A Clinical Phase II Study to Assess Efficacy, Safety, and Tolerability of Waterfree Cyclosporine Formulation for Treatment of Dry Eye Disease

BACKGROUND:

- Dry Eye Disease is characterized by inefficient tear production or incorrect tear production/film.
- Cyclosporine (CsA) is an immunomodulator in patients to reduce inflammation associated with keratoconjunctivitis sicca in patients with suppressed tear production. The challenge with topical cyclosporine is related to its high hydrophobicity so many of the formulations are oil-based emulsions; however, the oil formulations are poorly tolerated making them the ineffective choice for cyclosporine delivery.
- Waterfree cyclosporine formulation (CyclASol) lacks water, oils, surfactants, or preservatives to utilize cyclosporine's efficacy in a nonaqueous and clear solution to increase tolerability, onset of action, and local bioavailability. Restasis has typically been the mainstay of treatment but is accompanied by a high percentage of ADRs potentially related to the vehicle.

OBJECTIVE:

- This study was conducted to evaluate the safety, efficacy, and tolerability of water free cyclosporine formulation (CyclASol) at 2 concentrations (0.1% and 0.05%of cyclosporine [CsA]) to vehicle when applied twice daily for 16 weeks in patients with Dry Eye Disease (DED).

METHODS

- Design: exploratory phase II, randomize, vehicle-controlled clinical trial, double-masked between CyclASol and vehicle with an open-label comparator; Duration: 16 weeks
- Inclusion criteria: >18 years of age with history of DED , 1 eye (the same eye) met inclusion criteria at the time of randomization, Total CFS $\geq$ 6 (NEI scale), VAS dryness $\geq$40, Total lissamine green conjunctival score of $\geq$ 2 (Oxford scale), Schirmer test I score between $\geq$2 and $\leq$ 8 mm
- Exclusion criteria: Significant meibomian gland dysfunction, clinically significant slit-lamp findings or abnormal lid anatomy, trauma, SJS, active blepharitis, lid margin inflammation requiring therapeutic treatment, DED secondary to scarring, ocular or periocular malignancy, intraocular surgery or ocular laser surgery within 6 months, active ocular allergies, use of contact lenses within 3 months prior to screening, ongoing ocular or systemic infection, history of herpetic keratitis, history of no response to previous topical CsA and/or use of topical CsA within 6 months before screening
- Primary outcome: Change from baseline in total corneal fluorescein staining [CFS] (clinical sign, NEI scale) and visual analog scale [VAS] dryness (patient symptoms) in the worse eye after 16 weeks of treatment
- Secondary outcome measures: Treatment- emergent adverse events (TEAEs), total CFS, subregion CFS, conjunctival staining, unanesthetized Schirmer I test, tear film break-up time, VAS severity for dryness, burning/stinging, sticky feeling, foreign body sensation, itching, blurred vision, sensitivity to light, pain, and frequency for dryness, OSDI questionnaire, tear osmolality, HLA-DR determination on ocular surface, dry eye symptoms in diary
- 207 patients randomized in 1:1:1:1 ratio (CyclASol 0.05%n= 51, CsA 0.1% n= 51, Vehicle n= 52, Restasis n= 53)
- Safety data: treatment related adverse events occurred in 65 patients
- Efficacy outcomes: analyzed via analysis of covariance model (ANCOVA) 2 sided 95% Confidence Intervals , full analysis set population was analyzed via intent-to-treat model, nonlinear mixed-effects model

RESULTS

- Reduction in CFS in CyclASol 0.1%(-2.18 ± 2.378) at week 12 compared to Restasis (-1.17 ± 2.603) p= 0.0272
- Both CyclASol groups demonstrated a large and statistically significant reduction in mean total CFS staining at week 4 (CyclASol 0.05% -1.92 ± 2.108, CyclASol 0.1% -1.88 ± 2.046, versus Retasis -0.85 ± 2.475) [p= 0.0104 CyclASol 0.05% and p=0.0100 for CyclASol 1%)
- Change from baseline at week 4 in the worse-eye analysis of the central region showed that CyclASol 0.1% significantly reduced the extent of staining (and thus corneal damage) when compared with vehicle (CyclASol 0.1% −0.31±0.761; vehicle −0.08±0.752, P = 0.0299)
- CyclASol 0.05% had the most statistically significant change at week 12 for the total conjunctival staining score (−0.82±1.438, P = 0.0223) in comparison with vehicle (−0.24±1.238) and at week 4 (−0.74±1.103, P = 0.0321) when compared with Restasis (−0.38±1.270) in the worse-eye analysis
- All treatment groups showed an improvement in dryness symptoms, as measured by VAS (the primary symptom end point), with no statistical difference between CyclASol and vehicle groups
- No clear difference between the 2 CyclASol concentrations in signs, symptoms, or safety parameters.
- 200 patients completed the study (CyclASol 0.05%n= 50, CyclASol 0.1% n= 50, Vehicle n= 48, Restasis n= 52)
- Author conclusion: CyclASol showed efficacy, safety, and tolerability at 2 concentrations in moderate-to-severe DED.

STRENGTHS

- Randomized, vehicle-controlled trial with open-label comparator, blinded for 3/4 treatment groups, patients were followed for 16 weeks, compared 2 different concentrations in addition to a placebo and mainstay of treatment, adequate sample size, low number of adverse effects

LIMITATIONS

- Restasis was open-label and unblinded which could have influenced results and introduced bias, restasis is a water-based emulsion which is susceptible to bias of patient perception of their symptoms and low AE, and additional bias due to conflicts of interest are present due to the manufacturers involvement in the study

CONCLUSIONS

- This was a well-designed clinical trial that assessed not only signs and symptoms of DED but also CFA and OSDI which can aid in the anticipation of outcomes expected from a phase 3 trial including common adverse events.
- Cyclosporine concentrations indicated an earlier onset of action which can be important to improve patient adherence and reduce damage caused by DED especially to the central region of the cornea responsible for visual acuity.
- CyclASol had a low side effect profile reported which could provide another option to patients who fail Restasis or need faster onset of relief for their Dry Eye Disease.
- A phase 3 trial needs to be completed to increase the sample size to extrapolate the date to the masses and address any new adverse events that may occur in a larger scale.
- Specific inclusion and exclusion make it hard to extrapolate to the larger population but if the criteria is expanded in phase 3, it could give more insight into the potential use within the population.

Reference: Wirta DL, Torkildsen GL, Moreira HR, Lonsdale JD, Ciolino JB, Jentsch G, Beckert M, Ousler GW, Steven P, Krösser S. A Clinical Phase II Study to Assess Efficacy, Safety, and Tolerability of Waterfree Cyclosporine Formulation for Treatment of Dry Eye Disease. Ophthalmology. 2019 Jun;126(6):792-800. doi: 10.1016/j.ophtha.2019.01.024. Epub 2019 Jan 28. PubMed PMID: 30703441.

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