Efficacy and Safety of Artificial Tears Containing Lipidure and Hypromellose for the Treatment of Moderate Dry Eye Disease in Contact Lens Wearers

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Research Article

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Abstract

Purpose: Dry eye disease (DED) involves up to 50% of the global population. The present study compared efficacy, tolerability and safety of the novel Respilac artificial tears containing Lipidure and hypromellose (HPMC) to the widely used Nextal artificial tears, HPMC-based, for the treatment of moderate DED in contact lenses (CL) wearers.

Methods: In a prospective, single-center, randomized investigation, 30 patients aged ≥18 years, diagnosed with moderate DED and wearing CL were randomly assigned to Respilac (n=15) or to Nextal group (n=15). Patients self-administrated one drop of Respilac or Nextal in both eyes 3-times daily for 21 days. Changes in endpoints (Visual Analogue Scale (VAS) score for ocular tolerability, Symptom Assessment iN Dry Eye (SANDE) score, Non-Invasive First Break-Up Time (NIF-BUT) results, Tear analysis value, Meibography results, CL tolerability results were investigated, comparing treatment groups and time-points evaluations. Adverse events (AEs) were also recorded and evaluated.

Results: VAS scores decreased with time ($p<0.001$) in both groups showing no statistically significant difference among them ($p=0.13$). Improvements were also detected, from screening to end-of-treatment, by SANDE scores for severity and frequency ($p<0.001$) and by Tear analysis results ($p<0.001$) with no observed difference between Nextal and Respilac arm. NIF-BUT, Meibography and CL tolerability values showed to be non-significantly affected by treatment nor by time. No AEs were detected.

Conclusion: According to the study results, Respilac showed to be effective, safe and well-tolerated for the treatment of moderate DED in CL wearers. Lipidure-based ophthalmic solution resulted not inferior to the currently used Nextal.

Introduction

The most common problem associated with contact lens wear is the development of dry eye disease accounting for about 50% of contact lens wearers [1–3]. A recent review from the Tear Film & Ocular Surface Society Dry Eye Workshop (TFOS DEWS II) Committee estimated that the prevalence of DED ranged from 5 to 50% of the global population, both contact lens wearers and no-wearers, showing an increase with age especially in female and Asian [4, 5].

Dry eye is a multifactorial disorder of the tear film and of the interpalpebral ocular surface, resulting in ocular discomfort, visual disturbance and tear film instability. According to the TFOS DEWS II report, DED is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface [5, 6] and the main recognized etiological subtypes are tear evaporation, tear hyposecretion or their combination [5, 7].

DED is a chronic or intermittent condition characterized by symptoms of burning, redness, pruritus, itching, photosensitivity, visual blurring and foreign body sensation [8, 9]. Environmental factors, infections, endogenous stress, exposure to antigens, drugs and genetics are examples of the main risk

factors triggering this disorder [8–10]. The prolonged use of computer screens (e.g., computers, tablets, smart phones) and the use of contact lenses can lead to the common symptoms of dry eye [9, 11, 12]. In particular, the use of contact lenses can influence the tear evaporation rate, resulting in a greater incidence of DED [1, 13].

In addition, during the current coronavirus disease-2019 (COVID-19) pandemic, an increasing report of eye dryness and ocular disorder has been observed in face-mask wearers, leading the scientists from the Centre for Ocular Research & Education (CORE), Waterloo, Canada to define the mask-associated dry eye (MADE) condition [14, 15]. Besides increasing DED incidence, MADE condition can also aggravate symptoms in patients with pre-existing dry eye disease [14, 16]. Since the use of face-masks was made mandatory in many countries to counter the spread of COVID-19, it is critical to improve dry eye symptoms to not discourage people from wearing face-masks. On the other hand, subjects who are forced to wear masks for a long time (health workers, school workers, students, etc.) prefer the use of contact lenses rather than glasses to avoid fogging of the lenses which forces them to frequent and difficult cleansing.

The management of DED relies on a step-wise approach depending on its severity and cause [8]. The first line includes the removal of aggravating factors (e.g. smoke, prolonged screen viewing) and modification of environment conditions (e.g. more humidity setting), followed or associated with the application of topical ocular lubricants such as artificial tears, gels and ointments. WhenWhen the disease is more severe, further approaches include the administration of topical corticosteroids and anti-inflammatory therapies, topical antibiotics, or systemic use of antioxidants and the surgical punctual occlusion treatment [8, 9].

