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A MULTICENTRIC, DOUBLE BLIND, RANDOMIZED, ACTIVE CONTROL, PARALLEL GROUP, COMPARATIVE STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF REBAMIPIDE OPHTHALMIC SUSPENSION 2.0% W/V VS. SODIUM HYALURONATE OPHTHALMIC SOLUTION 0.1% W/V FOR THE TREATMENT OF PATIENTS WITH DRY EYE

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ABSTRACT

Background: The present study was designed to evaluate the efficacy, safety and tolerability of Rebamipide Ophthalmic Suspension 2.0% w/v (Arm A) Vs. Sodium Hyaluronate Ophthalmic Solution 0.1% w/v (Arm B) in patients suffering from Dry Eye. The main objective of the study was to compare patient-perceived relief from the symptoms of foreign body sensation, dryness, photophobia, eye pain, blurred vision. **Method:** It was a comparative, randomized, double blind, parallel group, active control, multi-centric clinical trial conducted in 8 centers across India in patients with signs and symptoms of dry eye. The recruitment has been start from Jun 09, 2015 to Mar 16, 2016. Total 236 patients (aged 18 – 65 years) were randomized in the ratio of 1:1 in both arms. All the patients were advised to instil one drop four times daily in affected eye of either Rebamipide Ophthalmic Suspension 2.0% w/v or Sodium Hyaluronate Ophthalmic Solution 0.1 % w/v as per randomization. The treatment continued for 168 days with periodic follow-up on 28th, 56th, 84th, 112th, 140th and 168th days from start of treatment. **Results:** The current study showed the Mean change in Fluorescein Corneal staining score from baseline to visit 7 for Rebamipide Ophthalmic Suspension 2.0% w/v and Sodium Hyaluronate Ophthalmic Solution 0.1% w/v as – 2.15 and – 1.9 respectively. There were 15 clinical adverse events reported (Rebamipide: 06, Sodium Hyaluronate: 09) in the study and which were mild and transient in nature. **Conclusion:** Rebamipide Ophthalmic Suspension 2.0% w/v has higher efficacy of improving clinical features of dry eye when compared with Sodium Hyaluronate Ophthalmic Solution 0.1% w/v and as safe as Sodium Hyaluronate Ophthalmic Solution 0.1% w/v.

INTRODUCTION

International Dry Eye Workshop (DEWS) defines Dry eye is a multifactorial disease of the tear film and ocular surface that results in symptoms of discomfort, visual disturbance, and tears film instability with potential damage to the ocular surface. It is accompanied by increased osmolality of tear film and inflammation of the ocular surface. Dry Eye is commonly called as keratoconjunctivitis sicca.[1]

DEWS recognized dry eye is a disturbance of the Lacrimal Functional Unit (LFU). It comprises of lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands) and lids, and the sensory and motor nerves that connect them. Abnormality in the lacrimal functional unit can be transferred across the entire system through its extensive neural connections. This results into an unstable and unrefreshed tear film having altered composition like elevated tear osmolarity, presence of proinflammatory mediators and proteases,

which no longer supports the normal functioning of the ocular surface.[2]

Dry eye is a very important public health problem causing ocular discomfort, fatigue, and visual disturbance that may interfere with daily activities.[3] The prevalence of dry eye around the world varies from 5% to 34%[4] and 5-16% in America and Australia respectively while it is as high as 27-33% in Asian countries.[5]

Older age and female gender (particularly peri and postmenopausal age) have been identified as risk factors for dry eye. Smoking and multivitamin use, hormone replacement therapy (especially when estrogen is used alone) were associated with an increased risk of dry eye, whereas caffeine use was associated with a decreased risk. Arthritis was also found to be associated with an increased risk of dry eye.[2]

Dry eye can be deteriorated by low relative humidity conditions like office environment, air-conditioned cars, airplane cabins and extreme hot or cold weather. Frequent use (>4-6 times daily) of preserved eye drops (including glaucoma medications and artificial tears) may contribute to dry eye, because of the well-established toxicity of preservatives like benzalkonium chloride.[3]

The causes of dry eye could be either aqueous deficiency which encompasses Sjogrens and Non-Sjogrens syndrome or due to excessive evaporation of tears due to defective tear film caused by improper mucin or lipids in tear film.[5]

The tear film consists of three important components: a mucin layer that coats the ocular surface epithelium, an aqueous layer that is present between the mucin and a lipid layer, and a lipid layer that overlays the surface of the tear film. The destabilization of the tear film caused by decreased tear production or altered tear composition can induce ocular surface damage, inflammation and ultimately further tear film instability. Therefore, the lack of mucins can reduce the stability of the tear film and lead to or aggravate dry eye disease.[3]

