Demonstration of Efficacy in the Treatment of Dry Eye Disease with 0.18% Sodium Hyaluronate Ophthalmic Solution (Vismed, Rejena)

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• PURPOSE: To evaluate the efficacy and safety of 0.18% sodium hyaluronate ophthalmic solution (Rejena, Vismed) compared with its vehicle for the treatment of signs and symptoms of dry eye disease.
• DESIGN: Randomized, placebo-controlled clinical trial.
• METHODS: A total of 444 subjects with dry eye disease were randomized 1:1 to active study drug (n = 221) or vehicle control (n = 223) in this multicenter, double-masked trial. Subjects instilled 1 to 2 drops, 3 to 6 times daily for 14 days, with evaluations at Days 7 and 14. The study's 2 primary efficacy endpoints were change from baseline at Day 7 in lissamine green staining scores (objective) and in global symptom frequency scores (subjective). Results were analyzed using Wilcoxon rank sum test and Student *t* test in the intent-to-treat (ITT) population with last observation carried forward (LOCF).
• RESULTS: At Day 7, the differences between the active and vehicle groups in change from baseline for lissamine green staining score ($P = .050$, Wilcoxon; $P = .029$, *t* test) and global symptom frequency score ($P = .050$, Wilcoxon; $P = .017$, *t* test) were both statistically significant. There were no clinically relevant safety findings related to the use of Rejena.
• CONCLUSIONS: This study demonstrated the clinical efficacy of Rejena in the treatment of dry eye disease in both a primary objective endpoint and a primary subjective endpoint when compared to its vehicle. The study results also supported the well-known safety profile of Rejena. (Am J Ophthalmol 2010;149:594–601. © 2010 by Elsevier Inc. All rights reserved.)

DRY EYE DISEASE IS A COMMON CLINICAL PROBLEM, with an estimated prevalence of 5% to 30% at various ages.[1] It is a multifactorial disease resulting in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface, and it is frequently accompanied by increased osmolarity of the tear film and subsequent inflammation of the ocular surface.[2] The tear film of the eye normally serves to nourish the ocular surface, provide lubrication between the eye surface and the lids, and act as the anterior refracting surface of the eye. It is thought to consist of an aqueous gel with mucin content decreasing in a gradient from the ocular surface to the undersurface of the outermost lipid layer. The lipid layer interacts with the underlying aqueous and mucin components, retarding evaporative loss of aqueous tears and contributing to the stability of the tear film between blinks.[3]

Goals for treatment of patients with dry eye disease are to improve the patient's ocular comfort and quality of life and to return the ocular surface and tear film to the normal homeostatic state.[4] Current therapies for the management of dry eye include therapies for tear supplementation, retention, and stimulation; anti-inflammatory agents; and environmental strategies.[4]

A patented formulation of 0.18% sodium hyaluronate ophthalmic solution is currently marketed in Europe and Asia alternatively under the brand names Vismed, Vislube, and Hylovis (TRB Chemedica AG, Haar/München, Germany), and is under development for the treatment of dry eye disease in the United States under the recently approved trade name Rejena. Hyaluronic acid occurs naturally in all vertebrates in the vitreous body of the eye, extracellular matrix of the skin, and synovial fluid. It is a biopolymer of disaccharide units composed of N-acetylglucosamine and glucuronic acid in linear chains of varying molecular weights. The sodium salt of hyaluronic acid, sodium hyaluronate (SH), is the active ingredient in this proprietary formulation of sodium hyaluronate ophthalmic solution. It is currently also used as an active ingredient in other medicinal products and medical devices, especially in ocular surgery involving the anterior or posterior segment of the eye, where it is used to maintain the shape of the globe, to cover surgical instruments, and to protect the sensitive corneal endothelium from further surgical damage. The unique viscoelastic properties of SH allow it to behave differently during and between blinks.[5,6] During blinks, SH molecules align with each other, resulting in an elastic and relatively nonviscous solution that spreads easily over the surface of the cornea. Between blinks, SH molecules form a tangled meshwork, resulting in a less elastic and more viscous solution that stabilizes the pre-

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TABLE 1. Study with Sodium Hyaluronate 0.18% Ophthalmic Solution: Schedule of Event