Artificial tears, that represents the mainstay for mild-to-moderate DED, are aqueous solutions containing polymers, electrolyte, solutes, and in some cases preservatives. In particular, the polymers used in dry eye lubricants, due to their viscosity characteristics, can increase tear film stability, reduce ocular surface stress, improve the optical quality of the surface, thus contrasting eye desiccation [5, 17]. Most commercially available solutions contain cellulose derivatives like hydroxypropyl methylcellulose (Hypromellose; HPMC) and carboxymethylcellulose (CMC), polyvinyl derivatives, chondroitin sulfate, and sodium hyaluronate [17].

Natural tears contain a complex composition of water, salts, hydrocarbons, proteins, and lipids [18] that artificial tears cannot mimic, thus leading to the production of new formulations capable of reproducing the beneficial properties of natural tears.

Respilac (Sooft Italia Spa) is a preservative-free ophthalmic solution, containing Lipidure (2.0%) and HPMC (0.1%) as main components. Lipidure is a novel polymer ingredient with high hygroscopicity and moisture retention capability, consisting of 2-methacryloyloxyethyl phosphorylcholine (MPC). Lipidure has the potential to be an ideal candidate for artificial tears, as it is characterized by a high biological compatibility thanks to the properties of the phosphorylcholine group, a living organism-derived functional group. Preclinical studies confirmed the protecting power of Lipidure on both corneal epithelial

cells and contact lenses from drying damage [19, 20]. As reported by Ayaki et al., Lipidure-containing eye drops were tolerated by the ocular surface cells, in the same way as single doses of clinically approved drugs containing sodium hyaluronate. They caused neither severe cytotoxicity nor aberrant cell proliferation. Olivieri et al. demonstrated that the MPC-containing ophthalmic solution was as effective as hyaluronic acid, HPMC, and trehalose-based eye drop in the desiccation damage prevention.

The purpose of this clinical study was to demonstrate the non-inferiority of Respilac eye drops to widely used Nextal artificial tears (containing HPMC 0.3%, N-hydroxymethyl glycinate and other amino acids; Sooft Italia Spa) in the treatment of moderate DED in contact lenses wearers.

Materials And Methods

Study design

This was a post-marketing, prospective, single-center, randomized single-blind investigation performed at the Ophthalmic Clinic of Santa Marta Hospital, Catania from January 2020 to February 2020. The study was conducted in accordance with the Declaration of Helsinki, good clinical practice and all applicable regulatory requirements. Patients provided informed consent before undertaking any treatment-related procedures.

Inclusion and exclusion criteria

Patients eligible for the study had age ≥ 18 years; were diagnosed with moderate dry eye - grade 1 or 2 according to the DE severity level table proposed by the report of the Diagnostic Methodology Subcommittee of the International Dry Eye Workshop and modified according to Sullivan et al. [21] for at least 6 months; wore contact lenses; had DED signs and symptoms at least in one eye; had best corrected distance visual acuity (BCDVA) ≥ 0.1 decimal units in both eyes at the screening visit. Patients were excluded from the study if they had medium-severe dry eye - grade 3 or 4 according to modified DE severity table; had BCDVA < 0.1 decimal units in both eyes at the screening visit; had active ocular infection in both eyes; had history or presence of ocular surface disorders or eyelid abnormality unrelated to dry eye in both eyes; had eye surgery in both eyes within the 90 days before enrollment; presented clinical conditions that could significantly alter the efficacy or evaluation of the medical device under investigation; had hypersensitivity and/or allergy to any of the investigational products; were enrolled in concomitant trial; were taking ocular products for the treatment of eye disorder or were taking topical cyclosporine, topical corticosteroids or any other drugs for the treatment of dry eye in both eyes within the 30 days before the screening visit. Female patients who were breastfeeding or pregnant at screening visit or refused to use a highly effective method of contraception were not eligible for the investigation.

Objective and endpoints

The primary objective of the study was to evaluate whether Respilac was not inferior to Nextal in terms of safety, tolerability, and efficacy in the treatment of dry eye in contact lenses wearers. The secondary objectives included assessing the efficacy and safety of the treatment with Respilac.