Currently, tear supplementation with artificial tears is considered a mainstay treatment for cases of mild-to moderate dry eye; however, frequent instillation often is required. Sodium hyaluronate has shown some effectiveness in patients with dry eye. Insertion of punctal plugs or permanent punctal occlusion also are options for cases of moderate or severe dry eye, although a reduction in symptom relief over time has been reported. Thus, treatment options are limited, especially for moderate-to-severe dry eye.[6]

Rebamipide was first approved in Japan as an oral medication for gastritis and gastric ulcer in 1990. A new formulation of Rebamipide for ocular use has been developed in Japan (approved by PMDA on Sep 26, 2011) as a treatment for dry eye disease. It restores the ocular surface mucosa and improve symptoms related to dry eye disease through the enhanced secretory and membranous mucin secretion, restoration of the barrier function of the corneal epithelium, the repair of epithelial damage, increased number of goblet cells and anti-inflammatory effects.[7]

Rebamipide has distinctive features compared with other drugs that are used in current therapies for dry eye. It has been shown to increase the number of periodic acid–Schiff-positive cells (commonly known as goblet cells – secrete gel-forming mucins) in the conjunctiva and the mucin level on the cornea and conjunctiva. Decreased mucin levels on the surface of the cornea and a decreased density of goblet cells have been reported in patients with dry eye, with this mechanism of action, Rebamipide is expected to be effective in patients with dry eye.[6]

The objective of present Study is to compare efficacy, safety and tolerability of Rebamipide Ophthalmic Suspension 2% w/v with Sodium Hyaluronate Ophthalmic Solution 0.1% w/v in patients with dry eye.

MATERIAL AND METHODOLOGY

Study Design

It was a comparative, randomized, double blind, parallel group, active control, multicentric clinical study conducted between Jun 09, 2015 to Sep 01, 2016 in 8 centers across India in patients with dry eye (CTRI No.:-CTRI/2015/05/005783).

All procedures followed the tenets of the Declaration of Helsinki, were in accordance with all regulatory standards, were approved by an Institutional Ethics Committee and all subjects signed an informed consent form. Protocols and Inform consent were approved by Indian Regulatory authority and Institutional Ethical Committee.

Subjects

The study enrolled 253 patients suffering from dry eye of age between 18 to 65 years, randomized by computer generated system to either of the study arms in 1:1 proportion. All sites had due approval from respective Ethics Committees.

All the subjects were advised to instil one drop, four times daily of either Rebamipide or Sodium Hyaluronate as per randomization. The treatment continued for 168 days with periodic follow-up on 28^{th}, 56^{th}, 84^{th}, 112^{th}, 140^{th} and 168^{th} days from start of treatment. All sites had due approval from respective Ethics Committee.

Study Eligibility Criteria

Subjects considered eligible for enrollment in the study were dry eye patients of age group 18 - 65 years (both male and female). Other inclusion criteria were as follows: (1) clinical diagnosis of dry eye at least since

from 20 months; (2) anesthetized schirmer test score of 0-9 mm/5 minutes, or tear breakup time is 5 second or less; (3) best corrected visual acuity of 0.2 or better in both eyes; (4) voluntary willingness to give written informed consent prior to participation in trial. And subjects who are on other medications for same condition will be undergo 3 days of washout period.

Patients were excluded from the study if they had active inflammation of eyes, blocked nasal duct, history of recurrent corneal erosions or epithelial basement membrane dystrophy or floppy eyelid syndrome or conjunctivochalasis, glaucoma or ocular hypertension or ocular surgery (within 12 months) or diabetes mellitus, using topically instilled ocular medication or systemic hormonal or corticosteroid therapy or contact lenses or having hypersensitivity with study medication or its components and female patients who are pregnant, lactating or child bearing potential.

Treatment and compliance

The subjects (n = 253 subjects) were randomly assigned to either of the arms in 1:1 proportion by simple block randomization. Each patient of dry eye had received one drop four times daily of either Rebamipide Ophthalmic Suspension 2.0% w/v or Sodium Hyaluronate Ophthalmic Solution 0.1% w/v in affected eye for 168 days.

Patients in the Control and Treatment Arm were taking medications at scheduled times and as per instructions provided to them ensuring the compliance to protocol.

Compliance to assigned regimen was assessed at the end study treatment by recording the amount of returned investigational products.

