A Phase 2 Randomized, Double-Masked, Placebo-Controlled Study of Novel Narrow Spectrum Kinase Inhibitor TOP1630 for the Treatment of Dry Eye Syndrome

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Purpose

- Small molecule narrow spectrum kinase inhibitor (NSKI) TOP1630 selectively targets key kinases fundamental to inflammatory cell signaling in innate and adaptive immune responses: p38-alpha, Src and Syk.
- Through synergistic effects on these kinases TOP1630 is a potent inhibitor of the inflammatory cascade and offers a novel mechanism for the treatment of Dry Eye Syndrome (DES).
- In this first-in-human study, we investigated the safety and efficacy of topical TOP1630 in DES.

Methods

- A randomized, double-masked, parallel-group trial of 0.1% TOP1630 topical ophthalmic solution TID or placebo (vehicle) TID was conducted in 61 DES subjects (31 randomized to TOP1630, 30 to Placebo).
- Key eligibility criteria: age ≥18 years; history of DES in both eyes for ≥6 months with associated use or desire to use eye drops for DES symptoms; OSDI© score ≥18; Schirmer test score of ≤10 and ≥1mm; tear film break up time of >1 and <7 seconds; dry eye exacerbation in corneal staining and ocular discomfort in a Controlled Adverse Environment (CAE®) challenge.
- After 7-day placebo run-in, eligible subjects were randomized to 28 days' treatment.
- Efficacy assessments included environmental and CAE change in DES symptoms and ocular surface staining.
- Analyses 2-sided; significance level 0.10.

Results (i) Safety & Tolerability

- TOP1630 was safe and well tolerated.
- No Serious Adverse Events (SAEs) or AEs leading to study discontinuation were reported.
- Ten ocular Treatment Emergent Adverse Events (TEAEs) were reported (5 TOP1630, 5 Placebo; 4 subjects in each group); none were severe or resulted in treatment withdrawal. Seven (3 TOP1630 and 4 Placebo; from 2 and 3 subjects in the respective groups) were considered treatment related (Table 1).

Treatment-Related TEAEs	TOP1630 (n=31)	Placebo (n=30)	All Subjects (n=61)
System Organ Class / Preferred Term	Subjects n (%)	Subjects n (%)	Subjects n (%)
Total	**2 (6.5%)**	**3 (10.0%)**	**5 (8.2%)**
Administration site conditions	1 (3.2%)	3 (10.0%)	4 (6.6%)
Instillation site pain Instillation site discomfort	1 (3.2%) 0	2 (6.7%) 1 (3.3%)	3 (4.9%) 1 (1.6%)
Eye disorders	1 (3.2%)	1 (3.3%)	2 (3.3%)
Eye discharge Vision blurred Vitreous floaters	0 1 (3.2%) 1 (3.2%)	1 (3.3%) 0 0	1 (1.6%) 1 (1.6%) 1 (1.6%)

Table 1: Treatment-Related Ocular TEAEs by Treatment Group

- Six non-ocular TEAEs were reported and all were considered unrelated to study drug.
- Drop comfort scores (0-10 where 10 indicates 'very uncomfortable') showed TOP1630 to be comfortable and comparable post-instillation to placebo: TOP1630 mean (SD) score 2.4 (1.98), Placebo 2.7 (1.86) p=0.5564.

Results (ii) Efficacy

- Significant improvements favoring TOP1630 versus placebo were seen for both symptoms and signs of DES, with improvements apparent in many cases by Day 15 (first assessment time point) and increasing at the Day 29 assessment:
  - Ocular discomfort (p=0.02 CAE)
  - Grittiness/foreign body sensation (on 4 independent assessment scales, each p<0.05, Figure 1 shows 1 scale)
  - Dryness (p=0.07 CAE)
  - Worst DES symptom (diary, p=0.06)
  - Ocular pain (VAS, p=0.03)
  - Total ocular surface staining (all-regions, p<0.05, Figure 2)
  - Corneal sum staining (p<0.05)
  - Conjunctival sum staining (p<0.05)

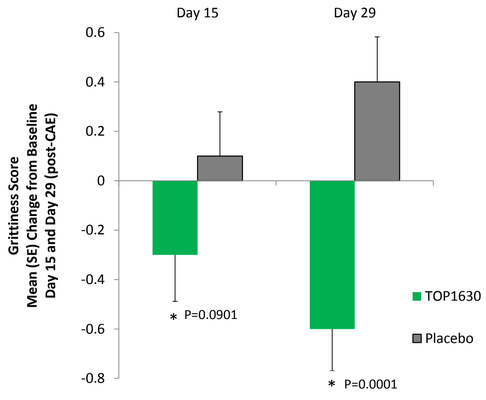

Figure 1: Grittiness score (Ora Calibra® Scale). Results show mean change from baseline to Day 29 (* ANCOVA test p<0.1)

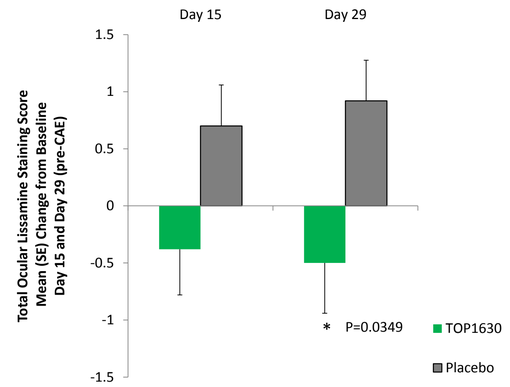

Figure 2: Total (cornea and conjunctiva) lissamine green staining score (Ora Calibra scale). Results show mean change from baseline to Day 29 (* ANCOVA test p<0.1)

Conclusions

In this first-in-human study, NSKI TOP1630:

- Was safe and well tolerated.
- Demonstrated placebo-like tolerability.
- Provided improvements in multiple symptom and sign endpoints, in both environmental and challenge settings, compared to placebo.

Overall, the results are highly promising and support future investigation of TOP1630 as a novel treatment for patients with DES.

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