Endpoints, related to the primary and secondary objectives of the study, were visual analogue scale (VAS) score for ocular tolerability; Symptom Assessment iN Dry Eye (SANDE) score; Non-Invasive First Break-Up Time (NIF-BUT) result; Tear analysis value; Meibography result; contact lenses (CL) tolerability results. Endpoints were evaluated according to protocol guideline at day − 3, day 0, day 7, day 14, day 21 and day 24.

Efficacy assessment. Foreign body sensation, burning/tingling, itching, pain, feeling of sticking, blurred vision, and photophobia were the parameters evaluated using a 100 mm VAS scale for the determination of ocular tolerability. The SANDE questionnaire utilized a 100 mm horizontal VAS scale to evaluate frequency and severity of symptoms related to dry eye disease [22, 23]. For the frequency score evaluation, ranged from “rarely” to “all of the time” while for the severity evaluation, score ranged from “very mild” to “very severe” [24]. For both VAS questionnaires for ocular tolerability and SANDE questionnaire, total VAS scores were reported as average scores (higher scores representing greater eye discomfort). NIF-BUT was measured using automated detection of first break-up, while the patients were asked to keep eyes open and to refrain from blinking. NIF-BUT was evaluated as the mean of three consecutive measures per eye [25]. Tear analysis value was assessed by meniscometry test, while changes in the meibomian gland were evaluate through images meibography and scored from 1 to 3 (Grade 1: mild; Grade 2: medium; and Grade 3: severe) [25–28].

Tolerability assessment. To assess CL tolerability, patients were instructed to record the daily number and level of discomfort events, according to a 4-points grading scale (0: normal, 1: mild, 2: moderate, 3: severe), on the ‘Patient Diary’ and to return the records to investigators.

Safety assessment. Patients were instructed to report to investigators any adverse event occurrence during treatment duration. Adverse events were also evaluated through slit lamp biomicroscopy. For sake of completeness, results of the Keratoscope analysis, Intraocular Pressure (IOP) test, and visual acuity test were also evaluated. Visual acuity and IOP were evaluated only at screening and day 21 [25].

Treatment and assessment

In this clinical investigation, patients were randomly assigned to Respilac or to the control group (Nextal) ophthalmic solution according to a randomization scheme provided by the website randomization.com. The treatment cycle duration was of 21 days. Patients were instructed to self-administer one drop of Respilac or Nextal (according to the assigned randomization code) in both eyes 3 times a day every 4h ± 1h. According to the protocol, patients underwent six clinical examinations. Patients performed: (i) screening visit (day − 3), scheduled three days before treatment initiation in order to allow the washout period using 3 days of saline-only eye drops; (ii) baseline visit (day 0), patients received randomization assignment and started the treatment; (iii) Follow-up 1 visit (day 7), 7 days after baseline ± 1, (iv) Follow-up 2 visit (day 14), 14 days after baseline ± 1, (v) Follow-up 3 visit (end of treatment, day 21), 21 days after baseline ± 1; (vi) last visit (day 24), 3 days after end of treatment for the washout period. No concomitant medications were allowed during the treatment period.

Statistical analysis

A preliminary correlation analysis using Pearson's Correlation Coefficient has been conducted between eyes on VAS, NIF-BUT, Tear Analysis and IOP. Variables with a significant correlation greater than 0.70 have been analyzed using the average of the right and left eye, otherwise both eyes were analyzed separately. Continuous variables were described by mean and standard deviation (SD) whereas categorical variables were listed as percentages, both by time and treatment. To investigate primary and secondary objectives, continuous variables were analyzed using a repeated measures mixed model, categorical variables (Meibography and CL Tolerability) by a repeated measures logistic regression analysis, reporting Odds Ratio (OR) with 95% Confidence Intervals (CI) [29, 30]. The models included terms for screening assessments, treatment, time, and treatment by time interaction. The studentized maximum modulus method for multiple adjustment was adopted. Outliers detected by the interquartile range (IQR) method were excluded from the analysis. Treatments comparisons between screening and 21 day time-point were assessed through unpaired t-test for IOP and Fisher's exact test for visual acuity analysis. All p-values were derived from two-sided statistical tests, considering p-value < 0.05 statistically significant. All analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Thirty patients diagnosed with moderate DED wearing contact lenses were enrolled into the study and treated according to randomization allocation (n = 15 in the Respilac arm, n = 15 in the Nextal arm). Subjects were followed for about one month (21 ± 3 days of treatment, 3 days of washout before and 3 days of washout after the treatment) and none of them discontinued the treatment.

