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CORNEA

Pooled results from two pivotal randomized controlled clinical trials: ESSENCE-1 and ESSENCE-2 to assess efficacy and safety of a water-free ciclosporin 0.1% formulation for the treatment of dry eye disease

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Abstract

Purpose This pooled analysis of two pivotal studies (ESSENCE-1 and ESSENCE-2) evaluated treatment effects of a water-free ciclosporin 0.1% solution in dry eye disease (DED) patients in the overall population and in subgroups according to sex, age, and baseline severity of disease.

Methods In these randomized, multicenter, double-masked, vehicle-controlled studies patients received ciclosporin 0.1% or vehicle (1:1 ratio) in both eyes twice daily for 85 and 29 days, respectively. Total and central corneal fluorescein staining (tCFS; cCFS; NEI scale, 0–15) were assessed at Day 15 and 29. Other endpoints included conjunctival staining and blurred vision scores. Safety and tolerability parameters comprised adverse events, ophthalmic examinations and drop comfort assessments.

Results In total 1162 patients were included in the analysis (585 ciclosporin 0.1%; 577 vehicle). Patients age (mean [SD]: 58.3 [15.23] years) and gender distribution (73% females) are consistent with DED epidemiology. Change from baseline (LS mean [SE]) in tCFS significantly improved compared to vehicle, both at Day 15 (ciclosporin: -3.24 [0.112]; vehicle -2.71 [0.113]; Δ= -0.52 [0.144], p=0.0003) and Day 29 (ciclosporin: -3.83 [0.115]; vehicle:-3.30 [0.116]; Δ: -0.53 [0.147], p=0.0003). 56.8% and 66.4% of patients responded to ciclosporin 0.1% with a tCFS improvement of ≥ 3 scores on Day 15 and 29, respectively. A consistent effect on tCFS favoring ciclosporin over vehicle was observed in all subgroups. Improvements favoring ciclosporin were seen in cCFS and conjunctival staining in the overall population and in blurred vision score in patients with significant corneal staining. Incidence of ocular adverse events was 13.2% in both treatment groups. Mild instillation site reactions were reported by 7.9% patients in the ciclosporin group. Discontinuation rates were low with 2.6% and 2.1% in ciclosporin and vehicle groups. Ciclosporin 0.1% was rated comfortable upon instillation by 84.7% of patients.

Conclusion The pooled analysis confirmed that the water-free ciclosporin 0.1% solution is effective in improving ocular surface staining after 2 weeks of treatment to a clinically relevant extent in more than 50% of patients in the overall population and subgroups. With an early onset and good tolerability, the product has the potential to address an unmet medical need in DED.

ClinicalTrials.gov identifier NCT03292809 on 21-July-2017; NCT04523129 on 20-August-2020

Key messages

What Was Known

- Ciclosporin eye drops are a standard of care in dry eye disease (DED) therapy not controlled by artificial tears. A novel water-free ciclosporin 0.1% ophthalmic solution with improved efficacy has recently been commercialized in the United States and approved in the European Union.

What This Paper Adds

- The water-free cyclosporine 0.1% solution showed consistent and early improvement of ocular surface damage in patients with moderate and severe dry eye disease as well as in subgroups according to age and sex.

The results were presented in parts at the DOG Annual Meeting in Berlin, Germany, on 28th September 2023.

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- Responder analysis showed the clinical relevance of these improvements in more than 50 % of treated patients after 2 weeks of treatments.
- This eye drop formulation was well tolerated and no new safety signals were detected.

Keywords Dry eye disease · Water-free · Ciclosporin 0.1% · Pooled analysis · Pivotal study

Introduction

Dry eye disease (DED), also known as keratoconjunctivitis sicca, is one of the most common ocular surface disorders. Over the past decades, the number of patients with DED has increased significantly [1]. The reported global prevalence of DED is high with up to 50% of individuals above the age of 50 years reporting dry eye symptoms [2]. DED becomes manifest in a wide range of signs and symptoms, including vision related impairments. This represents a significant negative impact to patients [3, 4] and leads to reduced workplace performance. Therefore, DED poses a substantial economic burden to society [5].

Corneal staining is considered the most critical clinical sign of DED, as stained areas represent punctate disruption and damage of the corneal epithelium [6] and as such an important parameter for determining the severity of the disease [7]. It correlates with visual function-related manifestation of the disease such as blurred and fluctuating vision or reading problems [8]. The severity of corneal staining in DED patients affects also reading speed [9]. These symptoms impact daily activities of DED patients and result in reduction of vision related quality of life; the impact is higher than that for other common vision-affecting eye disorders [9, 10].