Time and events schedule

Total 7 visits had conducted during this entire study after baseline investigation at visit 0. At visit 1 (day 1), visit 2 (day 28), visit 3 (day 56), visit 4 (day 84), visit 5 (day 112), visit 6 (day 140) and visit 7 (Day 168), Assessment of vital signs, primary and secondary efficacy parameters were performed.

Laboratory investigations such as CBC, ESR, LFT (SGOT, SGPT), urine analysis and ECG were done on visit 0 and visit 7. Safety Analysis such as tear break up time, anesthetized schirmer's test, visual acuity and slit lamp biomicroscopy were done on visit 0, visit 2, visit 4 and visit 7. Adverse event/Adverse drug reactions were assessed from visit 1 to end of the study. At the final visit overall response of clinical cure & overall global assessment (based on total score of signs & symptoms) were done by Patients and Investigators.

Safety and efficacy parameters

Evaluation of Visual Acuity (VA), Tear Break up Time, Slit Lamp Biomicroscopy and Anesthetized Schirmer's Tear Tests were done to evaluate the safety of Rebamipide Ophthalmic Suspension 2.0% w/v. All SAE and AE regardless of treatment group or suspected causal relationship to study drug were recorded on the adverse event page(s) of the Case Record Form.

Primary Efficacy Parameter

Change in Fluorescein Corneal Staining (FCS) score at all visits was assessed as per given scale in *Annexure 1*.

Secondary Efficacy Parameter

Change in mean score of Foreign body sensation, dryness, photophobia, eye pain and blurred vision were assessed as per given scale in *Annexure 2*.

Safety Parameter

Solicited and unsolicited adverse events, corrected distance visual acuity, slit-lamp biomicroscopy, Tear break up time and schirmer's test were assessed as per given scale in *Annexure 3*.

Statistical methods

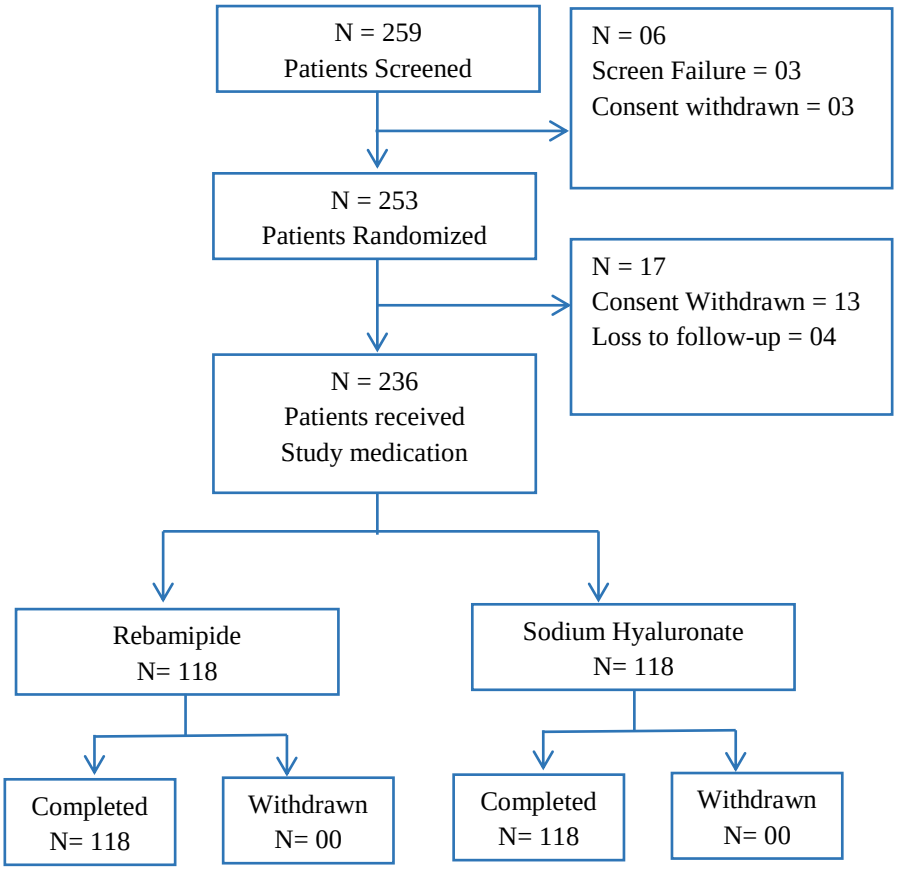
The sample size is based on change in score of Fluorescein Corneal Staining (FCS) from baseline in test product as compared to reference product. Considering 80% power to detect the primary efficacy variable between two study groups at 5% level of significance, the sample size decided was 118 completed patients in each arm. Considering the drop out of 15% the total sample size of 278 subjects will be enrolled so as to get 236 (at least 118 patients in each arm) evaluable subjects.