Left and right eyes were significantly correlated for VAS and NIF-BUT with a correlation coefficient of r^2 = 0.88 ($p < 0.0001$) and r^2 = 0.78 ($p < 0.0001$), respectively. As the coefficient was greater than 0.70, the VAS and NIF-BUT average values for right and left eye were analyzed together whereas Tear analysis and the IOP values for right and left eyes were analyzed separately as their correlation coefficients were inferior to the fixed limit.

The results of the VAS analysis showed a significant decreasing trend with time ($p < 0.001$) starting from an overall mean (SD) value of 25.0 (7.5) at screening visit to 3.5 (3.1) detected at day 21. At screening assessment, mean (SD) values for Nextal and Respilac were 21.3 (5.4) and 28.8 (7.5) ($p = 0.13$) respectively, with a similar and not significant difference at any time-points. Overall, there was no significant difference between Nextal and Respilac ($p = 0.73$) (Table 1).

Table 1
VAS for ocular tolerability average scores for both eyes by time and treatment.

	Treatment, Mean (SD)			
Visit time (days)	**All patients N = 30**	**Nextal N = 15**	**Respilac N = 15**	**p-value[a]**
Screening (day − 3)	25.0 (7.5)	21.3 (5.4)	28.8 (7.5)	0.13
Day 0	25.4 (7.6)	21.5 (5.2)	29.3 (7.6)	0.07
Day 7	14.4 (4.7)	13.9 (4.2)	14.9 (5.3)	1.00
Day 14	7.1 (3.4)	7.5 (3.2)	6.6 (3.5)	0.78
Day 21	3.5 (3.1)	4.3 (3.2)	2.7 (2.9)	0.36
Day 24	4.4 (2.5)	4.2 (2.7)	4.6 (2.3)	1.00
Overall	13.3 (10.5)	12.1 (8.4)	14.5 (12.2)	0.73
Main effects: Treatment, p = 0.73, Time p < 0.001; pre-treatment VAS p < 0.001; Interaction: Treatment x Time, p < 0.001; *a* Adjusted for multiple comparisons.				

A secondary analysis comparing average screening values to the average values detected at the following time-points, showed a greater VAS reduction in the investigational product arm at any time-points, with a mean (SD) reduction of -24.2 (9.4) for Respilac and − 17.1 (6.4) for Nextal group at day 24, even if this difference was not statistically significant (p = 1.00).

The SANDE severity and SANDE frequency scores showed a similar significant decreasing trend with time from screening to day 24 (p < 0.001). The mean (SD) values for SANDE Severity decreased from 35.5 (13.4) to 11.3 (6.8) and from 55.3 (10.8) to 7.4 (5.7) for Nextal and Respilac group (p = 0.05), respectively. The mean (SD) value for SANDE Frequency reduced from 39.9 (13.4) to 11.4 (6.8) and from 60.1 (9.9) to 8.3 (6.7) for Nextal and Respilac (p = 0.02), respectively. Statistically significant differences between the two treatment arms were highlighted at day 14 (p = 0.03) and day 21 (p = 0.003) for SANDE severity and a significant treatments difference at day 21 (p < 0.001) and at day 24 (p = 0.001) for SANDE frequency (Fig. 1).

No statistically significant trend with time was observed in the average values of NIF-BUT (p = 0.61). No significant difference between treatment arms were observed at any time-points, nor in the overall comparison (p = 0.06). Respilac mean values slightly increased from screening visit to day 21 from a mean (SD) of 8.1 (0.6) up to 12.0 (0.5), while Nextal mean values slightly decreased, starting from a mean (SD) value of 10.8 (6.3) at screening to 8.8 (4.6) at day 21 (Table 2).

Table 2
NIF-BUT average values (seconds) for both eyes by time and treatment.

