T113

EYS606 for the Treatment of Non-Infectious Uveitis (NIU)

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BACKGROUND and PURPOSE:

Tumor necrosis factor-alpha (TNFα) 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 therapies utilizing a proprietary electrotransfection 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 TNFα inhibitor, Protein 6, a recombinant fusion protein linking the TNFα p55 receptor 1 to the human IgG1 Fc domain with a higher affinity to TNFα than commercially available anti-TNF 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 electrotransfection procedure. In a pilot clinical study Murphy et. al. administered a p55 TNFα receptor fusion protein (TNFr-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.

Figure 1. EYS606 Induces Intraocular Expression of Protein 6, a Potent TNFα inhibitor

pEYS606 is a DNA plasmid encoding for a recombinant fusion protein consisting of the extracellular domain of the human TNF-α p55 receptor linked to the human IgG1 Fc domain (hTNFR-Is/hIgG1)

DRUG	KD in M
Protein 6	$1.34\ 10^{-11}$
Remicade (Infliximab)	$5.0\ 10^{-10}$
Enbrel (Etanercept)	$1.0\ 10^{-10}$
Humira (Adalimumab)	$5.5\ 10^{-10}$
Lenercept	$1.0\ 10^{-10}$
Onercept	$5.0\ 10^{-7}$

The Protein 6 expressed by pEYS606 has a higher affinity for TNF than other anti-TNF products

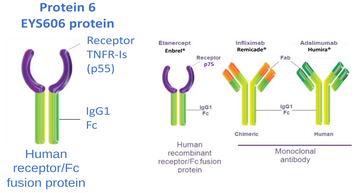
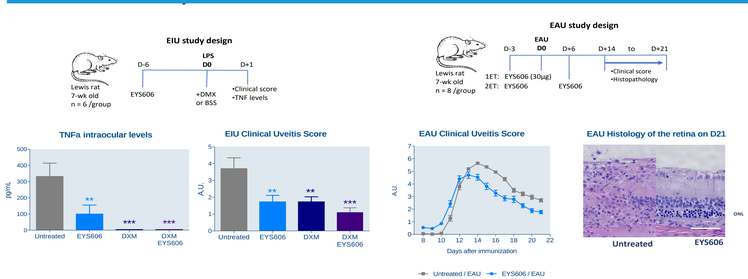


Figure 2. Efficacy of EYS606 in Rat EIU and EAU Models



In EIU model EYS606 was as effective as Dexamethasone (DXM) at dose equivalent to 0.5 mg IVT in patients and the combination of EYS606 and DXM seemed to have a synergistic effect.
In EAU model EYS606 reduced the disease severity and protected the retina from immune mediated damage.

METHODS:

EYS606-CT1 is a 24-week phase I/II, open-label, multicenter, dose escalation study assessing the safety and tolerability pEYS606 when administered by electrotransfer (ET) in the ciliary muscle of 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 pEYS606 and the expressed Protein 6, and to characterize indicators of immunogenicity 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 treatment with escalating EYS606 doses in one of three cohorts. In Part 2, patients with less severe, active NIU will receive the maximally tolerated EYS606 dose defined in Part 1. An independent data safety and management board (DSMB) is charged with reviewing the safety data from providing recommendations regarding dose escalation. **Figure 3** provides a schematic of the EYS606-CT1 study design.

Figure 3. EYS606-CT1 Study Design

Part 1: Dose Escalation Phase evaluating 3 EYS606 Doses in 3 Cohorts of adult patients with advanced/end stage posterior segment uveitis

Cohort 1 (n=3) lower dose 45µg EYS606/30 µL
Cohort 2: (n=3) intermediate dose 90µg EYS606 /60 µL
Cohort 3: (n=3) higher dose 135µg EYS606/90 µL

Key Inclusion Criteria
- BCVA ≤ 0.1 or 20/200 Snellen in the treated eye
- Macular atrophy or scar and/or degenerative macular edema and/or optic atrophy

Part 2: (n=6) Extension Phase evaluating maximum tolerated dose from Part 1 in adult patients with active posterior segment uveitis

Key Inclusion Criteria
- BCVA ≤ 0.32 or 20/63 Snellen in the treated eye
- Evidence of active uveitis as evidenced by at least one or more of the following:
  - Active inflammatory chorioretinal lesions or retinal vasculitis
  - Vitreous haze grade ≥ 2+ (SUN classification)
  - Anterior chamber cell grade ≥ 2+ (SUN classification)
  - Macular edema defined as central retinal thickness (CRT) > 300 µm on OCT
  - Need for treatment with oral prednisone ≥ 15 mg to control active uveitis

Screening Visit 0 | Baseline Treatment Visit 1 | Day 2/3 Visit 2 | Week 1 Visit 3 | Week 2 Visit 4* | Week 4 Visit 5 | Week 8 Visit 6 | Week 12 Visit 7* | Week 18 Visit 8 | End of Study Week 24 Visit 9*

24 week follow-up after EYS606 Electrotransfection

Safety Assessments
Adverse events.
Concomitant meds
Physical exam
Electrocardiogram
Routine labs
Visual acuity
Eye Exam
Electroretinogram

Efficacy Assessments
Visual acuity
Eye exam
Fundus photos
Ocular coherence tomography
Fluorescein Angiography

Exploratory Assessments
Plasmid shedding (Plasma, Urine, Saliva)
Protein 6 (aqueous* and serum)
Anti-drug and neutralizing antibodies (serum)

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 EYS606 doses have been completed. DSMB endorsement to escalate to the highest dose has been received and 3 patients have been screened for cohort 3. **Table 1** presents the demographic information for the 6 patients enrolled and treated with EYS606 in cohorts 1 and 2.