DED management is not uniform [11]. It often follows a stepwise approach, beginning with over-the-counter artificial tears therapies, eyelid hygiene measures, and modification of environmental factors [12].

Pharmacological treatments are initiated if the first line approaches provide insufficient control of the condition. Typically, anti-inflammatory or immune-modulatory therapeutics such as ciclosporin, lifitegrast, or short-term corticosteroid are added to interrupt the inflammatory cause of the disease. Ciclosporin is the most common drug in this category available in most geographical regions [13, 14].

Ciclosporin cannot be solubilized in aqueous ophthalmic vehicles because of its extremely low aqueous solubility. To date all topical ophthalmic formulations of ciclosporin on the market are therefore emulsions/nano-emulsions. Emulsions contain excipients, oils and surfactants which are often poorly tolerated and have a low local bioavailability for ciclosporin because ciclosporin is nonpolar and thus has a strong tendency to remain in the hydrophobic core of the micelle [15]. These formulations are associated with a slow onset of the anti-inflammatory effect and relative high rates of instillation site reactions [7, 16, 17].

The product under investigation is a clear solution of ciclosporin 0.1% in the novel vehicle, perfluorobutylpentane. This formulation leads to superior properties: It is water-free, without pH or osmolarity. The low surface tension leads to small droplets, fast spreading on the ocular surface as well as reduction of shear forces. Better penetration into the corneal epithelium and long residence time lead to improved bioavailability of ciclosporin and an early onset of ocular surface regeneration [18]. The absence of preservatives, oils, surfactants combined with the small drop size makes the product comfortable upon instillation. This water-free ciclosporin 0.1% solution was approved by FDA in May 2023 under its commercial name Vevye. In Europe it was recently approved under the commercial name Vevizye and in China it is currently under regulatory review.

The aim of this pooled data analysis from ESSENCE-1 and ESSSENCE-2 was to further evaluate treatment effects of ciclosporin 0.1% solution in the overall population of patients with dry eye disease and in patient subgroups defined by age, sex, and disease severity. Pooling of data also provides greater statistical power to perform subgroup analyses and increases the likelihood of identifying uncommon adverse events.

Methods

Data were pooled from two adequate controlled trials ESSENCE-1 (NCT03292809) and ESSENCE-2 (NCT04523129) to demonstrate efficacy and safety of the water-free ciclosporin 0.1% solution in the treatment of dry eye disease.

This research was reviewed by an independent ethical review board (Alpha IRB in SanClemente, California) and conforms with the principles and applicable guidelines for the protection of human subjects in biomedical research. Methodology and results from each study have been described previously [19, 20].

Similarities in study design allowed for pooling of patient-level data from ESSENCE-1 and ESSENCE-2. In both trials, patients not responding to artificial tears after a 2-week run-in phase and fulfilling the eligibility criteria were included in the studies and randomized in a 1:1 fashion to ciclosporin 0.1% solution or its vehicle. During the treatment period study participants dosed a single drop per eye twice daily.

Assessment of outcome measures

This pooled analysis focused on efficacy parameters related to ocular surface healing based on findings of individual studies. These efficacy parameters are consistent with the key secondary outcome parameter of ESSENCE-2, the second pivotal study which was designed based on ESSENCE-1 outcomes. They included change from baseline in tCFS at Day 15 and Day 29; tCFS responders at Day 15 and Day 29; change from baseline in conjunctival staining at Day 29; and change from baseline in central staining at Day 29. In addition, blurred vision was assessed due to the known impact of corneal damage on visual function. Change from baseline in blurred vision was assessed using VAS at Day 29 in the overall population and in patients with high central staining at baseline. Change from baseline in eye dryness was assessed as it was the second primary endpoint in ESSENCE-2.

The tCFS score was measured using the National Eye Institute (NEI) scale, which ranges from 0 (no staining) to 3 (heavy staining) for each of the five areas of the cornea (inferior, superior, central, nasal, and temporal). The total score ranges from 0 to 15 and is the sum of the five regions, the higher the worse. A tCFS responder was defined as ≥ 3 grades improvement in the central area of the cornea on the NEI scale. Conjunctival staining was determined using lissamine green dye and graded according to the Oxford grading scale (nasal and temporal regions were graded from 0 to 5 separately and the total score was the sum of both regions). The eye dryness and blurred vision scores were assessed using a visual analogue scale (VAS) ranging from 0 to 100 with 0 = no dryness feeling / blurring, 100 = maximal dryness feeling / blurring).