	Treatment, Mean (SD)			
Visit Time (Days)	**All patients N = 30**	**Nextal N = 15**	**Respilac N = 15**	**p-value[a]**
Screening (day − 3)	9.4 (4.6)	10.8 (6.3)	8.1 (0.6)	1.00
Day 0	9.2 (4.9)	10.7 (6.7)	7.6 (0.5)	0.94
Day 7	9.9 (2.7)	10.0 (3.7)	9.8 (1.1)	1.00
Day 14	10.2 (2.2)	9.0 (2.5)	11.3 (0.9)	0.75
Day 21	10.4 (3.6)	8.8 (4.6)	12.0 (0.5)	0.17
Day 24	9.2 (3.4)	7.7 (4.4)	10.8 (0.5)	0.23
Overall	9.7 (3.7)	9.5 (4.9)	9.9 (1.8)	0.06
Main effects: Treatment, p = 0.06, Time p = 0.61; pre-treatment NIF-BUT p < 0.001; Interaction: Treatment x Time, p < 0.001; *[a]* Adjusted for multiple comparisons.				

Data collected in the Tear analysis showed, for both right and left eyes evaluations, a statistically significant increase with time (p < 0.001), with no significant difference between treatments for any time-points comparisons; however, an overall significant treatment difference for both the right eye (p = 0.006) and the left eye (p = 0.03) was observed. Indeed, greater mean values of tear analysis for Respilac than Nextal, though non-significant, were recorded at any assessment time-points (Fig. 2).

Frequency distribution of Meibography scores were not significantly affected by treatment nor by time in both right-eye (p = 0.41) and the left eyes (p = 0.34) analysis. Overall, more than 90% of patients, for both right and left eyes assessments, had a score of 1 or 2 (mild to medium meibomian glands disease) at any time-points. Only one patient (6.7%) assigned to Nextal had a meibography score of 3 on pre-treatment and at the follow-up. In the Respilac arm, a score of 1 was assigned to 13 (86.7%) patients at day 14, 21 and 24 for both eyes, reaching the highest percentage of patients with grade 1 meibomian score. Overall, the Odds Ratios for a score of 2 or 3 vs 1 were OR = 3.0, 95%CI: (0.2–40.4) and OR = 3.6, 95% CI: (0.3–48.8) in favor of Nextal for the right and left eye, respectively (p = non-significative). Details were reported in Table 3.

Table 3
Meibography Analysis by time and treatment for right and left eye.

Right Eye				
		N (%)	**Treatment, N (col %)**	
Visit	**Score**	**All patients**	**Nextal**	**Respilac**
		N = 30	**N = 15**	**N = 15**
Screening (day − 3)	**1**	18 (60.0)	11 (73.3)	7 (46.7)
	2	11 (36.7)	3 (20.0)	8 (53.3)
	3	1 (3.3)	1 (6.7)	0
Day 0	**1**	16 (53.3)	8 (53.3)	8 (53.3)
	2	13 (43.3)	6 (40.0)	7 (46.7)
	3	1 (3.3)	1 (6.7)	0
Day 7	**1**	14 (46.7)	4 (26.7)	10 (66.7)
	2	16 (43.3)	11 (73.3)	5 (33.3)
	3	0	0	0
Day 14	**1**	19 (63.3)	6 (40.0)	13 (86.7)
	2	11 (36.7)	9 (60.0)	2 (13.3)
	3	0	0	0
Day 21	**1**	18 (60.0)	5 (33.3)	13 (86.7)
	2	12 (40.0)	10 (66.7)	2 (13.3)
	3	0	0	0
Day 24	**1**	17 (56.7)	4 (26.7)	13 (86.7)
	2	12 (40.0)	10 (66.7)	2 (13.3)
	3	1 (3.3)	1 (6.7)	0
Left eye				
	Score	**All patients**	**Nextal**	**Respilac**
		N = 30	**N = 15**	**N = 15**

Right eye. Main effects: Treatment, p = 0.41, Time p = 1.00; Interaction: Treatment x Time, p = 0.94.
Left eye. Main effects: Treatment, p = 0.34, Time p = 0.99; Interaction: Treatment x Time, p = 0.99.