Statistical analysis was done using SAS 9.2. Continuous variables were statistically tested using 2-Sample T Test. Categorical variables were tested using Fisher's Exact Test. Exact McNemar's Test was used to study within intervention group shifts in abnormality status. Primary efficacy analysis was done using 2-Sample t test and paired t test. Secondary efficacy analysis was done using Fisher's Exact Test and Pearson's Chi-Square Test. Overall Assessment was analyzed by Fisher's Exact Test. All safety parameter was analyzed by Chi Square Test.

RESULTS

The study was planned so as to obtain the data from 236 evaluable patients. All 236 patients completed the study and included as Intent To Treat (ITT) analysis. Out of 236 patients, 118 patients were in Rebamipide (Test Arm) and 118 patients were in Sodium Hyaluronate (Control arm).

Efficacy of the investigational product was analyzed on the basis of comparison of scores of Fluorescein Corneal Staining (FCS). FCS score comprised of Normal (0), Mild (1), Moderate (2) and Severe (3).[8] As per the statistical analysis plan, the efficacy data was analyzed for effect on individual and cumulative efficacy parameters.



Efficacy results

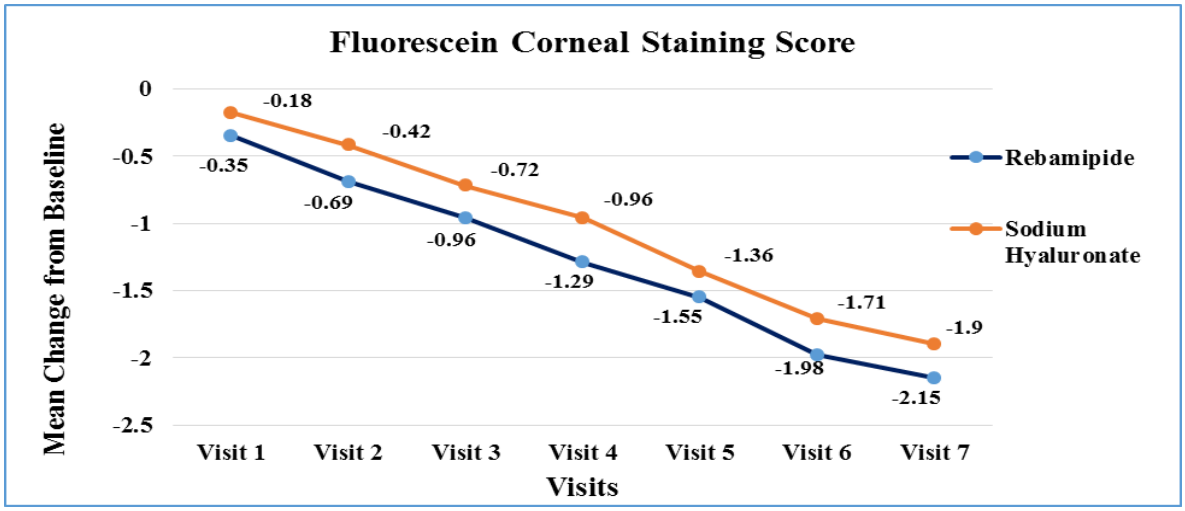
Primary efficacy parameters. i.e. Change in Fluorescein Corneal Staining Score were summarized in table no.1.

FCS Score by Treatment Group - Change from Baseline						
Assessment	**Change from Baseline to V1**		**Change from Baseline to V2**		**Change from Baseline to V3**	
	Rebamipide	**Sodium Hyaluronate**	**Rebamipide**	**Sodium Hyaluronate**	**Rebamipide**	**Sodium Hyaluronate**
N	118	118	118	118	118	118
Change Score (Mean (SD))	-0.35 (0.513)	-0.18 (0.384)	-0.69 (0.759)	-0.42 (0.561)	-0.96 (0.810)	-0.72 (0.639)
Within Group p1	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

FCS Score by Treatment Group - Change from Baseline								
Assessment	**Change from Baseline to V4**		**Change from Baseline to V5**		**Change from Baseline to V6**		**Change from Baseline to V7**	
	Rebamipide	**Sodium Hyaluronate**	**Rebamipide**	**Sodium Hyaluronate**	**Rebamipide**	**Sodium Hyaluronate**	**Rebamipide**	**Sodium Hyaluronate**
N	118	118	118	118	118	118	118	118
Change Score (Mean (SD))	-1.29 (0.775)	-0.96 (0.632)	-1.55 (0.812)	-1.36 (0.607)	-1.98 (0.762)	-1.71 (0.681)	-2.15 (0.712)	-1.90 (0.667)
Within Group p1	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

(P1-values for test of within-treatment group change from baseline score calculated using paired t-test.)