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) occurring after the first dose of randomized study treatment was administered. The investigator determined the severity and relationship to the study treatment. The drop comfort scale was assessed for each eye immediately upon instillation, and at 1 min and 2 min following initial dosing. The drop comfort scale ranges from 0 to 10, with 0 indicating very comfortable and 10 indicating very uncomfortable. Moreover, patients were asked to select 3 words out of 14 that describe the feeling of the drop.

Study participants

Populations in both studies were very similar enrolling adults with subject-reported history of DED who have used over-the-counter eye drops and gels, for dry eye symptoms, with a total corneal fluorescein staining (tCFS) ≥ 10 (NEI scale), unanesthetized Schirmer's test score between 1 and 10 mm, total lissamine green conjunctival score of ≥ 2 (Oxford scale), ocular surface disease index (OSDI) score ≥ 20 (ESSENCE-1 only) or dryness score ≥ 50 (ESSENCE-2 only). One eye of each study participant, with the highest tCFS, was designated as the "study eye". If tCFS score at baseline was the same, the right eye was designated as "study eye".

Statistical methods

The comparisons between ciclosporin 0.1% solution versus vehicle used the Full Analysis Set (FAS) with available data per subject. The Full Analysis Set (FAS) includes all randomized patients who received at least one dose of investigational product. The continuous efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model with terms for baseline score, site and treatment group, consistent with the individual ESSENCE-1 and ESSENCE-2 studies' analyses. The ANCOVA LS means for each treatment group and the ANCOVA LS mean difference between treatment groups were presented as well as two-sided p-values, and two-sided 95% CIs.

The dichotomous efficacy endpoints were analyzed using a logistic regression model with terms for baseline value, site, and treatment group. The predictive marginal proportions (PMP) and difference in predictive marginal proportions were reported from the logistic regression model. Two-sided 95% CIs and two-sided p-values for the difference of marginal proportions were reported from the logistic regression model.

Efficacy was analyzed for overall pooled population and patient subgroups by age (≥ 18 to < 65 years and ≥ 65 years), sex (male and female), baseline symptom severity (visual analog scale eye dryness score moderate: <75 and severe: ≥75), baseline sign severity (tCFS score of 10–11 [moderate] and 12–15 [severe] based on the NEI scale), and treatment differences for ciclosporin 0.1% solution versus vehicle were summarized using Forest plots.

Results

Study participant disposition

The pooled FAS included 1162 subjects, i.e., 328 subjects randomized in ESSENCE-1 and 834 subjects randomized in ESSENCE-2, of which 1135 (97.7%) completed the studies. The percentage of subjects discontinuing the studies was low and balanced between ciclosporin 0.1% and vehicle groups (2.6% and 2.1% in ciclosporin and vehicle groups). The most common reason for discontinuation was subject choice, reported for 13 (48%) of discontinued subjects overall.

Baseline characteristics

Demographics and baseline characteristics were balanced between treatment groups. The majority of patients were female (72.6%) and more than one third were at least 65 years of age (38.3%). Patients had significant corneal staining with an average score of 11.5 on the NEI scale and the central region was also affected (average 2.1) (Table 1). Patients had low Schirmer tear test scores with an average of around 5 mm and they were symptomatic with average dryness scores of around 70 and average blurred vision scores of around 50 (Table 1).

Efficacy

All endpoints related to ocular surface damage measured via corneal fluorescein staining and conjunctival lissamine staining were consistently more improved in the ciclosporin groups compared to the respective vehicle groups.

On Day 15, the LS mean change from baseline (ANCOVA, SE) for tCFS was − 3.24 (0.112) and − 2.71 (0.113) in the pooled ciclosporin 0.1% and vehicle groups, respectively. The between-treatment difference (ciclosporin 0.1% - vehicle) was −0.52 (0.144) and statistically significant ($p=0.0003$). On Day 29, the LS mean change from baseline was −3.83 (0.115) and −3.30 (0.116) in the ciclosporin 0.1% and vehicle groups, respectively. The between-treatment difference (ciclosporin 0.1% - vehicle) was −0.53 (0.147) and statistically significant ($p=0.0003$). All subgroups showed a treatment effect favoring ciclosporin 0.1% over vehicle (Fig. 1). The effect was statistically significant for most subgroups at Day 15 and in all subgroups on Day 29 except for males, who represent the smallest subgroup in the investigation. The magnitude of the treatment effect was comparable between patients with moderate and severe DED irrespective of the severity definition.

The ciclosporin group showed a significantly greater proportion of patients (56.8%) responding clinically meaningful on tCFS (improvement of ≥ 3 grades) to the treatment compared to the vehicle group (47.9%) already after 2 weeks ($p=0.0009$). At Day 29 the proportion of responders in the ciclosporin group was 66.4% and 54.1% in the vehicle group ($p<0.0001$), (Fig. 2). This response level was associated with a significant improvement in all symptoms measured by VAS, which were assessed in both studies (data not shown). In line with the mean tendency analysis, subgroups showed a comparable pattern for the responder analysis (Table 2).