Evaluation	Screening Days -7 to -5	Baseline Day 0	Day 7 ± 1	Day 14 ± 1	Telephone Safety Follow-up: Day 21 ± 3
Signed informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographics	X				
Medical history	X	X[a]			
Ocular history	X	X[a]			
Symptom intensity grading with VAS	X	X	X	X	
Symptom frequency rating	X	X	X	X	
Rating of impact of dry eye on daily life		X	X	X	
Best-corrected visual acuity	X	X	X	X	
Corneal fluorescein staining[b]	X	X	X	X	
Lissamine green staining	X	X	X	X	
Slit-lamp examination	X	X	X	X	
Schirmer I test		X	X	X	
Intraocular pressure[c]		X	X	X	
Dilated fundus examination	X			X	
Urine pregnancy test[d]	X			X	
Randomization		X			
Drug administration		X			
Drug accountability		X	X	X	
Adverse event assessment		X	X	X	X
Prior/concomitant med assessment	X	X	X	X	

VAS = visual analog scale.

[a]Brief review.

[b]Corneal fluorescein staining of the cornea preceded lissamine green staining. The procedures were separated by at least 15 minutes.

[c]Intraocular pressure was the last ophthalmic procedure to be performed except for at screening and Day 14, when it directly preceded the dilated fundus examination.

[d]Only female subjects of childbearing potential who are not postmenopausal (≥1 year), or are not surgically sterilized.

corneal tear film and maximizes the residence time of the solution on the surface, enabling it to lubricate and protect the ocular surface. Additionally, SH exhibits water entrapping and mucoadhesive properties that increase its retention time on the eye surface.[7–9]

Ten clinical efficacy and safety studies have been conducted with 0.18% sodium hyaluronate ophthalmic solution in which the safety and efficacy in short- and long-term clinical use have been established. However, confirmatory efficacy and safety studies in which improvement in a sign and a symptom occur simultaneously in a single study were not available. The purpose of this Phase 3 study was to confirm, as primary endpoints of efficacy, previously reported secondary endpoints in staining and symptoms from a study by Baeyens and associates (Baeyens, unpublished poster, ARVO annual meeting 2004). The tactic applied was to compare the efficacy and safety of 0.18% sodium hyaluronate ophthalmic solution with vehicle in subjects with dry eye disease. In particular, the superiority of the drug product was studied in both a primary objective endpoint (lissamine green staining score) and a primary subjective endpoint (global symptom frequency score).

METHODS

THIS PHASE 3, MULTICENTER, RANDOMIZED, PLACEBO-CONtrolled, double-masked clinical trial was conducted at 15 sites in the United States. Trial design specifications, including the duration of treatment, were created with the assistance of the Food and Drug Administration (FDA) via a Special Protocol Assessment. The trial started on December 13, 2006, and was completed on May 22, 2008.

For inclusion, subjects had to be ≥18 years of age with at least a 3-month documented history of dry eye in both eyes diagnosed as dry eye syndrome, keratoconjunctivitis sicca (KCS), or dry eye due to Sjögren syndrome (immune exocrinopathy). At screening and baseline visits, subjects had to experience at least 2 symptoms of dry eye (soreness, scratchiness, dryness, grittiness, and burning) rated as ≥2

TABLE 2. Study with Sodium Hyaluronate 0.18% Ophthalmic Solution: Summary of Disposition and Demographic Data

	Active (N = 221)	Vehicle (N = 223)	Overall (N = 444)
Disposition			
Completed the study	217 (98.2%)	219 (98.2%)	436 (98.2%)
Subjects withdrawn early	4 (1.8%)	4 (1.8%)	8 (1.8%)
Reason for early withdrawal			
Subject withdrew consent	1 (0.5%)	2 (0.9%)	3 (0.7%)
Lost to follow-up	1 (0.5%)	1 (0.4%)	2 (0.5%)
Adverse event	2 (0.9%)	1 (0.4%)	3 (0.7%)
Demographics			
Age (y), Mean (SD)	60.7 (12.6)	62.2 (14.8)	61.5 (13.7)
Gender, N (%)			
Male	49 (22.2%)	62 (27.8%)	111 (25.0%)
Female	172 (77.8%)	161 (72.2%)	333 (75.0%)
Ethnicity, N (%)			
Hispanic or Latino	17 (7.7%)	14 (6.3%)	31 (7.0%)
Not Hispanic or Latino	204 (92.3%)	209 (93.7%)	413 (93.0%)
Race, N (%)			
White	192 (86.9%)	188 (84.3%)	380 (85.6%)
Black/African American	20 (9.0%)	30 (13.5%)	50 (11.3%)
American Indian/Alaskan Native	1 (0.5%)	0	1 (0.2%)
Asian	3 (1.4%)	2 (0.9%)	5 (1.1%)
Other	5 (2.3%)	3 (1.3%)	8 (1.8%)

N = number of subjects in the ITT population in each treatment group, which is used as the denominator for all percentage calculations.

