Intravitreal IL-6 inducible retinal leukostasis by upregulating IL-6 signaling is implicated in several autoimmune inflammation and angiogenesis. Excessive IL-6 may lead to ineffective therapies to be administered either as intravitreal retention, and rapid systemic clearance.

**Purpose:**

**ABSTRACT**

Intravitreal IL-6 antagonism has been achieved using Eleven’s Amp-Rx™ platform to potently block Site 2 of the ligand-receptor complex.

**Purpose:**

- **EBOI-031 Engineering and Preclinical Data**
  - EBOI-031 is a proprietary, anti-IL-6 antibody that has been engineered using Eleven’s Amp-Rx™ platform to potently block Site 2 of the ligand-receptor complex.
  - **EBOI-031 Generation and Characterization**
    - Immune mice with recombinant human IL-6 and selected clones with potent blockage of IL-6 and the IL-6/IL-6Rα complex.
  - Humanized by CDR grafting and affinity matured using AMP-Rx™ platform to monovalent K_{eq} = 500 Fm
  - Reformed as IgG2 and introduced Fc mutation H310A to reduce FcN binding and increase systemic clearance.
  - EBOI-031 is well expressed, thermally stable (Tm = 76°C for its Fab fragment) and can be concentrated to >100 mg/mL with little measurable aggregation.
  - In cellular assays >900 fold more potently than the commercial IL-6 inhibitor α-IL6R.
  - EBI-031 Potently Blocks cis- and trans- IL-6 Signaling
  - Site 2 epitope is accessible in both free IL-6 and the IL-6/IL-6Rα complex, providing efficient blockades of cis- and trans-signaling.
  - Anti-IL6 receptor antibodies such as tocilizumab are cleared by Fc-mediated recycling such that systemic IL-6 levels after IVT injection were lower than the wild-type antibody or tocilizumab.

**EBI-031 Has Extended Vitreal Retention Compared to Existing Therapies**

- Pharmacokinetic studies performed in New Zealand White rabbits
  - Animals injected IVT bilaterally with 50 μL of test article formulated at 13.8 mg/mL.
  - Ocular tissues harvested and drug levels measured by ELISA
  - EBOI-031 is detected high levels in the retina, aqueous, and choroid following IVT administration.
  - Unable to assess PK beyond 1 week due to development of anti-drug antibodies in all tissues

**EBI-031 Has Rapid Systemic Clearance and Low Systemic Accumulation**

- **H10A point mutation in Fc domain of EBOI-031 eliminates binding to human and rabbit FcγRIIa.
  - Following iv administration in rabbits, EBOI-031 is cleared from systemic circulation ~2x faster than EBI-030, a variant with wild-type Fc.
  - EBOI-031 accumulates at lower systemic levels compared to EBI-030, aflibercept, or tocilizumab after IVT administration

**EBI-031 Efficiently Penetrates Ocular Tissues**

- **Modeling Predicts Extended Duration of EBI-031 Blockade**
  - Due to its high potency and long vitreal retention, EBI-031 is predicted to inhibit 95% of target signaling for >100 days following a single 50 mg/mL IVT injection in humans compared to 50 days for tocilizumab or 60 days for aflibercept.

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