Right Eye				
Screening (day − 3)	**1**	14 (46.7)	6 (40.0)	8 (53.3)
	2	16 (43.3)	9 (60.0)	7 (46.7)
	3	0	0	0
Day 0	**1**	13 (43.3)	6 (40.0)	7 (46.7)
	2	17 (56.7)	9 (60.0)	8 (53.3)
	3	0	0	0
Day 7	**1**	15 (50.0)	4 (26.7)	11 (73.3)
	2	15 (50.0)	11 (73.3)	4 (26.7)
	3	0	0	0
Day 14	**1**	18 (60.0)	5 (33.3)	13 (86.7)
	2	10 (33.3)	8 (53.3)	2 (13.3)
	3	2 (6.7)	2 (13.3)	0
Day 21	**1**	19 (63.3)	6 (40.0)	13 (86.7)
	2	10 (33.3)	8 (53.3)	2 (13.3)
	3	1 (3.3)	1 (6.7)	0
Day 24	**1**	18 (60.0)	5 (33.3)	13 (86.7)
	2	11 (36.7)	9 (60.0)	2 (13.3)
	3	1 (3.3)	1 (6.7)	0
Right eye. Main effects: Treatment, p = 0.41, Time p = 1.00; Interaction: Treatment x Time, p = 0.94.				
Left eye. Main effects: Treatment, p = 0.34, Time p = 0.99; Interaction: Treatment x Time, p = 0.99.				

The CL Tolerability analysis showed a decreasing trend from day 1 to day 21 in the total number of events per patient, with a discomfort level equal or superior to grade 1 (p = 0.43). In addition, CL tolerability evaluations resulted to be not significantly affected by treatment group (p = 0.80) (Table 4).

Table 4
Contact Lenses Tolerability: Total events (grade ≥ 1) by time and treatment

		Treatment, Total No. of events	
Visit time (days)	**All patients N = 30**	**Nextal N = 15**	**Respilac N = 15**
Day 1	14	9	5
Day 7	6	3	3
Day 14	8	5	3
Day 21	4	3	1
Main effects: Treatment, p = 0.80, Time p = 0.43; Interaction: Treatment x Time, p = 0.92.			

In the IOP analysis, no statistically significant differences were observed between the two treatment arms for both the right and left eyes assessments. For the right eye, a decrease in the mean (SD) value of -0.57 (1.22) mmHg was detected from screening to day 21 in the Nextal treatment compared to an increase of 0.13 (2.07) mmHg in Respilac treatment (p = 0.28). For the left eye, both treatment arms showed a non-significant decrease from screening to day 21 of -0.86 (1.74) mmHg and − 0.07 (2.09) mmHg for Nextal and Respilac, respectively (p = 1.00).

Overall, visual acuity analysis for both left and right eyes detected only three unique values (0.8, 0.9 and 1.0). Right eye visual acuity did not change at 21 days compared to pre-treatment for neither Nextal nor for Respilac while left eye visual acuity did not increase significantly (p = 1.00) from 0.9 to 1.0 at 21 day for one patient randomized to Nextal.

No adverse events were reported by patients during the assessment visits. This result was also confirmed by negative values at all the assessment time-points and in both treatment groups detected through keratoscope analysis and slit lamp biomicroscopy.

Discussion

The results of the present study demonstrated that ophthalmic solution Respilac was not inferior to the ophthalmic solution currently in use Nextal, in terms of safety, tolerability, and efficacy in the treatment of moderate DED in people wearing contact lenses.

The results of the ocular tolerability VAS analysis showed a significant decreasing trend with time in both groups, with non-significant difference between Nextal and Respilac. However, a significant difference was found between Respilac and Nextal when comparing with pre-treatment in favor of Respilac at all time-points. These results confirm the primary outcome of the study, i.e. Respilac is not inferior to Nextal

in terms of safety, tolerability, and efficacy. In addition, Respilac showed to have a greater VAS reduction trend compared to Nextal, even if this difference was not statistically significant. Both SANDE questionnaires analysis showed a decrease in the frequency and severity of dry eye symptoms with time after the treatment with Respilac or Nextal, confirming efficacy of both solutions in the treatment of DED. Moreover, Respilac seems to lead to better results than Nextal especially after 14–21 days of treatment. Regarding Tear analysis, Respilac was confirmed as a non-inferior treatment to Nextal and as an effective treatment for DED. Although the collected data showed a “normal” tear meniscus height, ranging between 0.2 and 0.5 mm [27], the present analysis detected a significant increasing trend with time with no significant difference between treatments.

