EYS606 for the Treatment of Non-Infectious Uveitis (NIU)
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BACKGROUND and PURPOSE:
Tumor necrosis factor-alpha (TNF-α) plays a role in the development of intraocular inflammation and is an effective target for the treatment of NIU. Eyevensys is developing non-viral gene therapy utilizing a recombinant electrotreatment system to deliver plasmids encoding therapeutic proteins to the ciliary muscle as an innovative, sustained ocular drug delivery platform for the treatment of ocular diseases. EYS606 encodes a potent TNF-α inhibitor, Protein 6, a recombinant fusion protein linking the TNF-α p55 receptor 1 to the human IgG1 Fc domain with a higher affinity to TNF-α than commercially available TNF-α inhibitors. (Figure 1). In rat models of endotoxin induced uveitis (EIU) EYS606 was demonstrated to have efficacy similar to corticosteroids, while in rat models of experimental autoimmune uveitis (EAU), EYS606 reduced the severity of the ocular inflammation and protected against immune mediated retinal damage. (Figure 2) Preclinical studies assessing the safety, tolerability and biodistribution of EYS606 revealed no safety concerns related to the administration of the plasmid, the expressed protein or the electrotreatment procedure. In a pilot clinical study Murphy et al, administered a p55 TNF receptor fusion protein (TNF-Ig) similar to Protein 6 to patients with refractory non-infectious posterior uveitis who showed improvements in vision, vitreous haze, macular edema and a reduction in concomitant immunosuppression within one month after a single intravenous treatment. On basis of these promising preclinical and clinical findings and need for a more convenient, safer and effective non-corticosteroid uveitis therapy, a clinical development program to evaluate EYS606 as the first minimally invasive, ocular gene therapy approach for NIU was initiated. Herein, we present preliminary results from an ongoing first-in-human study investigating the safety and tolerability of EYS606 in patients with NIU.

METHODS:
EYS606-CT1 is a 24-week phase III, open-label, multicenter, dose escalation study assessing the safety and tolerability pEYS606 when administered by electrotreatment (ET) in non-cicatrising patients with non-infectious posterior, intermediate or panuveitis (NCT03308045; EUDRACT Number: 2015-001391-22). The primary objective of the study is the assessment of the safety and tolerability of EYS606 after 4 weeks. Secondary objectives are additional indicators of long term safety and indicators of clinical activity. Exploratory objectives are to characterize the systemic biodistribution of EYS606 and to express Protein 6, and to characterize indicators of immune responses and biomarkers of clinical efficacy. The study is conducted in two parts. In Part 1, the dose escalation phase, end stage NIU patients are assigned to receive escalating doses of EYS606 doses in one of three cohorts. In Part 2, patients with less severe, active NIU will receive the maximally tolerated dose of EYS606 defined in Part 1. An independent data safety and monitoring board (DSMB) is consulted prior to providing recommendations regarding dose escalation. Figure 3 provides a schematic of the EYS606-CT1 study design.

RESULTS:
The study is currently ongoing with sites enrolling in France and the United Kingdom. To date, the 1st (n=3) and 2nd (n=3) cohorts evaluating the lowest and the intermediate dose level of EYS606 have been randomized and participants have completed the dose escalation to the highest dose has been received and 3 patients have been screened for eligibility in Part 2. Table 1 presents the demographic information for the 6 patients enrolled and treated with EYS606 in cohorts 1 and 2.

CONCLUSIONS:
The Eyevensys technology is a minimally invasive, non-viral gene therapy ocular drug delivery platform that turns the eye into a biofactory for the sustained delivery of therapeutic proteins. EYS606, the lead clinical candidate for Eyevensys, induces the intracocular expression of a potent anti-TNF-α protein for the treatment of NIU. As demonstrated in preclinical studies, the preliminary data from the ongoing EYS606-CT1 study suggest that the introduction of plasmids encoding therapeutic proteins into the eye using the Eyevensys propriety electrotreatment system is well tolerated and raises no significant safety concerns, with the early safety profile for the administration of EYS606 mirroring other routinely performed ophthalmic procedures. While the visual acuity gain observed in one patient maintains the promise that EYS606 will offer improved clinical outcomes while reducing the safety concerns and burdens associated with current standard of care uveitis treatments, demonstrating the potential efficacy of EYS606 as a novel uveitis treatment is only expected in Part 2 of the study in which patients with less advanced active uveitis will be treated with the highest tolerated EYS606 dose derived from Part 1 of the study.

Table 1. Cohorts 1 and 2 Patient Demographics

Table 2. Summary of Adverse Events Recorded in Cohort 1 and 2

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Disclosure: Ronald Buggage is an employee of Eyevensys. Professor Francine Behar-Cohen is the founder and board member of Eyevensys.