For conjunctival staining at Day 29, the LS mean change from baseline (SE) was −1.2 (0.066) and −0.8 (0.066) in the pooled ciclosporin 0.1% and vehicle groups, respectively. The between-treatment difference (ciclosporin 0.1% - vehicle) was 0.40 (0.085) and statistically significant ($p<0.0001$). All investigated subgroups also showed statistically significant improvements in the active group compared to the vehicle group of a similar effect size (see Fig. 3).

For central corneal staining at Day 29, the LS mean change from baseline (SE) was – 0.78 (0.036) and −0.63 (0.036) in the pooled ciclosporin 0.1% and vehicle groups, respectively. The between-treatment difference (ciclosporin 0.1% - vehicle) was −0.15 (0.046) and statistically significant ($p=0.0008$). All subgroups showed a treatment effect numerically favoring ciclosporin 0.1% over vehicle, the effect reached statistical significance in 5 out of the 8 subgroups (Fig. 3).

In the overall pooled population, eye dryness improved in both treatment arms significantly without a group difference: LS mean change from baseline (SE) of -11.8 (1.04) and −11.4 (1.04) in the ciclosporin 0.1% and vehicle groups, respectively. The subgroup results for this parameter were consistent with the result of the overall population.

In the overall pooled population, a trend towards an improvement in blurred vision was observed: the LS mean change from baseline (SE) was −8.1 (1.00) and −6.3 (1.01) in the ciclosporin 0.1% and vehicle groups, respectively. The between-treatment difference (ciclosporin 0.1% - vehicle) was −1.8 (1.29) and not statistically significant ($p=0.1513$). A similar trend was observed in all subgroups. The difference in blurred vision score in the subgroup of patients with corneal staining scores of 12–15, approached statistical significance: LS mean change from baseline (SE) was −9.8 (1.70) in the ciclosporin 0.1% and −5.9 (1.66) in the vehicle group with a between-treatment difference (ciclosporin 0.1% - vehicle) of -4.0 (2.05; $p=0.0521$). In patients with high central staining at baseline this effect on blurred vision was more pronounced and reached statistical significance, LS mean change (SE) from baseline was −12.6 (1.96) in the ciclosporin 0.1% and −4.1 (2.02) and vehicle group with a between-treatment difference (ciclosporin 0.1% - vehicle) of -8.5 (2.81; $p=0.0028$).

Safety

There were no meaningful imbalances between the ciclosporin and the vehicle group in the incidence of TEAEs overall, and of ocular and non-ocular TEAEs. There were 117 (20%) patients with any TEAEs and 77 [13.2%] with ocular TEAEs and 2 (0.3%) patients with Serious Adverse Events (SAEs) in the ciclosporin arm (all non-ocular). In the vehicle arm 117 (20.3%) patients reported any TEAEs and 76 [13.2%] reported ocular TEAEs and 6 (1.0%) patients experienced SAEs (of which 1 [0.2%] was ocular). For all of the SAEs, the relationship was assessed as not suspected to be related to study drug. Eight (0.7%) patients discontinued treatment due to an AE, 5 (0.9%) in the ciclosporin 0.1% arm and 3 (0.5%) patients in the vehicle arm (see Table 3). None of the AEs reported resulted in death.

Table 1 Demographics and Mean baseline characteristics (pooled FAS)

Pooled Analysis	Ciclosporin 0.1%	Vehicle
Pooled population n (%)	585 (100.0%)	577 (100.0%)
ESSENCE-1, n (%)	162 (27.7%)	166 (28.8%)
ESSENCE-2, n (%)	423 (72.3%)	411 (71.2%)
Demographics		
Mean age (SD)	58.7 (14.98)	57.9 (15.48)
≥65 years, n (%)	220 (37.6%)	225 (39.0%)
Female, n (%)	422 (72.1%)	422 (73.1%)
Race, n (%)		
White	453 (77.4%)	439 (76.1%)
Black	69 (11.8%)	69 (12.0%)
Asian	54 (9.2%)	58 (10.1%)
Baseline ocular characteristics		
tCFS (NEI scale 0–15)	11.5 (1.37)	11.5 (1.33)
cCFS (NEI scale 0–3)	2.1 (0.60)	2.1 (0.60)
TBUT (sec)	3.08 (1.40)	2.99 (1.49)
Schirmer (mm)	5.1 (2.92)	4.8 (2.74)
Dryness (VAS)	69.9 (15.60)	69.9 (15.26)
Blurred vision (VAS)	52.4 (27.42)	52.0 (26.02)

The only single AE term reported in more than 2% of subjects overall was instillation site pain occurring in about 8.0% of subjects in the ciclosporin 0.1% group, which was of mild intensity in nearly all cases. The only other term occurring in more than 2% of subjects was visual acuity reduced.

