A Clinical Phase 2 Study to Assess Safety, Efficacy, and Tolerability of CyclASol® for the Treatment of Dry Eye Disease

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Introduction and Purpose

Dry Eye Disease (DED) is a complex and multifactorial disease where ocular surface inflammation and autoimmune dysregulation plays a key etiological role.[1] CyclASol® is a cyclosporine A containing water-free solution with superior spreading properties and increased local bioavailability. Cyclosporine A interrupts the vicious cycle of DED at different levels via its anti-inflammatory and immuno-modulating properties.

The objective of this multicenter, randomized, double-masked vehicle controlled Phase 2 study was to compare the safety, efficacy and tolerability of CyclASol at two concentrations (0.1% and 0.05%) to vehicle in subjects with DED. An open lable Restasis™ arm was included to allow a direct comparison with an established therapy.

Methods

Key inclusion criteria:

- At least 18 years of age
- Reported history of DED (OU) for at least 6 months
- Current use of eye drops for dry eye symptoms
- Dryness visual analog scale (VAS) ≥ 40
- Total corneal fluorescein staining (CFS) score ≥ 6 (NEI scale)
- Total lissamine conjunctival staining ≥ 2 (Oxford scale)
- Schirmer's test 1 score between ≥ 2 and ≤ 8

The study design is illustrated in Figure 1.

Statistics: The primary treatment comparisons were between CyclASol® (0.05% and 0.1%) and vehicle. Efficacy endpoints were analyzed separately using an analysis of covariance (ANCOVA) model with terms for baseline value. Modeling of response variables as a function of CyclASol® or vehicle were performed using non-linear mixed effect modeling. This analysis takes the totality of data into account and provides higher power in such explorative setting.

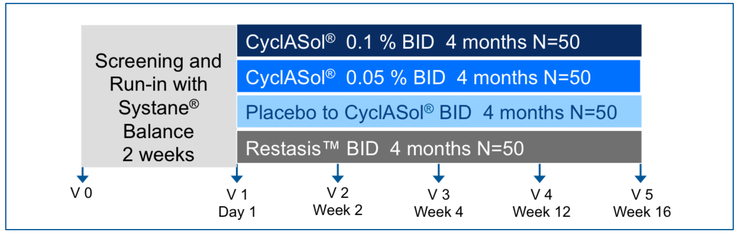

Figure 1: Phase 2 study design

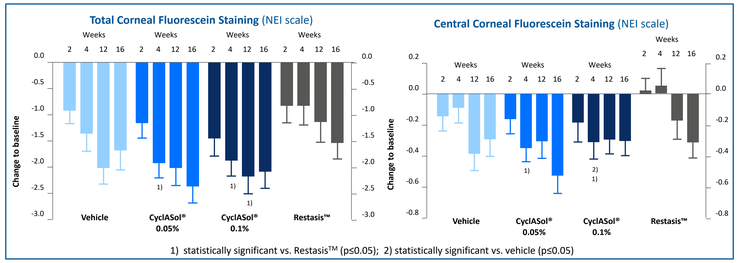

Figure 2: Change form baseline in total (left) and corneal (right) fluorescein staining (left) for all treatment groups in the FAS population

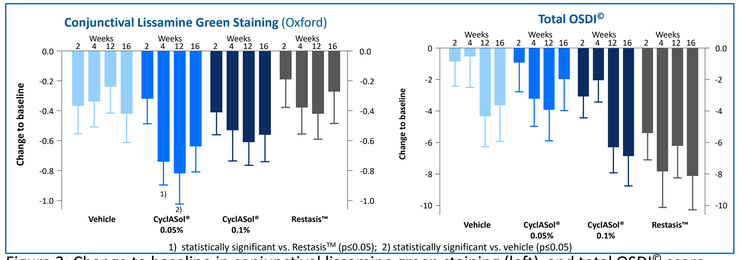

Figure 3: Change to baseline in conjunctival lissamine green staining (left) and total OSDI© score (right)

Results

Age and gender between all four treatment groups were well balanced (Table 1).

Sign efficacy: All treatment groups showed improvement in both total and central CFS however, CyclASol® trended towards a stronger and more consistent improvement compared to both vehicle and Restasis™. Statistical significance (p≤ 0.05) was reached over both vehicle and Restasis™ with both CyclASol® groups exhibiting an early onset of action as little as after 14 days when compared to Restasis™. Similar results were also obtained with conjunctival lissamine staining, where CyclASol® showed stronger improvements compared to both vehicle and Restasis™ in addition to an earlier onset of action (Figure 3, left). Further analysis using a non-linear mixed-effects modeling approach showed that the drug effect of CyclASol® became statistically significant over vehicle in total CFS (p<0.1), central CFS (p<0.001) and conjunctival staining (p<0.01).

Symptom efficacy: All treatment groups showed improvements in dryness as measured by the VAS, with CyclASol® showing more pronounced improvements in subgroups when compared to vehicle. CyclASol® also showed a larger and promising effect on visual function related symptoms (OSDI©) when compared to vehicle, particularly with questions 6 through 9 and the impact on reading question. Patient reported symptoms by Restasis™ users may have been unduly influenced by the open label study design. Non-linear mixed-effects modeling demonstrated a statistical significant drug effect by CyclASol® on total OSDI© (p<0.01) and in a number of other subgroups.

Safety and tolerability: 98% of the 207 enrolled subjects completed the 16 week treatment period. No clinically significant findings or changes were observed for any laboratory parameter, slit-lamp biomicroscopies or by dilated fundoscopy. These results and the relatively few subjects who experienced ocular treatment emergent adverse events (TEAEs) (Table 2) supports CyclASol®'s excellent safety and tolerability profile.

Table 1: Population characteristics and demographics

	CyclASol® 0.05%	CyclASol® 0.1%	Restasis™	Vehicle	All Subjects
Randomized					
N	51	51	53	52	207
Completers					
N	50	50	52	48	200
Discontinued					
N	1	1	1	4	7
Key Demographics					
Age (Years)					
Mean	64.3	61.1	62.8	61.3	62.4
Sex					
Male	13	15	13	13	54
Female	38	36	40	39	153

Table 2: Adverse event Summary

N= subjects	CyclASol® 0.05%	CyclASol® 0.1%	Restasis™	Vehicle
Subjects with at least one ocular TEAE	7	7	11	8
Visual acuity related	2	4	4	1
Conjunctival hemorrhage	1	0	2	0
Eye irritation	0	0	1	2
Vision blurred	0	1	2	0
Eye pain	1	0	0	1
Instillation site pain	1	1	2	1
Conjunctivitis	0	1	1	1
Subjects withdrawn due to an ocular TEAE	1 Eye pain	0	1 Conjunctivitis	1 Chemical Conjunctivitis
Subjects with ≥ any TEAE	18	12	21	14

- **CyclASol® showed consistent improvement in the signs of DED compared to vehicle and Restasis™ (corneal and conjunctival staining)**
- **CyclASol® showed a larger effects on visual function related symptoms compared to vehicle (OSDI©, OSDI©Q6-9 and reading)**
- **Earlier onset of action compared to Restasis™**
- **Excellent safety and tolerability profile**

Reference

1:Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf 2017;15:276-83.

2: De Paiva CS, Pflugfelder SC. Rationale for anti-inflammatory therapy in dry eye syndrome. Arq Bras Oftamol 2008;71:89-95.

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