("often") on the symptom frequency scale and scored as ≥50 mm on the 0- to 100-mm visual analog scale (VAS) in the same eye. Additionally, subjects had to demonstrate objective parameters of dry eye at baseline and screening visits of corneal fluorescein staining total score of ≥3 and lissamine green staining total score of ≥3. Subjects were excluded if they had undergone ocular surgery (of any type, including laser surgery) or ocular trauma within the 4 months prior to screening, had punctal occlusion or diathermy within 3 months prior to screening, had abnormality of the nasolacrimal drainage apparatus, had any active inflammation of the eye not attributable to KCS (eg, iritis, scleritis, etc), or had other diseases or characteristics judged by the investigator to be incompatible with the assessments needed in the study or with reliable instillation of the study drug.

This study was double-masked; the treating physician, site personnel, and subjects were masked as to treatment assignment. The packaging of the study drug (active and vehicle) was identical, and each monodose unit was labeled with the study number and a codified lot number to avoid potential identification of the product by site personnel or subjects.

The screening visit occurred between Days -7 and -5 to allow a minimum 5-day run-in period prior to entry into the study. Subjects who met the eligibility criteria discontinued the use of all artificial tears and were given a supply of vehicle eye drops with instructions to instill 1 to 2 drops per eye at least 3 times and up to 6 times daily during the run-in period. Subjects discontinued the use of the vehicle eye drops at least 4 hours prior to the assessments performed at Day 0 (baseline). Subjects who continued to meet eligibility criteria at the baseline (Day 0) visit were randomized 1:1 to receive active study drug (0.18% sodium hyaluronate ophthalmic solution) or its vehicle (identical to active study drug except lacking sodium hyaluronate). Subjects were randomized by assigning each consecutive subject to the lowest numbered study kit provided to the study center. The kit numbers were assigned according to a block randomization list generated by an independent statistician. After randomization, subjects were given an adequate supply of their assigned study drug (active or vehicle) for the entire 14-day treatment period, with instructions to instill 1 to 2 drops per eye at least 3 times and up to 6 times daily during that time period. Subjects returned to the clinical site at Days 7 and 14 for efficacy and safety evaluations (see Table 1, Schedule of Events), which were performed in the study eye and the fellow eye. The study eye was defined as the eye with the worse Schirmer I score at baseline; if both eyes were equal, the right eye was designated at the study eye. Follow-up safety evaluations were conducted at Day 21 via a telephone interview unless the subject experienced an adverse event

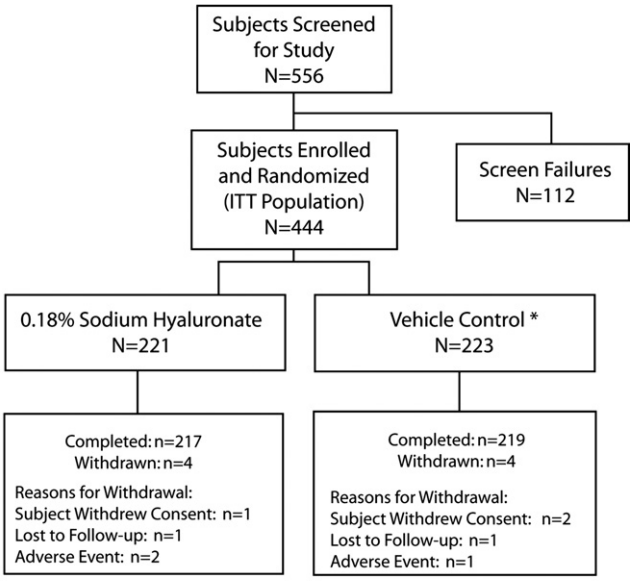

FIGURE 1. Overview of subject disposition in the study of 0.18% sodium hyaluronate for dry eye disease.

(AE), in which case the subject was asked to return to the clinical site for Day-21 assessments.

