NONCLINICAL EVALUATION OF NCX 4251, A NOVEL STEROID THERAPY FOR BLEPHARITIS, TARGETED DIRECTLY TO THE EYELID MARGIN TO IMPROVE EFFICACY AND REDUCE THE POTENTIAL FOR IOP ELEVATIONS

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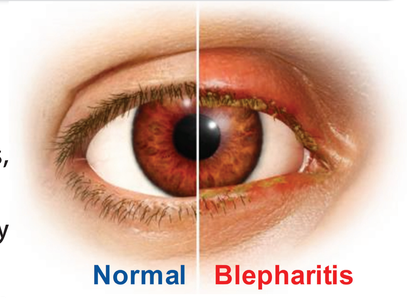
PURPOSE

Blepharitis: An Unmet Medical Need

- Just like dry eye 15 years ago, **blepharitis is poorly understood**[1]
- No U.S. FDA-approved product to **specifically treat blepharitis**
- Annual U.S. revenues of standard-of-care treatments (topical steroids, antibiotics and their combinations) total more than **$500 million**[2]
- Blepharitis encountered by **37% and 47% of all patients** seen by ophthalmologists and optometrists in U.S.[1]
- The incidence of blepharitis is **similar or higher than dry eye** in evaluation of patients with symptoms (24% blepharitis, 21% dry eye)[3]
- Ophthalmic practitioners consider **anti-inflammatory activity** the most important product attribute to selecting a blepharitis treatment[4]



METHODS

NCX 4251 - Ophthalmic Suspension of Fluticasone Propionate Nanocrystals

- Targeted topical treatment of the eyelid margin for patients with acute exacerbations of blepharitis
- Selected fluticasone, which is broadly used outside of ophthalmology, and is a ten-fold more potent molecule on the glucocorticoid receptor than dexamethasone
- Applied via an eyelid applicator at the eyelid margin directly to the site of inflammation to potentially decrease steroid induced ocular adverse events often seen with steroid eye drops
- U.S. IND submitted in Q4 2018 following a positive pre-IND meeting with U.S. FDA. (U.S. patent coverage to 2033)
- Planned U.S. multi-center, Phase 2 study to evaluate safety and tolerability of NCX 4251 versus placebo[5]

Example of prototype applicator in use (non-diseased eye)

Fluticasone Propionate Molecule - Key Properties

- Fluticasone propionate (FP) binding affinity for glucocorticoid receptor (GCR) is 500 pMolar (~18-fold higher vs. dexamethasone and 20-fold higher vs. triamcinolone)
- The rate of association with GCR is faster and the rate of dissociation is slower than other steroids
- FP is 1000-fold more lipophilic vs. triamcinolone and binds in tissue rapidly and strongly
- The resulting half-life of the FP-GCR active steroid-complex is > 10 hours
- FP interferes with transcription factors that activate inflammation and vaso-relaxation

7-Day Repeated Dose Toxicity Study of NCX 4251 Ophthalmic Suspension in Beagle Dogs

Study Design – Material and Methods

- Route: Dosing by eyelid applicator directly to the upper and lower eyelids of both eyes
- Frequency: Twice daily (BID, minimum of 6 hours between doses) for 7 consecutive days
- Test system: Beagle dogs, approximately 5 months and weighing 6.6 – 9.1 kg for males and female on Day 1 (start of the study)
- Non-GLP study

Group	Dose Volume (µL/eye/dose)	Frequency	Total daily volume (µL/day)	Dose (µg/day)	Dose (µg/eye/day)	Number of animals	
						Male	Female
Vehicle	16	BID	64	0	0	1	1
0.005%	16	BID	64	3.2	1.6	1	1
0.03%	16	BID	64	19.2	9.6	1	1
0.1%	16	BID	64	64	32	1	1

14-Day Repeated Dose Toxicity Study of NCX 4251 Ophthalmic Suspension in Beagle Dogs

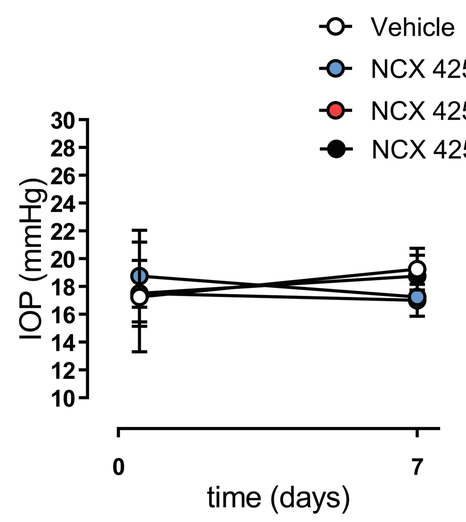
Study Design – Material and Methods

- Route: Dosing by eyelid applicator directly to the upper and lower eyelids of both eyes
- Frequency: Once daily (QD) or twice daily (BID, minimum of 6 hours between doses) for 14 consecutive days
- Test system: Beagle dogs, approximately 5-6 months at start of dosing; 5.7 – 8.8 kg for males and 5.8 – 7.4 kg for female on Day 1 (start of the study)
- GLP study

Group	Dose Volume (µL/eye/dose)	Frequency	Total daily volume (µL/day)	Dose (µg/day)	Dose (µg/eye/day)	Number of animals	
						Male	Female
Vehicle	16	BID	64	0	0	5	5
0.005%	16	QD	32	1.6	0.8	5	5
0.03%	16	QD	32	9.6	4.8	5	5
0.1%	16	QD	32	32	16	5	5
0.1%	16	BID	64	64	32	5	5