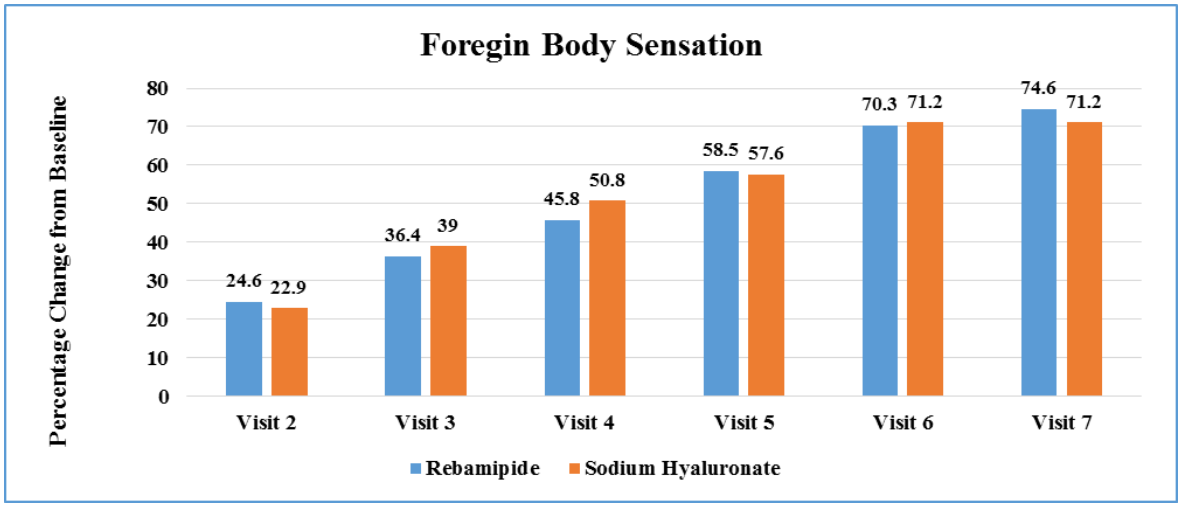
The graph no.1 depicts the change in Fluorescein Corneal Staining Score by Rebamipide and Sodium Hyaluronate at visit 1, 2, 3, 4, 5, 6 and 7.



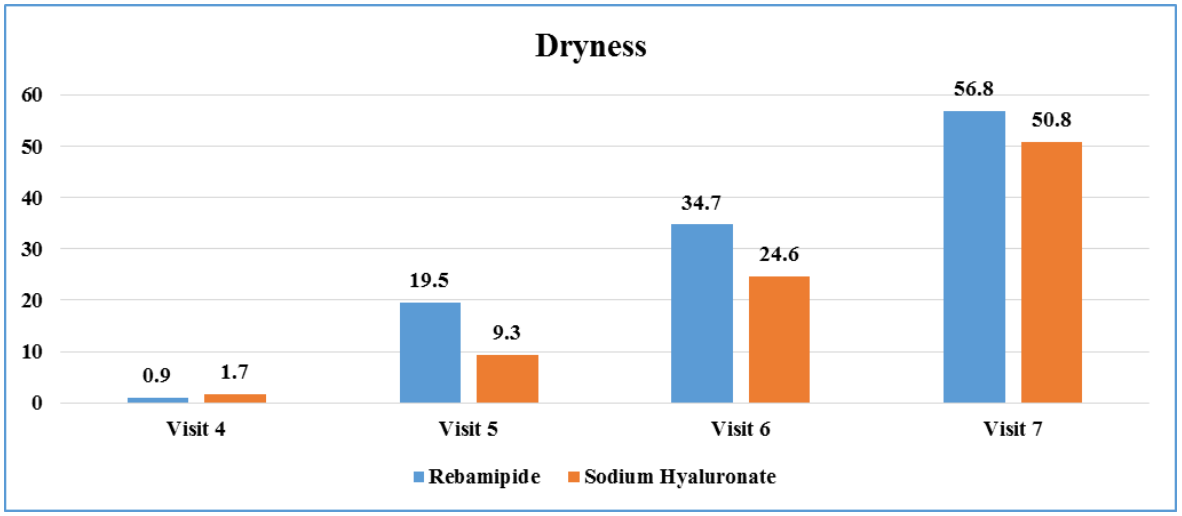
Graph no.1: Mean change in fluorescein corneal staining score by Rebamipide and Sodium Hyaluronate at visit 1, 2, 3, 4, 5, 6 and 7.