On the other hand, NIF-BUT showed a non-significant trend with time, neither for Nextal nor for Respilac. However, all the values obtained in both the treatment groups were around 10 seconds, which is the threshold value to diagnose a tear film instability [28, 31]. For this reason, it could be assumed that the use of Respilac and Nextal contributed to maintain a rather constant NIF-BUT value over time. In both randomized arms, meibography scores were not significantly affected by treatment nor by time. Even in this case, it could be assumed that the use of Respilac and Nextal allowed to improve the Meibography score over time, or, as a minimum, to keep it constant. The tolerability of Respilac was evaluated also by means of CL tolerability analysis, showing an overall decreasing trend in the number of events from day 1 to day 21.

Concerning safety, both Respilac and Nextal eye drops presented an excellent safety profile as the results obtained through keratoscope analysis were “negative” at all the time-points and in both treatment’s group and no adverse events were reported by patients for the entire study duration.

The present study demonstrated, for the first time in a clinical trial, that the novel Respilac ophthalmic solution, containing Lipidure, is safe and effective in the treatment of moderate DED in contact lenses wearers. The data collected in this investigation showed the protective value of Lipidure from eye desiccation damage, probably due to its hydrating characteristics, as already observed in preclinical studies [19, 20].

Up to now, artificial tears containing HA, HPMC and CMC have been considered as the medical devices directed to the treatment of DED which provide the greatest comfort results [17, 32]. Thus, by demonstrating the non-inferiority of Respilac compared to an extensively used HPMC artificial tear (Nextal), it can be assumed that even the MPC plus HPMC containing eye drops could be considered an effective device for the treatment of moderate dry eye.

Both subjective and objective parameters were collected and analyzed. In our study, patient-reported symptoms by VAS and SANDE questionnaires and clinical signs evaluated according to NIF-BUT and Meibography showed an overall lack of concordance. These results are in agreement with previous published studies [33, 34] reporting no correlation between signs and symptoms of DED. These observations can be explained by the deep impact of DE symptoms, rather than signs, has on the quality of life (QoL) of patients and, in particular, on the vision-related QoL [35, 36]. Foreign body sensation,

burning, itching, pain, feeling of sticking, blurred vision, and photophobia represent a limitation in everyday life aspects, especially in vision-related activities like reading, driving and working at the computer. Therefore, in addition to clinical examinations, it is also important to assess patients' symptoms and QoL scores in order to better assess patients' responses to treatment.

The limits of the present investigation are represented by the small cohort of patients and by the short-term follow-up. Further studies with a larger sample size are needed to soundly demonstrate the efficacy of Respilac in the treatment of DED. Since dry eye is a chronic or intermittent condition disease [9], studies with longer on-treatment duration and post-treatment phase would allow a more accurate examination of the safety profile of this device.

In conclusion, the present study shows that Respilac is effective, safe and well-tolerated, as well as a currently used HPMC ophthalmic solution, for the treatment of moderate dry eye disease in subjects that wear contact lenses.

Declarations

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Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Catania1 “Gaspare Rodolico” Catania (Date 26/07/2019).

Consent to participate: Written informed consent was obtained from each subject prior to evaluations performed for eligibility