Patient comfort was confirmed to be high with 84.7% of patients using a positive descriptor when they were asked to choose three words that best characterize how the drop of ciclosporin solution felt in both eyes. Most frequent descriptors were comfortable, smooth and soothing. Mean values of drop comfort were ≤2.5 (on a scale from 0 = very comfortable to 10 = very uncomfortable), which is in line with the previously reported comfort level of water-based artificial tears [21].

Discussion

The pooled analysis of ESSENCE-1 and ESSENCE-2 studies demonstrated that the water-free ciclosporin 0.1% solution (development name CyclASol, US brand name Vevye, EU brand name Vevizye) had very consistent and significant improvements on all ocular surface endpoints over vehicle in the overall population as well as multiple patient subgroups.

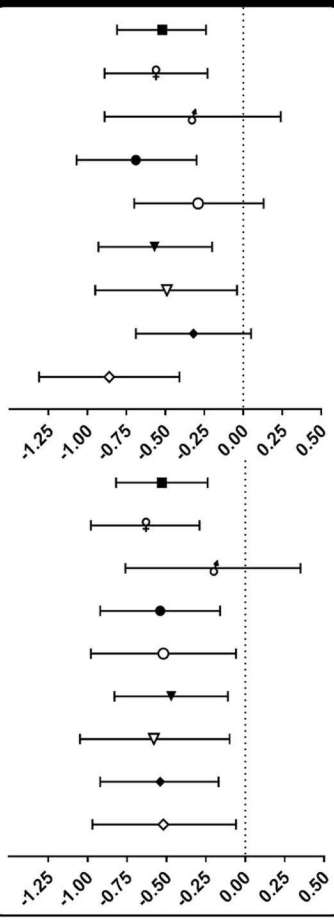
The onset of effect was rapid, at the first follow up visit at Day 15 more than 50% of patients treated with ciclosporin 0.1% solution showed an improvement of ≥3 grades on the total corneal staining on the NEI scale. This proportion increased to 66% at Day 29. The degree of corneal staining improvement (≥3 grades) is clinically meaningful based on literature and feedback from clinicians who unanimously consider such an effect as immediately noticeable and relevant to the patient [22, 23]. In addition, this magnitude of improvement has been shown to be associated with symptom improvement and visual function improvement [19, 20, 24, 25]. This correlation is also reflected in the finding that patients with high central corneal staining had significantly higher reduction in their blurred vision scores in the active arm compared to the vehicle arm.

The observed early onset of improvement of ocular surface damage was earlier than reported for other ciclosporin products used for treatment of DED [17, 26, 27]. The late onset of effect of ciclosporin containing emulsions is attributed to its effect on T-cells which depends on T-cell turnover rate. However, ciclosporin also possesses immediate, T-cell independent, anti-inflammatory mechanisms such as inhibition of apoptosis in conjunctival cells and induction of T-cell apoptosis as well as NFkB inhibition [28, 29, 30], which have an immediate onset of action. Data from the current study show that the formulation plays a critical role for the onset of effect. In solution, the active ingredient does not require liberation from micelles and in combination with the physical properties of the water-free vehicle ciclosporin is brought more efficiently to the target tissue [31]. Moreover, the novel formulation does not contain additives such as phosphates or surfactants that potentially could counteract beneficial effects of the active substance. These formulation characteristics potentially lead to the early onset of effect.

The analysis confirmed the good tolerability profile of the water-free ciclosporin 0.1% solution with 8% of patients reporting only mild instillation site reactions and the majority of patients describing the drop as comfortable, smooth and soothing. Ciclosporin containing emulsions have substantially higher rates of adverse reaction upon instillation; for a 0.05% ciclosporin containing emulsion 17% of patients reported ocular burning [32], for a 0.09% ciclosporin nanoemulsion 22% reported instillation site pain and 6% conjunctival hyperemia [33]. The most frequently reported ocular adverse event deemed possibly related to a 0.1% cationic emulsion were instillation site pain (12.1%), eye irritation (10.1%) and instillation site irritation (5.1%) [27].