Secondary efficacy parameters

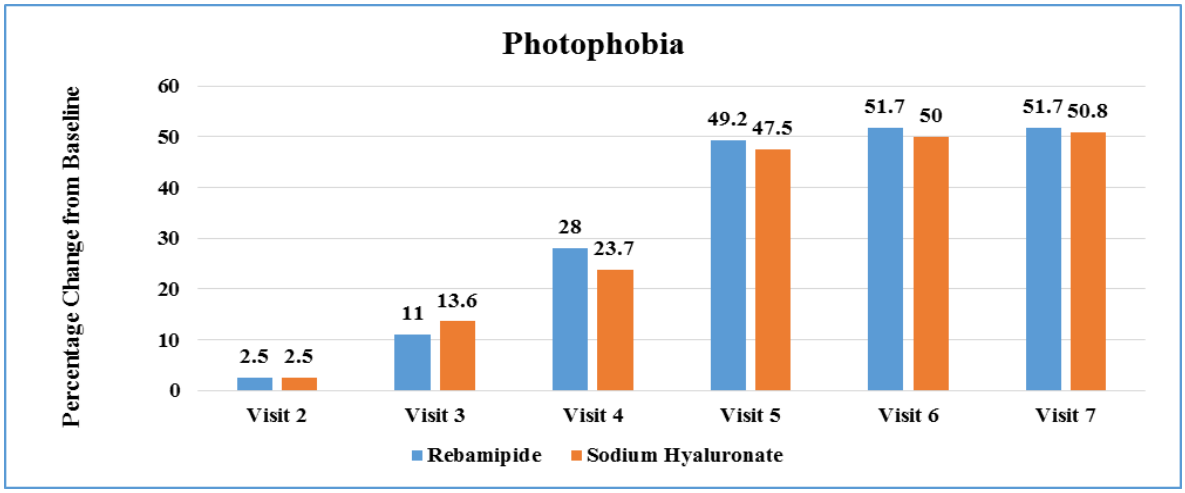
Rebamipide (n=118) and Sodium Hyaluronate (n=118) showed reduction in foreign body sensation, dryness, photophobia, eye pain and blurred vision scores as seen in graph 2, 3, 4, 5 and 6.



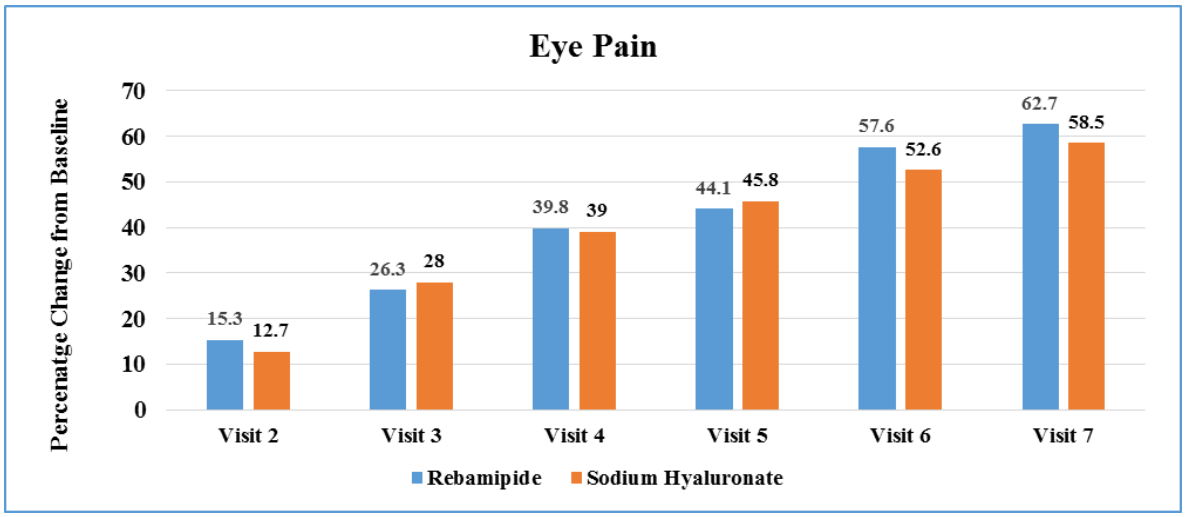
Graph no.2: Mean change in foreign body sensation score by Rebamipide and Sodium Hyaluronate at visit 2, 3, 4, 5, 6 and 7.