Table 1. Cohorts 1 and 2 Patient Demographics

Cohort ID	Gender	Study Eye	Baseline Visual Acuity ETDRS (Snellen)	Anatomic Subtype Uveitis Diagnosis	Screening & Treatment Dates	Last Completed Study Visit
1 02-101	42F	RIGHT	0 (~20/1000)	Panuveitis Idiopathic	04 APR 2017 10 APR 2017	V9 (End of study)
1 02-102	74F	RIGHT	~22 (20/400)	Posterior Uveitis Birdshot Choroidopathy	14 NOV 2017 04 DEC 2017	V9 (End of study)
1 03-101	69F	LEFT	28 (~20/320)	Posterior Uveitis Birdshot Choroidopathy	05 JAN 2018 08 JAN 2018	V9 (End of study)
2 03-102	55F	LEFT	Light Perception	Posterior Uveitis Birdshot Choroidopathy	26 FEB 2018 12 MAR 2018	V9 (End of study)
2 06-101	50F	RIGHT	29 (~20/320)	Panuveitis Multifocal choroiditis and panuveitis	06 JUN 2018 27 JUN 2018	V6 (Week 8)
2 02-103	67M	LEFT	0 (~20/1000)	Panuveitis Behçet Disease	26 JUN 2018 06 JUL 2018	V6 (Week 8)

RESULTS:

Table 2 shows a listing of the 24 adverse events (AE) that have been recorded in the EYS606-CT1 study to date. The majority of AE were mild or moderate in severity and were reported from cohort 1 suggesting no correlation with the pEYS606 dose. 13/24 AE were ocular in nature and 11/24 were related to the installation of the electrotransfection system ocular device. Ocular AE in order of decreasing frequency included 4-keratitis/epithelial defects, 3-conjunctival hemorrhage, 2-eye pain, 2-foreign body sensation, 1-conjunctival tears and 1-vitreous floaters. Only one serious adverse event was reported that was unrelated to the study drug or medical device. Although efficacy was not the objective of Part 1 of the study, one patient (03-101) noted within 2 weeks of the EYS606 administration improved vision that was maintained at the week 24 end of study visit with a ≥10 ETDRS letter gain recorded relative to the screening/baseline visits.

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

Cohort/Study ID	Event Term	Severity	SAE	Onset ≤4 weeks after treatment	Relationship with Study Drug	Relationship with Medical Device
Cohort 1 02-101	Eye pain	mild	no	yes	unrelated	related
	Foreign body sensation	moderate	no	yes	unrelated	related
	Keratitis	mild	no	yes	unrelated	related
	Headache	moderate	no	yes	unrelated	unrelated
	Eye pain	mild	no	yes	unrelated	related
	Headache	mild	no	yes	unrelated	unrelated
	Joint swelling	moderate	no	no	unrelated	unrelated
	Back pain	moderate	no	no	unrelated	unrelated
	arthralgia	moderate	no	no	unrelated	unrelated
Cohort 1 02-102	Conjunctival hemorrhage	mild	no	yes	unrelated	related
	Vitreous floaters	mild	no	yes	unrelated	unrelated
	Headache	mild	no	no	unrelated	unrelated
Cohort 1 03-101	Keratitis	moderate	no	yes	unrelated	related
	Dry mouth	mild	no	no	unrelated	unrelated
	Limb discomfort	mild	no	no	unrelated	unrelated
Cohort 2 03-102	Corneal epithelium defect	severe	no	yes	unrelated	related
	Rash	mild	no	no	unrelated	unrelated
	Onchyomadesis	mild	no	no	unrelated	unrelated
Cohort 2 06-101	Conjunctival laceration	moderate	no	yes	unrelated	related
	Corneal epithelium defect	moderate	no	yes	unrelated	related
	Conjunctival hemorrhage	moderate	no	yes	unrelated	related
Cohort 2 02-103	Cellulitis	severe	yes	yes	unrelated	unrelated
	Conjunctival hemorrhage	moderate	no	yes	unrelated	related
	Foreign body sensation	moderate	no	yes	unrelated	related

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 intraocular expression of a potent anti-TNFα protein for the treatment of NIU. As was demonstrated in preclinical studies, the preliminary safety data from the ongoing ESY606-CT1 study suggest that the introduction of plasmids encoding therapeutic proteins into the eye using the Eyevensys propriety electrotransfection 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 systemic standard of care uveitis treatments, demonstration of 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.

EYS606-CT1 Investigators: (France) 02-Cochin Hopital, Lead (LI) and Principal Investigator (PI): Pr. Antoine Brézin; 03-CHU Grenoble, PI: Pr. Christope Chiquet; 04-CHU Limoges, PI: Pr. Pierre-Yves Robert; 05-CHU Lyon, PI: Pr. Laurent Kodjikian; (United Kingdom) LI: Mr. Andrew Dick; 06-Bristol Eye Hospital , PI: Mr. Mo Majid; 07-Moorfields Eye Hospital, PI: Mr. Carlos Pavesio

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

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