Superiority of Vismed® (Sodium Hyaluronate Ophthalmic Solution 0.18%) Compared with its Vehicle in the Treatment of the Signs and Symptoms of Dry Eye Disease

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Abstract

Purpose: Dry eye disease can affect tear production and the ocular surface, resulting in discomfort, corneal damage, and decreased vision. This Phase 3, randomized, placebo-controlled trial evaluated the efficacy and safety of a proprietary formulation of sodium hyaluronate ophthalmic solution 0.18% (Vismed®), compared with its vehicle for the treatment of signs and symptoms of dry eye disease.

Methods: 444 subjects with dry eye disease received the product (n=221) or its vehicle control (n=223). Subjects instilled 1 to 2 drops of study drug into each eye 3 to 6 times daily for 14 days, with evaluations at Days 7 and 14. The study had two primary efficacy endpoints, one objective and one subjective; change from baseline at Day 7 in lissamine green staining scores and in global symptom frequency scores, respectively. Results were analyzed using Wilcoxon rank sum and Student's t-tests. Several secondary endpoints were also evaluated.

Results: The decrease from baseline at Day 7 in lissamine green staining scores (product -1.1, vehicle -0.7) was statistically significant using the t-test (p=0.0291) and essentially significant using the Wilcoxon rank sum test (p=0.0502). A statistically significant improvement was observed at Day 7 in global symptom frequency scores (product -1.7, vehicle -1.1; p=0.0173 [t-test] and p=0.0497 [Wilcoxon]). Several secondary efficacy endpoints reached statistical significance at Days 7 and/or 14, demonstrating that the beneficial effects of the product were sustained and detectable at Day 14. There was no clinically relevant difference in safety findings related to the use of the product as compared to vehicle.

Conclusions: This study demonstrated the efficacy of sodium hyaluronate ophthalmic solution 0.18% (Vismed®) in the treatment of dry eye disease in both an objective and a subjective endpoint as compared with its vehicle. Achieving significance in both endpoints has historically been a challenge for new drugs in the treatment of dry eye disease. These results provide robust evidence of the efficacy and safety of the product for the treatment of the signs and symptoms of dry eye disease.

Purpose

The purpose of this study was to evaluate the efficacy and safety of a proprietary formulation of 0.18% sodium hyaluronate ophthalmic solution (Vismed®) compared with its vehicle for the treatment of signs and symptoms of dry eye disease.

Methods

Study Design

- This was a Phase 3, multicenter, randomized, placebo-controlled, double-masked, clinical trial.
- Subjects 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 instructed to instill 1 to 2 drops per eye at least 3 times and up to 6 times daily during the 14-day treatment period.
- The study eye was defined as the eye with the worst Schirmer I score at baseline; if both eyes were equal, the right eye was chosen.

Endpoints

- This study had two primary efficacy endpoints, one objective sign (mean change from baseline at Day 7 in lissamine green staining of the cornea, conjunctiva, and temporal conjunctiva) and one subjective symptom (change from baseline at Day 7 in the summed scores for global symptom frequency in both eyes [soreness, scratchiness, dryness, grittiness, and burning]).
- Several secondary efficacy endpoints were also evaluated at Day 7 and/or Day 14.
- Safety assessments included slit lamp examination, best corrected visual acuity, intraocular pressure, dilated fundus examination, and collection of adverse events (AEs).

Statistics

- Analyses were conducted using the Student's t-test and Wilcoxon rank sum test
- An alpha level of 0.050 (two sided) was used to determine statistical significance.
- The primary analyses of the endpoints for the study were conducted in the intent-to-treat population (all randomized subjects), using last observation carried forward data including baseline data.

Results

Demographics and Disposition

- A total of 444 subjects were enrolled and treated (active: n=221, vehicle: n=223).
- 333 (75%) subjects 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 two treatment groups.
- A total of three subjects (active: 2/221 [0.9%]; vehicle: 1/223 [0.4%]) withdrew due to an AE.