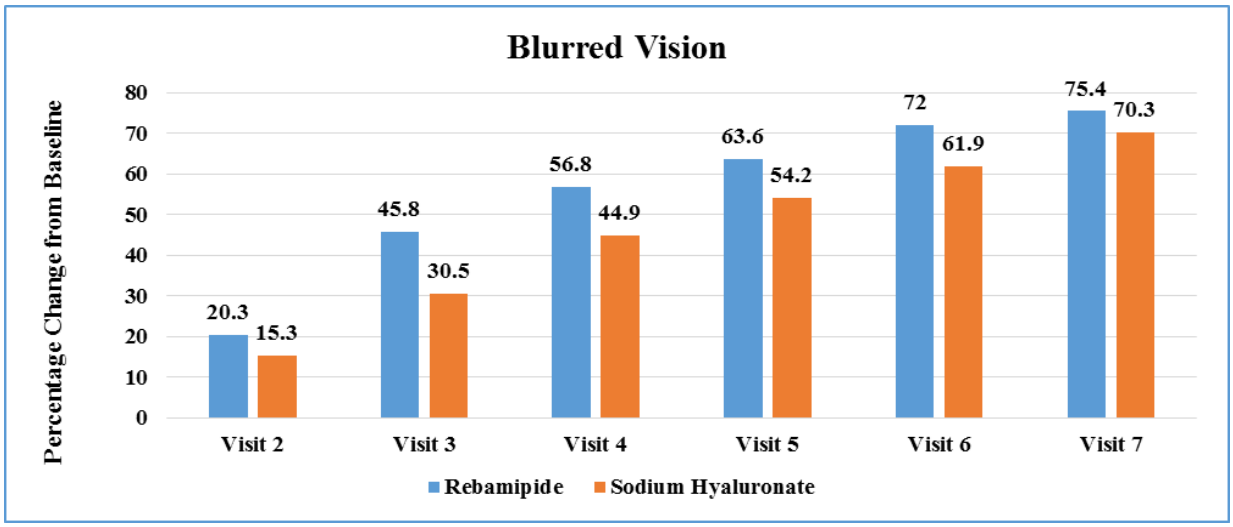
Graph no.3: Mean change in dryness score by Rebamipide and Sodium Hyaluronate at visit 4, 5, 6 and 7.



Graph no.4: Mean change in photophobia score by Rebamipide and Sodium Hyaluronate at visit 2, 3, 4, 5, 6 and 7.



Graph no.5: Mean change in eye pain score by Rebamipide and Sodium Hyaluronate at visit 2, 3, 4, 5, 6 and 7.



Graph no.6: Mean change in blurred vision score by Rebamipide and Sodium Hyaluronate at visit 2, 3, 4, 5, 6 and 7.

Safety and tolerability evaluation

There were 15 clinical adverse events reported in 15 subjects. The adverse events were mainly eye pain, eye itching, eye irritation, cough, cold, sore throat, bitter taste in mouth and headache. All Adverse events were followed up until they were completely resolved. No

adverse event led to serious adverse event. There were no mortalities or hospitalizations reported in both the arms throughout the trial period.

DISCUSSION

Dry eye is mainly caused by the destabilization of the tear film due to decreased tear production or altered tear composition can induce ocular surface damage, inflammation and ultimately further tear film instability. The deficiency of mucins can reduce the stability of the tear film and lead to or aggravate dry eye disease. Rebamipide is a quinolinone derivative with mucin secretagogue activity was recently approved for the treatment of dry eye in Japan as an Ophthalmic Suspension. The therapeutic effect of Rebamipide ophthalmic suspension is considered to be due to the increase of corneal and conjunctival mucin.[3]

The current study was demonstrated statistically superior results with Rebamipide Ophthalmic Suspension 2.0% w/v compared with Sodium Hyaluronate Ophthalmic Solution 0.1% w/v in the 24 weeks of treatment. In the efficacy analysis, in relation to the change from baseline in FCS score, Rebamipide Ophthalmic Suspension 2.0% w/v clearly demonstrated a marked improvement at all visits than Sodium Hyaluronate Ophthalmic Solution 0.1% w/v. The improvements in staining scores are important because it indicate an improvement in the ocular surface.[9] FCS score reflects corneal epithelium integrity and is the standard method used to demonstrate ocular surface damage.[9]