The study had 2 primary efficacy endpoints. The primary objective efficacy endpoint (sign) in the study eye was the change from baseline at Day 7 in lissamine green staining of the cornea, nasal conjunctiva, and temporal conjunctiva, with each graded on a 0 to 4 scale (0 = 0%; 1 = 1%-15%; 2 = 16%-30%; 3 = 31%-45%; 4 = >45%), for a maximum score of 12. Lissamine green staining was performed in both eyes using 1 drop of 1% lissamine green solution, with results observed in the low- to moderate-intensity white light of the slit lamp between 1 minute and 4 minutes following instillation. The primary subjective efficacy endpoint (symptom) was the change from baseline at Day 7 in the summed scores for global symptom frequency in both eyes (soreness, scratchiness, dryness, grittiness, and burning), with each rated on a 0 to 3 scale (0 = Never; 1 = Sometimes; 2 = Often; 3 = Constantly), for a maximum score of 15.

The primary efficacy endpoints were analyzed using Wilcoxon rank sum test as the primary statistical method and the Student *t* test as a supportive method. A 2-sided alpha level of .050 was used to determine statistical significance. To achieve study success, both primary endpoints were required to reach significance. The primary analysis of the endpoints for the study were conducted in the intent-to-treat (ITT) population (all randomized subjects, N = 444), using last-observation-carried-forward (LOCF) data including baseline data.

The secondary efficacy endpoints, analyzed by Student *t* test according to the statistical plan of the study, were the change from baseline in lissamine green staining scores at Day 14 in the study eye, the change from baseline in global symptom frequency scores at Day 14 in both eyes, the percentage change from baseline at Day 7 and Day 14 in corneal fluorescein staining in the study eye, Schirmer I testing, summed VAS symptom scores, composite index of global symptom intensity and global symptom frequency scores, and global impact of dry eye on daily life activities.

Safety assessments included slit-lamp examination, best-corrected visual acuity (BCVA), intraocular pressure (IOP), dilated fundus examination, and collection of AEs.

An interim analysis to re-estimate sample size was performed after 211 subjects (approximately 70% of the original planned sample size) completed Day-7 treatment. The masked interim analysis included the primary efficacy endpoints and was conducted by biostatisticians at The EMMES Corp (Rockville, Maryland, USA), who did not have access to the randomization code. The planned sample size of 300 subjects (150 per group) was increased to 440 subjects (220 per group) based on the greater-than-expected variability results of this masked interim analysis. All personnel connected with the trial (eg, sponsor, trial statistician, monitors, site) remained masked. The final analysis was performed after all subjects completed the 3-week study or discontinued.

RESULTS

SUBJECT DEMOGRAPHICS AND DISPOSITION ARE SUMMARIZED in Table 2 and Figure 1, respectively. A total of 444 subjects were enrolled and treated (active: n = 221; vehicle: n = 223). Of these, 333 subjects (75%) were female and the mean age (± SD) of all subjects was 61.5 ± 13.7 years. The randomized groups were similar with respect to age, gender, ethnicity, and race. The majority of subjects (436/444; 98.2%) completed the study and the proportion of subjects who withdrew early from study treatment was equal for the 2 treatment groups. A total of 3 subjects (active: 2/221 [0.9%]; vehicle: 1/223 [0.4%]) withdrew because of an AE. None of the subjects' treatment assignments were unmasked during the study.

The majority of protocol violations/deviations were failure to return study drugs on time and failure to complete a treatment-phase study visit within the window of time specified in the protocol. There were 270 cases of failure to return drug, and these were distributed evenly between the treatment groups (active: n = 133; vehicle: n = 137), with all occurrences among 208 of the subjects in the study. Among the violations cited, those for 178 subjects (active: n = 92; vehicle: n = 86) were reconciled by final collection of study drug at a visit other than the protocol-specified visit. The ITT population included all subjects enrolled in the study, including those for which protocol deviations were recorded. Of these protocol deviations, assessments performed outside the protocol-spec-

TABLE 3. Results for the Primary Objective and Subjective Endpoints at Day 7 With Sodium Hyaluronate 0.18% Ophthalmic Solution (Active) and Vehicle

Measure	Visit	Study Drug	Mean (SD)	*P* Value Student *t* Test[a]	*P* Value Wilcoxon Rank Sum Test	*P* Value van Elteren
Lissamine green staining	D0	Active	5.71 (2.421)	.413	.416	–
		Vehicle	5.52 (2.357)			
	D7	Active	−1.1 (2.01)	**.029**	**.050**	**.035**
		Vehicle	−0.7 (1.79)			
Global symptom frequency	D0	Active	8.33 (2.231)	.621	.387	–
		Vehicle	8.22 (2.470)			
	D7	Active	−1.7 (2.78)	**.017**	**.050**	**.045**
		Vehicle	−1.1 (2.62)			

D = day; SD = standard deviation.
[a]Student *t* test *P* values were confirmed by permutation test *P* values.
Bold values are statistically significant.

