OVERVIEW OF CLINICAL EFFICACY AND SAFETY OF A WATER-FREE CYCLOSPORINE, 0.1% SOLUTION FOR TREATMENT OF DRY EYE DISEASE

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Introduction and Purpose

Recently the water insoluble cyclosporine has been developed as a clear water-free 0.1% solution without the need of oils, surfactants or preservatives. The drug was approved for treatment of Dry Eye Disease (DED) in May 2023 by US FDA as Vevye® and in September 2024 in the European Union under the name Vevizye®.
The aim of this study is to evaluate the combined evidence of the efficacy and safety of this novel cyclosporine 0.1% solution for the treatment of Dry Eye Disease (DED) from a global clinical development program.

Methods

The first investigation was a cross-over study focusing on safety and pharmacokinetics in 18 healthy volunteers. Four studies were randomized double-masked and vehicle-controlled, including one phase 2 dose finding trial with an open label active comparator (Restasis), two pivotal studies ESSENCE-1 and ESSENCE-2, and a bridging study for China (SHR8028-301). The sixth study was an open label extension study of ESSENCE-2 treating 202 DED patients for one year (Table 1). All patients in ESSENCE-2 OLE received cyclosporine 0.1%.

Table 1: Global studies in DED patients for cyclosporine 0.1% solution.

	CYS-002[1]	ESSENCE-1 (CYS-003)[2]	ESSENCE-2 (CYS-004)[3]	SHR 8028-301[4]	ESSENCE-2 OLE (CYS-005)[5]
ClinicalTrial ID	NCT02617667	NCT03292809	NCT04523129	NCT05841043	NCT04523142
Patients N/ Country	207 Germany	328 US	834 US	206 China	202* US
Treatment (weeks)	Cyclosporine 0.05% or 0.1% or Restasis or vehicle (16)	Cyclosporine 0.1% or vehicle (12)	Cyclosporine 0.1% or vehicle (4)	Cyclosporine 0.1% or vehicle (4)	Cyclosporine 0.1% (52)
Primary Endpoints	tCFS (NEI) Dryness (VAS)	tCFS (NEI) total OSDI	tCFS (NEI) Dryness (VAS)		Safety
Key Inclusion Criteria	tCFS ≥6, Dryness Score ≥ 40, tLGS ≥2 (Oxford), Schirmer's 2-8 mm	tCFS ≥10, OSDI score ≥20, tLGS ≥2 (Oxford), Schirmer's 1-10mm	tCFS ≥10, Dryness score ≥ 50, tLGS≥2 (Oxford), Schirmer's 1-10 mm		

NEI= National Eye Institute; OSDI= ocular surface disease index; tCFS= total corneal fluorescein staining; tLGS= total lissamine green staining; VAS= Visual Analogue Scale; *rolled over from CYS-004

Sign endpoints included total corneal fluorescein staining score (tCFS, NEI scale [0-15]) tCFS responders (improvement of ≥ 3 tCFS grades); central staining score (cCFS) and conjunctival lissamine green staining (tLGS, Oxford; 0-10). Symptom assessments included subject reported OSDI and Dryness Score (VAS; 0-100, the higher the worst).

Results

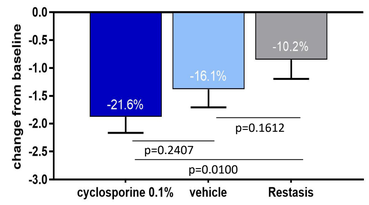
- The studies were conducted in Germany, US and China and comprised 1593 participants.
- The demographics and baseline charateristics were balanced between treatment groups.
- Based on baseline charateristics the population can be characterized as moderate to severe DED patients with aqueous deficiency and epithelial damage.

CYS-001: Results showed favorable safety and tolerability profile of the water-free cyclopsporine solution in healthy subjects. Systemic exposure to cyclosporine as well as to the vehicle perfluorobutylpentane were negligible.

Efficacy

CYS-002 (exploratory): The cyclosporine 0.05% and 0.1% showed consistent improvements in corneal and conjunctival staining compared to vehicle and Restasis over the 4 months treatment period. At Day 29, the primary timepoint for efficacy measures at subsequent trials, the 0.1% concentration was significant over Restasis and numerically better than vehicle (Figure 1). There was no clear dose response observed in the study, based on trends in symptoms outcomes the 0.1% dose was selected for further trials.

Figure 1:
CYS-002 change from baseline in tCFS at Day29



CYS-003/CYS-004 (pivotal) and SHR8028-301 (CN, bridging): All three studies demonstrated a significant improvement from baseline in tCFS compared to vehicle at Day 29 (Figure 2), thereby meeting the primary sign endpoint. All three studies showed significant improvements in the primary symptom endpoints compared to baseline without a clear difference over vehicle.
Early onset was demonstrated by statistically significant improvements in staining parameters starting at Day 15 (Figure 2).
Additionally, the majority of patients met responder criteria which demonstrated the clinical relevance of the effects (Figure 3).

