**EBI-005: An IL-1 Receptor Inhibitor Designed for the Treatment of Dry Eye Syndrome**

**Background**

Dry eye syndrome (DES) is an ocular surface inflammatory condition induced by desiccating stress and mediated by IL-1 stimulation of the Th17 pathway. **DES affects approximately 10% of individuals between 30 to 60 years of age, and up to 15% of those over 65. Despite its prevalence and impact on quality of life, DES is under-diagnosed, under-treated and has few safe and effective treatment options. IL-1α and IL-1β are key mediators of DES inflammation. 1) Both agonists are upregulated in the human syndrome and mouse models of the syndrome. 2) IL-1 receptor KO mice have reduced signs of disease (corneal fluorescence staining or CF) and IL-1β and IL-1β-33 influence at most one or two of these biological pathways. These data indicate that IL-1 inhibition may uniquely block both signs (CFs induced by ocular surface inflammation) and symptoms (pain exacerbated by hyperalgesia) of DES. In fact, in a Phase 2 clinical study, anakinra topically applied to eye 3x/day substantially reduced signs and symptoms of DES. However, anakinra is not optimized for topical ocular administration.

**Figure 1. IL-1 is Central in Modulating Signs and Symptoms of DES**

**Figure 2. Initiation, Maintenance, and Pain are Driven by IL-1**

**Figure 3. Design of EBI-005**

EBI-005 was 9°C more thermally stable than anakinra or IL-1α, with a Tm of ~65°C.

**Figure 4. Biological Activity of EBI-005**

EBI-005 blocks IL-1β-induced IL-6 Production in MG63 Cells

**Figure 5. In Vivo Potency**

Novel Mouse Model

- **C57BL/6 female mice**
- **30% relative humidity and an air flow rate of ~21 L/min/cage En-**

**Figure 6. EBI-005 Penetrates Key Ocular Surface Tissues with Minimal Systemic Exposure**

**Figure 7. Manufacturing and Formulation**

EBI-005 was 5°C more thermally stable than anakinra or IL-1, with a Tm of ~65°C.

**Summary**

- DES is an ocular surface inflammatory condition induced by desiccating stress and mediated by IL-1 stimulation of the Th17 pathway.
- IL-1 antagonism attenuates both signs and symptoms of DES in a Phase 2 study.
- EBI-005 is an IL-1 receptor blocker optimized for topical ocular delivery.
- EBI-005 binds IL-1R1 -30-fold more potently than anakinra which may optimize frequency of administration as a result of long receptor occupancy time.
- EBI-005 was more active than topical cyclosporin (the active ingredient of Restasis™) at reducing disease signs in a mouse model of DES.
- The high thermal stability of EBI-005 creates the potential for an ambient temperature-stable product.
- EBI-005 distributed well to ocular surface tissues and had low systemic exposure to reduce the risk of immune suppression related adverse events associated with systemic IL-1 antagonism.
- EBI-005 is Eleven Biotherapeutics’ lead program and is targeted to enter the clinic in 2012.

**References**

1. International Dry Eye Workshop (DEWS) Report.
2. Evans RJ, Bray J, et al. Mapping receptor binding sites in interleukin (IL) 1 receptor antagonist and IL-1β.
6. Presenting and corresponding author: Eric S. Furfine, Eleven Biotherapeutics, eric@elevenbio.com

---

**Program 2012 ARVO Annual Meeting, May 20-24, 2012, Orlando, Florida 32818, Dry Eye Disease II**

**Poster #A357**

**ELEVEN BIOThERAPEUTICS**