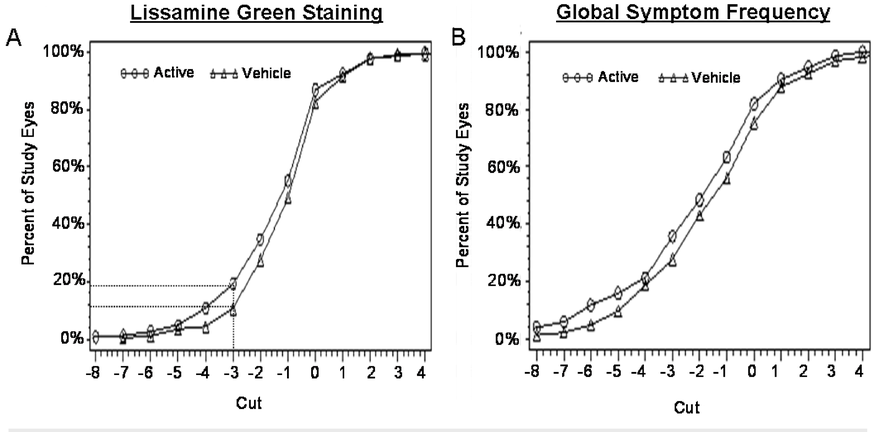
Efficacy

Results for the Primary Objective and Subjective Endpoints at Day 7

Measure	Visit	Study Drug	Mean (SD)	Median	*P* Value Student's t-test [a]	*P* Value Wilcoxon rank sum test
Lissamine green staining	D0	Active	5.71 (2.421)	5.00	0.4132	0.4157
		Vehicle	5.52 (2.357)	5.00		
	D7 [b]	Active	-1.1 (2.01)	-1.0	**0.0291**	**0.0502**
		Vehicle	-0.7 (1.79)	0.0		
Global symptom frequency	D0	Active	8.33 (2.231)	8.00	0.6208	0.3865
		Vehicle	8.22 (2.470)	8.00		
	D7 [b]	Active	-1.7 (2.78)	-1.0	**0.0173**	**0.0497**
		Vehicle	-1.1 (2.62)	-1.0		

D=day; SD=standard deviation.
a. Student's t-test p-values were confirmed by permutation test p-values.
b. Day 7 mean and median values represent the change from Day 0.

- At Day 7, the difference of the means in the change from baseline between the active and vehicle arms for lissamine green staining scores (objective) was statistically significant using the t-test (active: -1.1, vehicle: -0.7; p=0.0291) and essentially significant using the Wilcoxon rank sum test (p=0.0502).
- At Day 7, the difference in means in the change from baseline between active and vehicle arms for the global symptom frequency scores (subjective) was statistically significant (active: -1.7, vehicle: -1.1; p=0.0173 [t-test], p=0.0497 [Wilcoxon]).



- 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 the figure above. This figure shows the cumulative proportion of study eyes achieving a change score that reaches a specified threshold (i.e., the number of scale units decreased from baseline). For example, in Panel A for lissamine green staining, in the active treatment group, 19% of the study eyes achieved a change score from baseline of ≤ -3, while that proportion was only 11% in the vehicle treatment group.

Results for the Secondary Objective and Subjective Endpoints at Day 7 and/or 14

- Treatment effects were noted in several secondary objective and subjective efficacy endpoints.
- At Day 14, the difference in means from baseline for lissamine green staining scores in the active and vehicle arms were: active: -1.4, vehicle: -1.0; p=0.0243 (t-test) and p=0.0461 (Wilcoxon).
- At Day 7, efficacy results were noted in the mean summed visual analog scale symptoms intensity scores using the t-test (active: -22.81, vehicle:-14.91; p=0.0301).
- Efficacy results were also detected in the mean percent change from baseline in the composite index of global symptom intensity and global symptom frequency scores at Day 7 (active: -31.36, vehicle: -18.73; p=0.0095 [t-test]).
- The Global Impact of Dry Eye on Daily Life at baseline demonstrated that the majority of subjects reported an impact of dry eye on their daily life. Approximately 10% more subjects in the active arm than in the vehicle arm reported an improvement of at least 1 grade at Day 7, and about 7% more reported this at Day 14.

Safety

- Approximately 25% of subjects in each treatment group reported an AE (active: 25.8%; vehicle: 21.6%).
- The most frequent AEs in both treatment groups were dry eye (active: 8.1%; vehicle: 6.3%), eye pain (active: 5.9%; vehicle: 3.2%), and foreign body sensation (active: 2.3%; vehicle: 3.2%).
- There were no significant changes from baseline in the slit lamp examinations, best corrected visual acuity, intraocular pressure, or dilated fundus examination variables.
- Overall, there were no clinically important safety findings related to the use of the active study drug, which appeared to be well-tolerated.

Conclusions

- This study demonstrated the efficacy of sodium hyaluronate ophthalmic solution 0.18% (Vismed®) in the treatment of the signs and symptoms of dry eye disease in both an objective and a subjective endpoint as compared with its vehicle.
- The trend observed in treatment effects in secondary efficacy endpoints at Day 7 and/or Day 14 demonstrated the beneficial effects of the drug at and beyond the initial 7-day endpoint, 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.
- Although more than 20 drug products have undergone clinical testing in the U.S. for the treatment of dry eye disease, no product has been approved for the indication of dry eye disease. The FDA's criteria of primary efficacy endpoints for this indication (one objective and one subjective endpoint which are both statistically and clinically significant) have been difficult to achieve. In our study, treatment effects in both primary endpoints of efficacy were achieved.
- These results provide robust evidence of the efficacy and safety of the product for the treatment of the signs and symptoms of dry eye disease.

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