In addition to its benefits on objective measures, Rebamipide was more effective than sodium Hyaluronate on subjective outcomes, showing greater improvements in symptoms like foreign body sensation, eye pain, blurred vision and dryness. The assessment of efficacy using subjective measures (symptoms) as well as objective measures (signs) is particularly important in patients with dry eye because it has been shown that there is poor correlation between symptoms and signs of dry eye; for instance, In one of the study found that only 57% of symptomatic patients were shown to have objective signs of dry eye.[10] Improvements in symptoms are important, given the impact of dry eye on quality of life.[9]

Rebamipide has characteristic features compared with other drugs that are used in current therapies for dry eye. Cyclosporine, another ophthalmic solution used for the treatment of dry eye, showed significant improvement in FCS score, although efficacy was demonstrated only after 4 months.[11] Sodium hyaluronate also has shown effectiveness in patients with dry eye, with FCS scores demonstrating significant improvement at 4 weeks.[12] In the current study, Rebamipide showed statistically significant improvement in FCS scores after 4 weeks of treatment compared with Sodium Hyaluronate. Cyclosporine has an anti-inflammatory and immunomodulatory mode of action, and Sodium Hyaluronate is a viscous material intended to increasing tear retention and wound healing effects.

Rebamipide has been shown to increase the number of periodic acid–Schiff-positive cells (goblet cells) in the conjunctiva[13] and the mucin level on the cornea and conjunctiva.[13,14] Decreased mucin levels on the surface of the cornea and a decreased density of goblet cells have been observed in patients with dry eye.[15] The mode of action of Rebamipide is expected to be beneficial for dry eye. Rebamipide is expected to be effective in patients with dry eye resulting from short tear film breakup time (TBUT), because disturbance of ocular surface mucin is thought to be one of the main causes of tear film instability and the accompanying shorter TBUT.[1]

In one of the study, Rebamipide Ophthalmic Suspension 2.0% w/v is effective in improving both the objective signs and subjective symptoms in patients with dry eye, and its efficacy was maintained up to 52 weeks with no particular safety concerns. The ability of Rebamipide Ophthalmic Suspension 2% w/v is to reduce the corneal and conjunctival epithelial damage and symptoms associated with dry eye, together with its well-tolerated safety profile, make it a promising treatment option for patients with dry eye.[16]

In the current study, Rebamipide and Sodium Hyaluronate were comparable in safety evaluation. Rebamipide was ascertained to be equivalent to Sodium Hyaluronate in safety as per clinical and laboratory evaluation. Both Rebamipide and Sodium Hyaluronate have no hepatic and hematological effect. The adverse events include routine eye irritation, eye pain, eye itching, cough, cold, bitter taste in mouth, headache and fever. Total 15 AEs were reported in 15 patients. All AEs were mild in nature. None of the AEs were related to the Investigational product. No SAEs were reported during the study. Anterior eye structure, retina, moisture and vision of both eyes were demonstrated by Schirmer's Test, slit lamp biomicroscopy and Visual Acuity test and found to be normal after completion of the treatment. There were no mortalities or hospitalizations reported in treatment group throughout the trial period.

CONCLUSION

Dry Eye is often considered as a chronic disease and it requires long term treatment. The present study showed that Rebamipide Ophthalmic Suspension 2.0% w/v is effective in improving both the objective signs and subjective symptoms in patients with dry eye, and its efficacy was maintained for upto 24 weeks. In fact, Rebamipide has superior efficacy and comparable safety to Sodium Hyaluronate Ophthalmic Solution 0.1% w/v in the management of dry eye, make it a potential treatment option for patients with dry eye.

FUNDING

Ajanta Pharma Limited.

Annexure 1: Fluorescein corneal staining (FCS) score.

Evaluation of Fluorescein corneal staining score will be assessed as per below mention scale.

0	Normal
1	Mild
2	Moderate
3	Severe

Annexure 2: Secondary Efficacy Parameters.

Foreign body sensation, dryness, photophobia, eye pain and blurred vision will be assessed as per below mention scale.

0	None
1	Trace
2	Mild
3	Moderate
4	Severe

Annexure 3: Safety Parameters.

Tear break up time will be assessed as per below mention scale:

>10	Normal
5 to 10	Marginal

Schirmer's Test will be assessed as per below mention scale:

≥15 mm	Normal
10-14 mm	Mild
4-9 mm	Moderate
<4 mm	Severe

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