In real world, about two thirds of patient discontinue treatment within 12 months after treatment initiation. The key reasons being discussed are adverse effects e.g., instillation site pain and late onset of effect [34]. European DED experts recommend initiating a ciclosporin dry eye disease drug therapy concomitant with 4–8 weeks corticosteroid

Pooled Analysis			Active N	Vehicle N	Group Difference 95% CI	p-value
tCFS Day 15	Overall		585	577	-0.52 (-0.81; -0.24)	0.0003
	Sex	Female	422	422	-0.56 (-0.89; -0.23)	0.0010
		Male	163	155	-0.33 (-0.89; 0.24)	0.2598
	Age	18- <65 years	365	352	-0.69 (-1.07; -0.30)	0.0005
		≥ 65 years	220	225	-0.29 (-0.70; 0.13)	0.1794
	Severity	Moderate tCFS[a]	334	325	-0.57 (-0.93; -0.20)	0.0023
		Severe tCFS[b]	251	251	-0.49 (-0.95; -0.04)	0.0342
		Moderate Dryness[c]	353	345	-0.32 (-0.69; 0.05)	0.0854
		Severe Dryness[d]	232	232	-0.86 (-1.31; -0.41)	0.0002
tCFS Day 29	Overall		585	577	-0.53 (-0.82; -0.24)	0.0003
	Sex	Female	422	422	-0.63 (-0.98; -0.29)	0.0004
		Male	163	155	-0.20 (-0.76; 0.35)	0.4712
	Age	18- <65 years	365	352	-0.54 (-0.92; -0.16)	0.0053
		≥ 65 years	220	225	-0.52 (-0.98; -0.06)	0.0268
	Severity	Moderate tCFS[a]	334	325	-0.47 (-0.83; -0.11)	0.0115
		Severe tCFS[b]	251	251	-0.58 (-1.05; -0.10)	0.0170
		Moderate Dryness[c]	353	345	-0.54 (-0.92; -0.17)	0.0046
		Severe Dryness[d]	232	232	-0.52 (-0.97; -0.06)	0.0265



[a]Moderate tCFS=10-11 score, [b]severe tCFS=12-15 score; [c]moderate Dryness < 75, [d]severe Dryness ≥ 75

Fig. 1 Forest Plot tCFS at Day 15 and Day 29.[a]Moderate tCFS = 10–11 score, [b]severe tCFS = 12–15 score, [c]moderate Dryness < 75, [d]severe Dryness ≥ 75

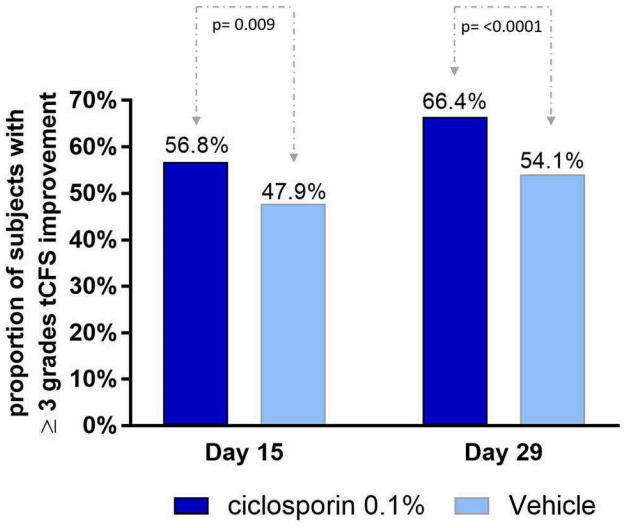


Fig. 2 Proportion of study participants with tCFS improvement of 3 grades or more