Consent for publication: Not applicable

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Figures

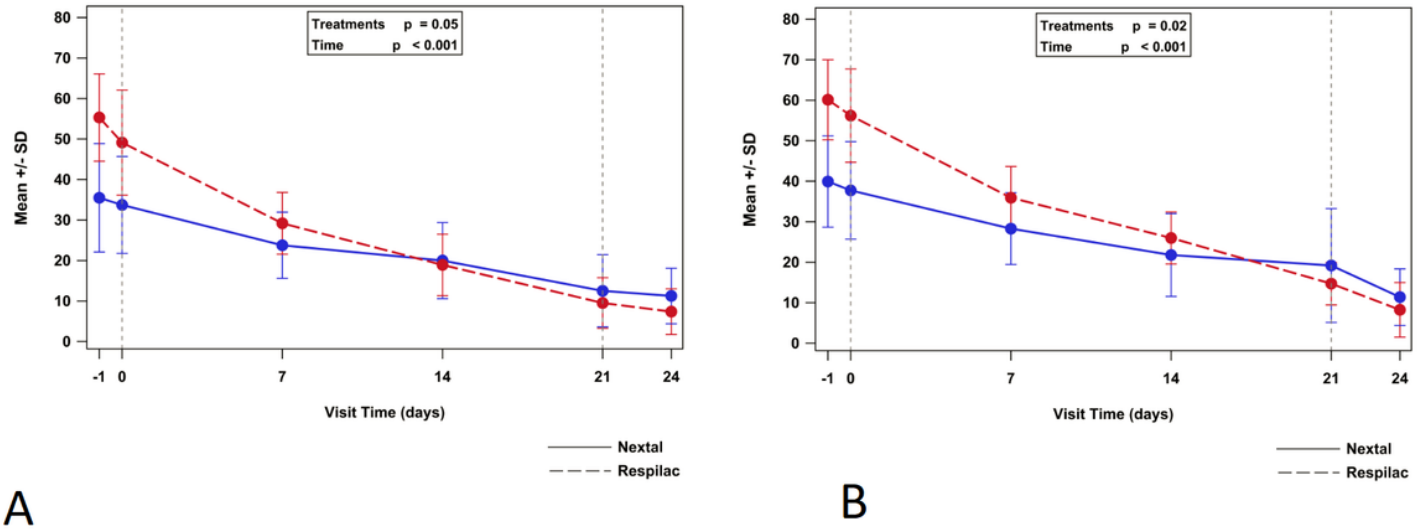

Figure 1

Trend for SANDE Severity (A) and SANDE Frequency (B). *p-value <0.05 in the comparison between Respilac and Nextal ophtalmic solutions.

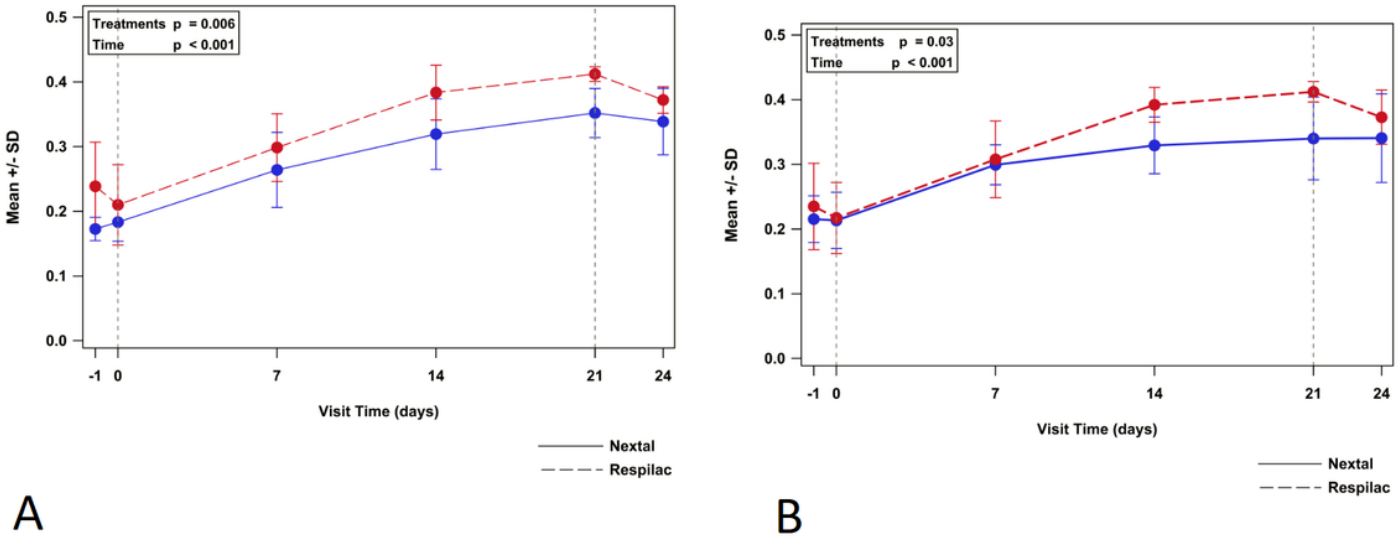

Figure 2

Trend for Tear analysis mean values (mm) for right (A) and left (B) eye.