RESULTS

Intraocular Pressure Following 7-Day Consecutive Dosing of NCX 4251 Ophthalmic Suspension in Beagle Dogs



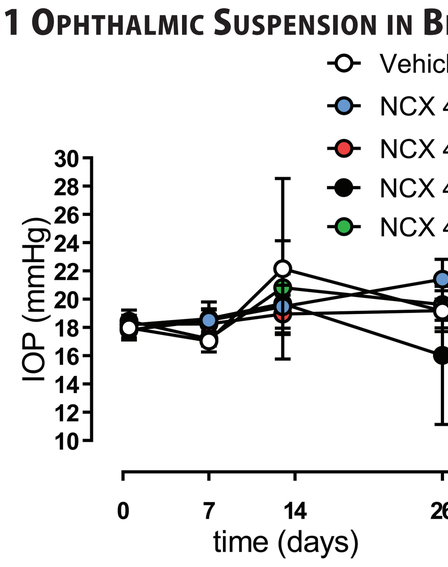
Animals (n=4 eyes/group) were dosed via topical application directly to the upper and lower eyelids of both eyes with vehicle or NCX 4251 (0.005%; 0.03% and 0.1% BID; minimum of 6 hours between doses) for 7 consecutive days. IOP was measured prior to treatment (baseline) and on day 7.

7-Day Repeated Dose Toxicity Study of NCX 4251 Ophthalmic Suspension in Beagle Dogs

Results and Conclusions

- Male and female beagle dogs well tolerated NCX 4251 ophthalmic suspension when administered directly to the upper and lower eyelid via an eyelid applicator for 7 consecutive days
- There were no clinical signs and no signs of ocular irritation or ophthalmological findings
- Systemic exposure to fluticasone propionate was dose dependent and increased with increasing doses
- There were no gender-related differences in exposure
- IOP did not increase following 7 consecutive days of treatment

Intraocular Pressure Following 14-Day Repeated Dose Toxicity Study of NCX 4251 Ophthalmic Suspension in Beagle Dogs



Animals (n=10/group) were dosed via topical application directly to the upper and lower eyelids of both eyes with vehicle or NCX 4251 (0.005% BID; 0.03% QD, 0.1% QD and 0.1% BID; minimum of 6 hours between doses) for 14 consecutive days. IOP was measured prior to treatment (baseline) and on day 7 and day 14. In addition, IOP was measured following 14-day of recovery (day 26).

14-Day Repeated Dose Toxicity Study of NCX 4251 Ophthalmic Suspension in Beagle Dogs

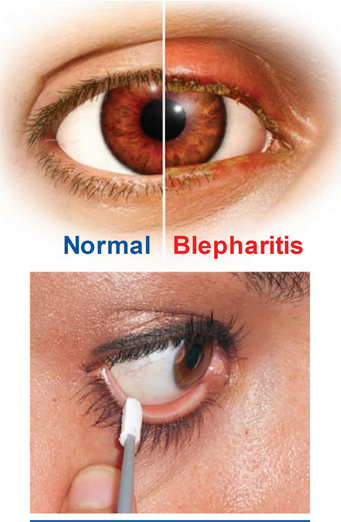
Results and Conclusions

- Male and female beagle dogs well tolerated NCX 4251 ophthalmic suspension when administered directly to the upper and lower eyelid via an eyelid applicator for 14 consecutive days
- There was no evidence of local or systemic toxicity. The no observed adverse effect level (NOAEL) for NCX 4251 was determined to be the highest dose tested of 0.1% BID (32 ug/eye/day; 64 ug/day)
- Systemic exposure to fluticasone propionate was dose dependent increasing with increasing doses
- There was no accumulation in male and female animals and there were no gender-related differences in exposure
- IOP did not increase following 14 consecutive days of treatment

CONCLUSIONS

NCX 4251 - Ophthalmic Suspension of Fluticasone Propionate Nanocrystals

- **NCX 4251** is based on **fluticasone**, ten-fold more potent than dexamethasone, and targets the **topical treatment of the eyelid margin** for patients with acute exacerbations of blepharitis
- **NCX 4251** is applied via an eyelid applicator at the eyelid margin directly to the site of inflammation to **potentially decrease steroid induced ocular adverse events** often seen with eye drops
- **NCX 4251** was evaluated in 7-day non-GLP toxicology study and 14-day GLP toxicology study
- **There were no dose limiting toxicology findings and no IOP increases, thus enabling the highest dose tested in toxicology studies to proceed into Phase 2 clinical study**



Example of prototype applicator in use (non-diseased eye)

IND in effect for forthcoming first-in-human, randomized, placebo-controlled Phase 2 clinical study in the U.S. to evaluate safety and tolerability of NCX 4251 vs placebo

Top-line results expected in Q4 2019

REFERENCES

1. Lemp MA, Nichols KK. Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment, ***Ocul Surf***. 2009 Apr;7(2 Suppl):S1-S14
2. Internal estimate based on IQVIA Health Analytics data 2017
3. Venturino et al. Chronic blepharitis: treatment patterns and prevalence. ***Invest Ophthalmol Vis Sci***. 2003(44);774.
4. Lemp et al. Blepharitis in the United States 2009: A survey-based perspective on prevalence and treatment. ***The Ocular Surface***, supplement April 2009, vol 7, N° 2
5. Subject to successful completion of formulation and IND-enabling non-clinical studies