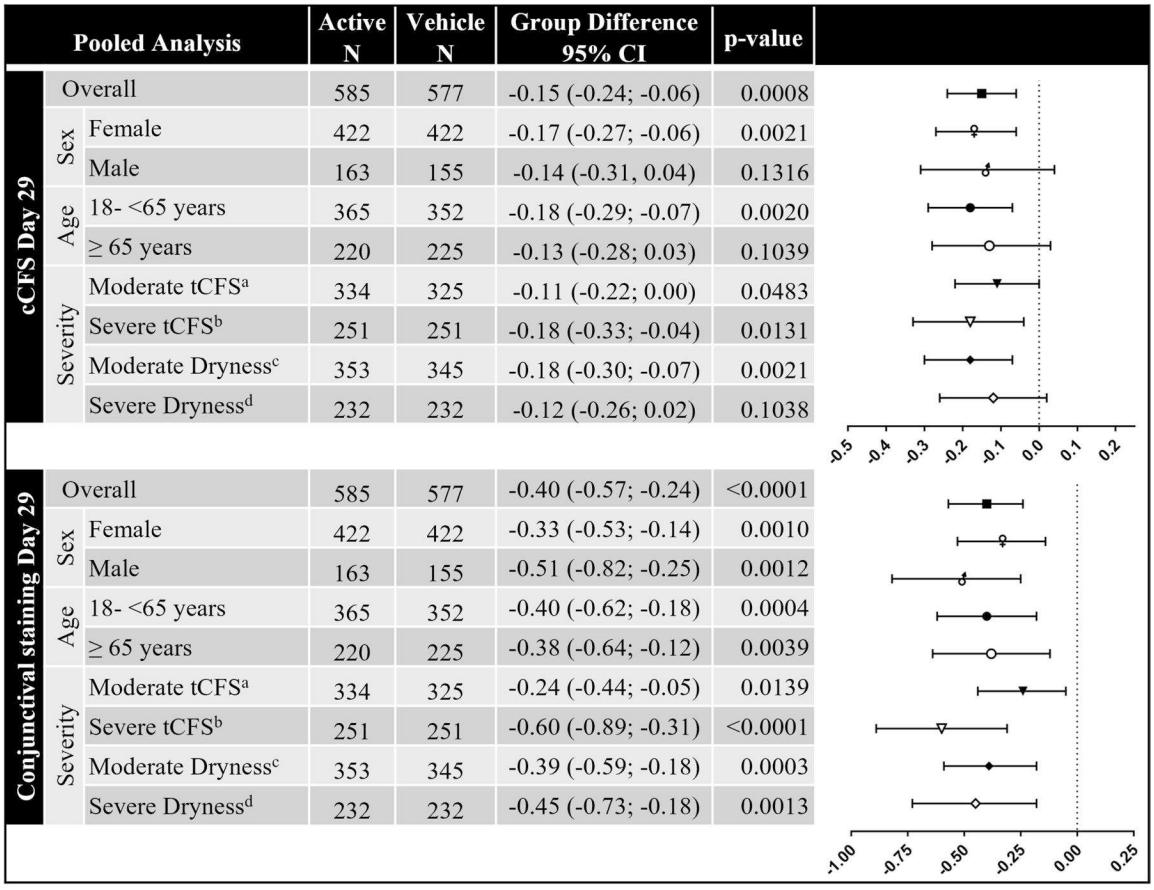
treatment, a strategy called "induction to maintenance" or the "bridging approach". In the current treatment landscape, this approach has two potential advantages for patients: (1) faster onset of effect and (2) better tolerability. Corticosteroids address ocular inflammation rapidly and effectively. Their use, however, is limited to short term treatment due to potential side effects; namely, increased IOP and increased risk of cataract development [35]. The fast onset of effect, combined with the good tolerability of the herein investigated water-freeciclosporin-solution-formulation may obviate the need for bridging ciclosporin treatment with topical corticosteroids, thereby sparing steroids and addressing an important medical need.

The presented analysis further demonstrated efficacy across multiple patient subgroups based on age, gender, baseline severity of corneal staining and baseline severity of symptomatology. Regardless of which criterion was applied to define DED severity, patients with moderate and

Table 2 Proportion of responders in tCFS ≥ 3 improvement on NEI scale and cCFS ≥ 1 improvement on NEI scale at Day 29

	n (Ciclosporin/Vehicle)	% Responder		Difference of PMP* (CI)	*p*-value
		Ciclosporin 0.1%	Vehicle		
tCFS ≥ 3					
Female	406/411	67.0%	52.6%	14.44% (7.79%, 21.09%)	< 0.0001
Male	160/149	65.0%	58.4%	6.61% (-4.22%, 17.44%)	0.2315
Age: 18- <65 years	355/339	70.1%	58.4%	11.73% (4.65%, 18.82%)	0.0012
Age: ≥ 65 years	211/221	60.2%	47.5%	12.68% (3.35%, 22.00%)	0.0077
Moderate tCFS score: 10–11	327/314	65.7%	54.1%	11.61% (4.07%, 19.15%)	0.0025
Severe tCFS score: 12–15	239/246	67.4%	54.1%	13.30% (4.69%, 21.91%)	0.0025
Moderate Dryness score < 75	339/334	69.6%	56.0%	13.63% (6.40%, 20.86%)	0.0002
Severe Dryness score ≥ 75	227/226	61.7%	51.3%	10.35% (1.27%, 19.43%)	0.0255
cCFS ≥ 1					
Female	406/411	64.5%	53.0%	11.49% (4.79%, 18.19%)	0.0008
Male	160/149	65.6%	60.4%	5.22% (-5.54%, 15.98%)	0.3416
Age: 18- <65 years	355/339	69.6%	59.9%	9.70% (2.62%, 16.78%)	0.0073
Age: ≥ 65 years	211/221	56.9%	47.5%	9.36% (-0.02%, 18.74%)	0.0505
Moderate tCFS score: 10–11	327/314	66.1%	55.7%	10.32% (2.80%, 17.84%)	0.0071
Severe tCFS score: 12–15	239/246	63.2%	54.1%	9.11% (0.39%, 17.84%)	0.0407
Moderate Dryness score < 75	339/334	66.1%	56.0%	10.09% (2.76%, 17.42%)	0.0070
Severe Dryness score ≥ 75	227/226	63.0%	53.5%	9.46% (0.42%, 18.50%)	0.0404