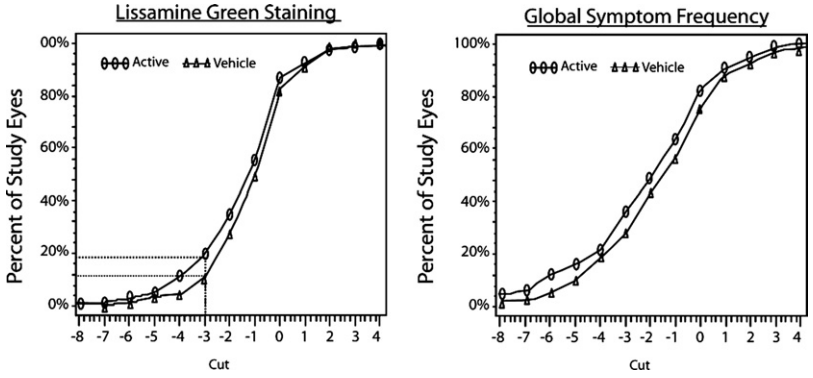

FIGURE 2. Cumulative distributions of primary endpoints in the study of 0.18% sodium hyaluronate for dry eye disease. Shown is the cumulative distribution of study eyes versus the change score from baseline ("cut") in the primary endpoints for active and vehicle-controlled subjects with dry eye disease. (Left) Proportion of study eyes at Day 7 with changes less than or equal to a change score or "cut" in lissamine green staining in study eye and fellow eye. (Right) Proportion of study eyes at Day 7 with changes less than or equal to a change score or "cut" in global symptom frequency.

ified range of days were reported for 61 subjects. The range of days outside the allowed time frame was 1 to 13 days (mean, 2.24 ± 2.65). Most of the out-of-window assessments were judged to be nondetrimental to the interpretation of the primary outcomes and the lissamine green staining and global symptom frequency scores for 2 subjects (active group) were interpreted with the application of LOCF.

LOCF was applied to the ITT population for any assessment that was missing at Day 7 or Day 14, including baseline values (ie, pretreatment values). For example, for lissamine green staining, LOCF was applied to missing values of 12 subjects at Day 7 (active = 6; vehicle = 6). Similarly, for global symptom frequency score at Day 7, LOCF was applied to missing values of 10 subjects (active = 5; vehicle = 5).

The results of the primary objective and subjective efficacy endpoints are summarized in Table 3. At Day 7, the difference in the change from baseline between the active and vehicle arms for lissamine green staining scores (objective) was statistically significant in the ITT population with LOCF using the Wilcoxon rank sum test (active: −1.1; vehicle: −0.7; $P = .050$) and the *t* test ($P = .029$). The decrease from baseline in lissamine green staining in the Rejena treatment group was 57% greater than the decrease in the vehicle group. At Day 7, the difference in the change from baseline between active and vehicle arms for the global symptom frequency score (subjective) was statistically significant for the ITT population with LOCF (active: −1.7; vehicle: −1.1; $P = .050$ [Wilcoxon]; $P = .017$ [*t* test]). The decrease from baseline in the global symptom score in the Rejena group was 54.5% greater than the decrease in the vehicle group.

P values were also calculated for both primary endpoints using the van Elteren test.[10] The van Elteren test is a version of the Wilcoxon test that employs adjustment for individual study sites in a manner that is comparable to a 2-way analysis of variance. As shown in Table 3, the van

TABLE 4. Study With Sodium Hyaluronate 0.18% Ophthalmic Solution: Results for Global Impact of Dry Eye on Daily Life at Day 7 and Day 14

Study Drug	% Reporting a Global Impact at Baseline	% Reporting Improvement by 1 or More Grades	
		Day 7	Day 14
Active	55.7%	40.3%	50.3%
Vehicle	53.4%	30.4%	43.4%

Elteren test *P* values were somewhat smaller than the corresponding unstratified Wilcoxon *P* values and were confirmatory of the observations found in the primary endpoints analyses.