Figure 2: ESSENCE-1, ESSENCE-2 and SHR8028-301, tCFS, cCFS tLGS at Day 15 and Day 29

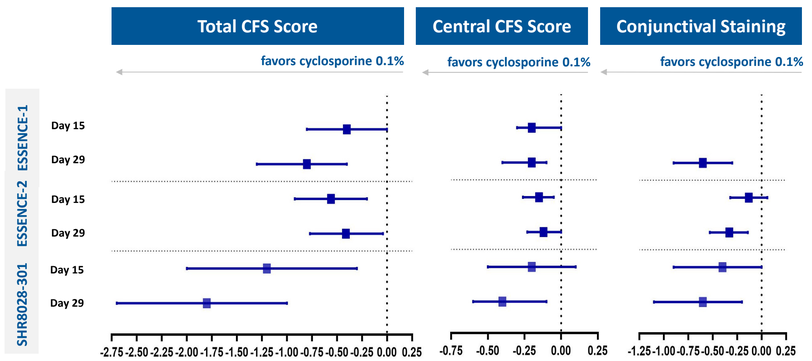
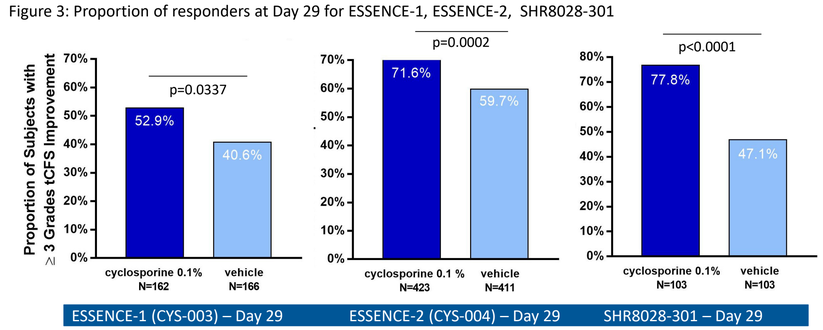
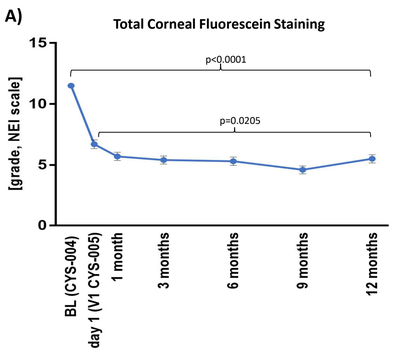


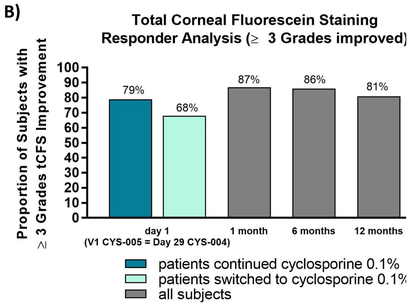
Figure 3: Proportion of responders at Day 29 for ESSENCE-1, ESSENCE-2, SHR8028-301

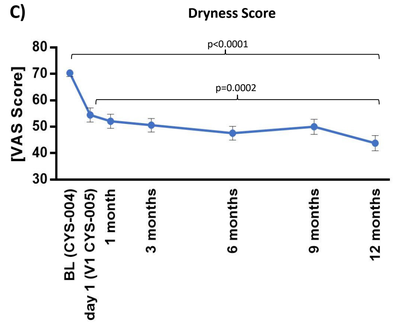


CYS-005: The one year elongation study demonstrated sustained efficacy in both signs and symptoms of DED. After 4 weeks, more than 80% of all patients showed a clinically meaningful improvement of ≥ 3 grades in tCFS score, which was sustained throughout the study, underlining that a large proportion of patients benefit from the therapy (Figure 4 A+B). Symptoms improved throughout the study, reaching their minimum at the end of the observation period (Figure 4 C).

Figure 4: A) tCFS B) tCFS responder and C) VAS Dryness score over a 1-year observation period







Safety and Tolerability

The majority of subjects completed the studies (>95%) and discontinuation was balanced between treatment groups.[2-5]

In vehicle controlled studies TEAEs were balanced between the cyclosporine 0.1% and the vehicle group. The most common ocular TEAEs occurring in > 2% patients were instillation site pain (7.9% [combined US studies]) and temporally visual acuity reduced (2.7% [combined US studies]). In all studies ophthalmologic examinations of visual acuity, slit-lamp biomicroscopy, IOP, and dilated fundoscopy showed no meaningful differences between active and vehicle and no treatment related changes.

High tolerability was shown by good drop comfort ratings comparable to lubricant eye drops. Additionally, positive descriptors were used on the drop comfort questionnaire in >80%, with most common descriptors being comfortable, smooth and soothing.

Conclusions

The global program with a novel water-free cyclosporine 0.1% solution showed consistently:

- **Early and significant improvement in corneal staining starting at Day 15**
- **Majority of patients benefit from treatment after 1 month**
- **Improvements on sign and symptoms were maintained over 1 year**
- **The formulation demonstrated to be safe with excellent comfort**

References: 1) Wirta DL et al. Ophthalmology. 2019; 126:793-800; **2)** Sheppard JD et al. Cornea. 2021; 40:1290-1297; **3)** Akpek EK et al. JAMA Ophthalmology. 2023; 141(5):459-466.; **4)** Peng R et al. JAMA Ophthalmol. 2024 Apr 1;142(4):337-343; **5)** Wirta DL et al. Cornea. 2024 May 21

Disclosures: A. Galor and P. Karpecki (consultants to Novaliq); S. Krösser and A. Meides (employees of Novaliq)