* PMP=predictive marginal proportions



[a]Moderate tCFS=10-11 score, [b]severe tCFS=12-15 score; [c]moderate Dryness < 75, [d]severe Dryness ≥ 75

Fig. 3 Forest Plot cCFS and conjunctival staining at Day 29.[a]Moderate tCFS = 10–11 score, [b]severe tCFS = 12–15 score, [c]moderate Dryness < 75, [d]severe Dryness ≥ 75

Table 3 Summary of adverse events

All Adverse Events (number of patients/percentage)	Ciclosporin 0.1% ($N=585$)	Vehicle ($N=577$)	All patients ($N=1162$)
TEAE	117 (20.0%)	117 (20.3%)	234 (20.1%)
SAEs	2 (0.3%)	6 (1.0%)	8 (0.7%)
Treatment discontinuation due to an AE	5 (0.9%)	3 (0.5%)	8 (0.7%)
Ocular AEs			
Ocular TEAE	77 (13.2%)	76 (13.2%)	153 (13.2%)
Ocular TEAEs occurring in more than 2% of patients			
Instillation site pain/pruritus	47 (8.0%)	39 6.8%)	86 (7.4%)
Mild	46 (7.9%)	38 (6.6%)	84 (7.2%)
Moderate	1 (0.2%)	1 (0.2%)	2 (0.2%)
Severe	0	0	0
Visual acuity reduced (temporally)	12 (2.1%)	16 (2.8%)	28 (2.4%)

severe DED treated with the water-free ciclosporin 0.1% solution experienced a similar magnitude of improvement compared to vehicle across all ocular surface staining outcomes demonstrating efficacy for a wide range of patients with aqueous deficient DED. This is important as some approved treatments have shown only effects in severe patients and therefore are approved to only treat severe DED [36]. The water-free ciclosporin, 0.1% solution was also efficacious across age groups and both female and male, though the difference in male did not always reach statistical significance which may be attributed to the smaller group size.

Limitations

Limitations of this pooled analysis include the post-hoc nature of the analysis and the relatively short duration of the included studies. As ESSENCE-2 was the second pivotal study, which was designed based on ESSENCE-1 outcomes, primary and key secondary endpoints of ESSENCE-2 were selected as endpoints for the current analysis as well to avoid bias. With regard to study duration, the ESSENCE-2 open label extension study provided additional long-term safety and long-term efficacy data for the product [37].

The ESSENCE-1 and ESSENCE-2 studies were conducted in different years with the latter being conducted during the COVID-19 pandemic and they differed related to their symptom inclusion criterion, which may limit the comparability of results. As baseline characteristics of both trials were similar reflecting moderate to severe predominantly aqueous deficient DED patients the pooling is well justified. Moreover, both studies showed very consistent results across sex, age, and baseline severity of disease.

Conclusion

There is a high unmet need for effective treatments with better tolerability and earlier onset of effect to better serve moderate to severe DED patients not responding to first line therapies such as artificial tears. The novel water-free ciclosporin 0.1% formulation addresses several unmet medical needs: The fast onset of effect, combined with good tolerability may obviate the need for bridging ciclosporin treatment with topical corticosteroids and thereby further contributing to the overall safety of patient treatment.

Author contributions Concept, design and interpretation: S Krösser, JD Sheppard, EK Akpek, T Kaercher; statistical analyses: A Hamm; T Kaercher and S Krösser had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declarations

Ethical approval - Research involving human participants All procedures were in accordance with the ethical standards and principles of the Declaration of Helsinki and its later amendments and approved by a properly constituted IRB (Alpha IRB, San Clemente, CA) per the International Conference on Harmonization (ICH) and applicable local regulatory requirements and laws.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest T Kaercher is a member of the supervisory board of Novaliq and did not receive funding to assist with the preparation of this manuscript, JD Sheppard and EK Akpek are consultants to Novaliq. A Hamm is employee of SDC, the company that did the statistical analysis in these studies, as consultant for Novaliq. S. Krösser is an employee of Novaliq.

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