9643 as a novel therapeutic option for treating dry eye disease