Title: Topical Interleukin-1 (IL-1) Receptor Inhibition Reduces Ocular Pain

INTRODUCTION

Dry Eye Disease (DED) affects the ocular surface and is characterized by symptoms of dryness, eye pain, ocular discomfort and irritation. In severe cases, patients with DED may suffer chronic ocular pain and dilation of vision that can significantly reduce their quality of life. DED is one of the leading causes of patient visits to eye care professionals in the United States. Approximately 18 million people in the United States have DED, including approximately seven million people who suffer from moderate to severe forms of dry eye disease (Market Scope). The signs and symptoms of DED are driven by different biological processes but IL-1 is a major mediator of all of these biological processes (Figure 1). Neurotrophic eye pain symptoms are commonly reported by subjects as burning or stinging, ocular grittiness, foreign body sensation, and photophobia (Rosenthal 2005; Marzotto 2005). Neurotrophic ocular pain or illness is likely mediated directly and indirectly through IL-1 (Figure 2). IL-1 induces hyperalgesia and astrogliosis (Simonen et al. 2014). Numerous animal model studies indicate that microglia produce the IL-1 that mediates the hyperalgesia (Makotka et al. 2014). It is likely that IL-1 in the peripheral nervous system or the cornea. Direct effects on neurons are implicated by the expression of IL-1R1 on neuronal cell surface (Rubio et al. 2004). IL-1β and the effects on neuronal signaling/cytokine can occur within 1 minute of IL-1 β expression (Fukunaga et al. 2003). IL-1 receptor stimulation of cultured corneal fibroblasts, causing interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-α), and other cytokines (Ratnikov et al. 2004) (see Figure 3). Blockade of IL-1β in DED might reduce ocular pain and discomfort associated with DED.

METHODS AND RESULTS

Measurement of EBI-005 Effects on Pain in DED

- **EBI-005 is an engineered human monoclonal antibody to IL-1R1 agonists.**
- **EBI-005 was administered to subjects with moderate to severe DED in a parallel phase II study.**
- **Subjects were randomized to topical vehicle control or EBI-005 (5 or 20 mg/mL), treated 3x/day for 12 weeks.**
- **Treatment was initiated at baseline and continued for 12 weeks.**
- **Subjects were evaluated for response using the DED Symptom Index (OSDI) Pain domain.**

Early Assessment of IL-1 Blockade in Dry Eye Disease

- **Topical Interleukin-1 (IL-1) Receptor Inhibition Reduces Ocular Pain and Tremor EBI-005**
- **Subjects were randomized to topical vehicle control or EBI-005 (5 or 20 mg/mL), treated 3x/day for 12 weeks.**
- **Subjects were evaluated for response using the DED Symptom Index (OSDI) Pain domain.**

IL-1 Blockade Reduces Effect on Patient Sense of Pain or Soreness of the Eyes

- **EBI-005 reduces painful or sore eyes in DED.**
- **A retrospective analysis of Amparo et al. 2013 and the EBI-005-2 study showed a decrease in painful or sore eyes.**
- **There was an overall 46% decrease in painful or sore eyes measured at 6 weeks post initiation of therapy.**

EBI-005 Reduces Painful or Sore Eyes in DED

- **Treatment of subjects with moderate to severe DED with EBI-005 was associated with a decrease in painful or sore eyes, as measured by the DED Symptom Index (OSDI) Pain domain.**
- **There was an overall 46% decrease in painful or sore eyes, as measured by the DED Symptom Index (OSDI) Pain domain.**
- **The effect was seen as early as two weeks.**
- **The effect was greater over time and the EBI-005-2 study showed a decrease in painful or sore eyes.**

CONCLUSIONS

- **IL-1 signaling directly or IL-1 receptors on neurons and indirectly drives hyperalgesia based on preclinical models.**
- **EBI-005 blocks IL-signaling resulting in a reduction in hyperalgesia.**
- **EBI-005 does not affect corneal sensation.**
- **Blockade of IL-1 in two separate clinical studies reduced subjects’ frequency of painful or sore eyes and was clinically relevant.**
- **Painful or sore eyes was the most commonly observed question of the OSDI of DED subjects in our study, indicating that patients find it relevant to their disease.**
- **These data also indicate that painful or sore eyes is a viable symptom to measure in clinical studies to distinguish drug effects from placebo.**
- **Painful or sore eyes assessment is the primary symptom endpoint of the on-going EBI-005 Phase 3 study.**

REFERENCES