To better understand the beneficial effect of treatment in the populations studied at Day 7, the cumulative distribution of the change score from baseline in the primary endpoints is provided in Figure 2. This figure shows the cumulative proportion of study eyes achieving a change score that reached a specified threshold or "cut" (ie, the number of scale units decreased from baseline). For example, in Figure 2 for lissamine green staining (Left), the active treatment group in the ITT population with LOCF showed 11% of the study eyes with a change score from baseline that is ≤ -4, while only 4.5% of the study eyes in the vehicle treatment group met this condition. Similarly, in the active treatment group, 19% of the study eyes achieved a lissamine green staining change score from baseline of ≤ -3, while that proportion was only 11% in the vehicle treatment group. Left and right panels in Figure 2 show that the distributions for the active group were all shifted to the left of their counterparts for the vehicle treatment group, indicating a higher proportion of eyes showing treatment effects of Rejena, both in a sign (lissamine green staining) and in a symptom (global symptom frequency score). These results are supportive of the observed statistically significant differences between active and vehicle treatments reported above.

The results of the secondary endpoints were analyzed by *t* test as prescribed in the statistical plan of the study. The secondary objective endpoints were lissamine green staining (Day 14), corneal fluorescein staining (Day 7 and Day14), and Schirmer test (Day 7 and Day 14). At Day 14, the change from baseline for lissamine green staining scores was statistically significant (active: −1.4; vehicle: −1.0; $P = .024$). There were no significant differences in the change from baseline for corneal fluorescein staining scores and Schirmer test between treatment groups at either time point.

The secondary subjective endpoints were global symptom frequency scores at Day 14, summed VAS symptom intensity scores, composite index of global symptom intensity and symptom frequency scores, and the global impact of dry eye on daily life at Day 7 and Day 14. There were no significant differences between treatment groups in changes from baseline for the global symptom frequency scores at Day 14 ($P = .314$). The summed VAS symptom intensity scores at Day 7 showed that the percent change from baseline was statistically significant (active: −22.81; vehicle: −14.91; $P = .030$) only at this time point. The composite index of global symptom intensity and symptom frequency scores at Day 7 showed a statistically significant percent change from baseline (active: −31.36; vehicle: −18.73; $P = .010$) only at this time point. The global impact of dry eye on daily life showed that at baseline, the majority of the subjects reported an impact of dry eye on their daily life (active: 55.7%; vehicle: 53.4%). Of those, approximately 30% more subjects in the Rejena group compared with the vehicle group reported an improvement of at least 1 grade at Day 7 (active: 40.3%; vehicle: 30.4%, Table 4), and approximately 16% more reported an improvement at Day 14 (active: 50.3%; vehicle: 43.4%, Table 4).

The safety population for this study included all subjects who were administered at least 1 dose of study drug (N = 443; active: n = 221; vehicle: n = 222). One subject in the vehicle treatment group withdrew consent prior to instilling the study drug, and therefore was excluded from the safety population analysis. Approximately 25% of subjects in each treatment group reported an AE (active: 57/221, 25.8%; vehicle: 48/222, 21.6%). The most frequent AEs in both treatment groups were dry eye (active: 18/221, 8.1%; vehicle: 14/222, 6.3%), eye pain (active: 13/221, 5.9%; vehicle: 7/222, 3.2%), and foreign body sensation (active: 5/221, 2.3%; vehicle: 7/222, 3.2%). There was 1 serious AE (SAE) reported in each treatment group. Both SAEs were considered unrelated to the study drug. Three subjects (active: 2/221, 0.9%; vehicle: 1/222, 0.05%) withdrew from the study because of AEs. There were no significant changes from baseline in the slit-lamp examinations, BCVA, IOP, or dilated fundus examination variables. Overall, there were no clinically important safety findings related to the use of Rejena, which appeared to be well tolerated.

DISCUSSION

THIS PHASE 3, MULTICENTER, RANDOMIZED, PLACEBO-CONtrolled, double-masked trial compared the efficacy and safety of Rejena, 0.18% (sodium hyaluronate ophthalmic solution) with its vehicle. The study assessed early effects of Rejena and the onset of action of the product. Though the treatment and reporting of observations through 14 days of exposure to Rejena was limited in duration, this study was one of many in a clinical development program, including studies of longer duration (up to 2 months).

The primary endpoints in the study were analyzed by Wilcoxon rank sum test, which is adequate for ordinal data. However, the Student *t* test was also judged to be

appropriate for the data and was included as a supportive analytical method. As discussed by Shuster,[11] the *t* test is also valid for ordinal data such as those collected for the primary objective and subjective endpoints. The results obtained by the 2 statistical methods, Wilcoxon and *t* test, support each other in this study. Analysis using van Elteren and the cumulative distribution of the change score from baseline reinforced the data obtained for the primary endpoints. In particular, the superiority of sodium hyaluronate was established in both a primary objective endpoint (lissamine green staining scores) and a primary subjective endpoint (global symptom frequency scores) in the same study.

Regardless of effect size, we considered any decrease from baseline in the scores of these primary endpoints to be a clinically significant improvement, as a decrease reflects corneal and conjunctival integrity improvement and improvement in symptoms. For both primary endpoints, the magnitude of the improvements observed from baseline to Day 7 for lissamine green staining and global symptoms was greater in both the treatment and vehicle groups as compared to the statistically significant differences that were measured between them at Day 7. We found an improvement from baseline of similar magnitude when we reanalyzed (not shown) the data from Baeyens and associates (Baeyens, unpublished poster, ARVO annual meeting 2004), which used saline in the placebo arm. Thus, the improvement from baseline in the placebo arm is considered a recurrent problem encountered in this type of controlled clinical trial for dry eye disease. Subjects treated with vehicle or placebos tend to show improvements owing to the efficacy of these agents. Possible reasons for this include greater compliance in subjects participating in clinical trials; the general lubrication effects of the vehicle or placebo, which behave as artificial tears; and a regression to the mean in subjects recruited on the basis of findings that may be variable over time.[3,12,13]

The trend observed in certain secondary objective and subjective efficacy endpoints at Day 7 and/or Day 14 demonstrated the beneficial effects of the drug at and beyond the initial (7-day) endpoint observation, providing additional reinforcement to the findings in the primary endpoints.

There was no clinically important increase in any AE or safety findings related to the use of the active study drug. The AEs reported were similar in both treatment groups, and the majority of the AEs were related to the underlying condition (ie, dry eye, KCS, or Sjögren syndrome).

As described above, a development program of clinical trials has established the efficacy and safety of 0.18% sodium hyaluronate ophthalmic solution for the treatment of dry eye disease. In 9 other clinical studies and in technical development studies, the optimum concentration of sodium hyaluronate (0.18%) and the average dosing regimen (4 instillations per day) for this formulation have been determined. The 9 supportive clinical studies include published[14–18] and unpublished studies (Rapisarda, unpublished poster, ISOPT, 2008; Baeyens, unpublished poster, ARVO annual meeting 2004; Rolando, unpublished data; Rimmer, unpublished data). To date, a total of 512 subjects (including those enrolled in this study) have been treated with the product for time periods ranging from a single instillation to repeated instillations daily for up to 2 months. In these studies, relevant clinical endpoints of efficacy, such as corneal and conjunctival staining, tear break-up time, osmolarity, impression cytology, and symptoms scores, showed improvement in response to treatment with Rejena.

Although more than 20 drug products have undergone clinical testing in the United States for the treatment of dry eye disease, no product has been approved for this indication. The FDA's criteria of primary efficacy endpoints for the indication have been difficult to achieve, since these endpoints usually include statistically significant improvement in at least 1 sign (objective endpoint) and 1 symptom (subjective endpoint).

In this study with Rejena, the FDA requirements were achieved. In addition, it was possible to confirm and reproduce the hypothesis-generating findings of Baeyens and associates (Baeyens, unpublished poster, ARVO annual meeting 2004) at 7 days. The rapid treatment effect realized by administration of 0.18% sodium hyaluronate is highly relevant in the treatment of this disease, given its propensity to irritate subjects' eyes, affect vision, and decrease daily quality of life. The results of this study complement those of other studies of the product with durations up to 2 months.

Postmarketing safety data received by the Medical Device Vigilance Department at TRB Chemedica International SA (Geneva, Switzerland) summarized 39 adverse events reported (ie, burning sensation, intolerance, red eyes), from an estimated 9.5 million boxes (20 monodoses/box) sold and utilized across 27 countries.

Further, since the safety of sodium hyaluronate was widely established in the studies referenced above and elsewhere, the benefit-to-risk evaluation is overwhelmingly positive. Thus, the importance of this study in providing the scientific evidence supporting the efficacy of Rejena in the treatment of the signs and symptoms of dry eye disease is considerable and warrants the performance of additional clinical research and postmarketing studies.

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