Original Article

Safety and efficacy of ALG-1007 topical ophthalmic solution – A synthetic peptide that regulates inflammation, in patients with dry eye disease: An exploratory Phase I, open-label, single-center clinical study

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ABSTRACT

Objectives: The objective of the study was to evaluate the safety and efficacy of ALG-1007 topical ophthalmic solution in patients with dry eye disease (DED).

Materials and Methods: This Phase I, prospective, open-label, 12-week study enrolled subjects ≥18 years old with symptoms of DED for at least 6 months and at least one of the following: Total ocular staining score ≥2 or tear film breakup time (TBUT) ≤7 s. Subjects were randomized to four treatment arms: 0.125%, 0.25%, 0.4%, and 0.6% ALG-1007. Subjects received the test drug, 1 drop twice daily, and were followed at multiple time points for 12 weeks. SICCA total ocular staining score, corneal and conjunctival staining score, TBUT, and subject-reported symptoms using the visual analog scale (VAS) symptom index were assessed at baseline and at every visit. The primary safety outcome was percentage and severity of adverse events (AEs).

Results: Forty eyes (21 patients) were assigned randomly to four treatment groups (n = 10 per group). Improvement in TBUT, SICCA, and VAS was seen in all groups. The highest dose tested (0.6%) was compared to the lowest dose tested (0.125%) based on change from baseline for all assessments using analysis of variance. Improvement was significantly greater in 0.6% treatment group in terms of TBUT, conjunctiva staining, SICCA, burning, discomfort, photophobia, and the composite symptom score. No serious AEs were reported after 12 weeks of treatment.

Conclusion: Outcome measures improved in all the treatment groups. At the highest dose, ALG-1007 demonstrated statistically significant improvement compared to the lowest dose in 7 out of 12 assessments, indicating a dose response. This suggests that the active pharmaceutical ingredient in ALG-1007 is effective in improving signs and symptoms of DED. ALG-1007 was well-tolerated with minimal instillation discomfort and no reported serious AEs.

Keywords: Keratoconjunctivitis sicca, Integrin, Visual analog scale, Ocular staining

INTRODUCTION

Dry eye disease (DED) is an ocular condition that is estimated to affect more than 30 million adults ≥18 years old in the United States1,2. The central mechanism in the initiation and
perpetuation of DED is evaporative water loss which leads to hyperosmolar tissue damage which, in turn, leads to a loss of both epithelial and goblet cells, either directly or through inflammation. This results in a decrease in surface wettability and early tear film breakup which further amplifies hyperosmolarity and completes the “vicious circle” of disease self-perpetuation.\(^3\)

Ocular lubricants, which have long been a mainstay in the initial management of DED, are palliative. Topical corticosteroids are effective and have been used to target the inflammation in DED but have limited long-term use for this chronic disease due to the risk of glaucoma, infection, and cataract formation.\(^4\)

The current drug development for the treatment of DED addresses the need to find medications that are well tolerated and can be used chronically and safely to treat inflammation and break the cycle that drives progression of disease and ocular surface damage.

At present, three medications are approved by the United States Food and Drug Administration for the treatment of DED: Cyclosporine (CsA) 0.05% ophthalmic emulsion (Restasis\(^\text{®}\); Allergan, Irvine, CA, USA),\(^5\) CsA 0.09% (Cequa\(^\text{®}\); Sun Pharmaceutical, Mumbai, India),\(^6\) and lifitegrast ophthalmic solution 5.0% (Xiidra\(^\text{®}\); Shire, Lexington, USA).\(^7,8\) While these medications have proven effective in relieving signs and/or symptoms of DED, side effects such as ocular pain and discomfort have resulted in poor tolerance and eventual discontinuation in a significant number of patients.\(^9,10\) This population of DED patients – those who are unable to tolerate chronic use of these existing drugs and adhere to a long-term treatment regimen – presents an area of unmet need in the treatment lineup for DED.

ALG-1007 (Allegro Ophthalmics, San Juan Capistrano, CA, USA) is a topical application of risuteganib, a small peptide integrin regulator that modulates multiple integrin subunits, including integrin αM and β2, the subunits involved in complement 3 inflammatory pathways.\(^11,12\) Gene expression studies have demonstrated reduced gene level of integrin αM and β2 subunits in mice retina treated with risuteganib. Gene level of complement, leukocyte adhesion, and migration pathways were elevated in untreated, inflammatory-activated oxygen-induced retinopathy mice but moderated with risuteganib treatment (Donnenfeld \textit{et al.} presented at 2019 American Society of Cataract and Refractive Surgery Annual Meeting).

By suppressing αM and β2 integrin subunits, risuteganib likely interferes with leukocyte adhesion and transendothelial migration, thereby downregulating ocular surface inflammation and mitigating signs and symptoms of DED [Figure 1].

When tested in a mouse model of dry eye, ALG-1007 reduced corneal and conjunctival staining for cellular damage when compared to untreated control. Corneal levels of markers for immune response and inflammation (IL-1B, IL-6, and TNF-α), neurodegeneration (glial acidic fibrillary protein), and apoptosis (TSPO and caspase 6 and 9) also appeared to be reduced after treatment with ALG-1007 while antioxidant markers (superoxide dismutase, glutathione peroxidase, and catalase) were increased (Quiroz-Mercado \textit{et al.} presented at 2019 Association for Research in Vision and Ophthalmology Annual Meeting). These pre-clinical findings suggest that ALG-1007 is a potential candidate for use in treatment of the inflammation associated with DED.

**MATERIALS AND METHODS**

This was a single-center, randomized, prospective, open-label, non-controlled, dose-ranging study. The study was conducted...
under the approval of an Institutional Review Board and adhered to good clinical practice and the provisions of the Declaration of Helsinki and its amendments.

Participants

Eligible participants were adults aged ≥18 years with a history of DED symptoms for ≥6 months and at least one of the following: Total ocular staining score ≥2 and tear film breakup time (TBUT) ≤7 s.

Exclusion criteria included known allergies to any of the drug ingredients, presence of corneal scarring, history of ocular chemical burn, active DED treatment (with corticosteroids, CsA, lifitegrast, mast cell stabilizers, or antihistamines), participation in any investigational drug (within 60 days) or device (within 30 days) study, use of any topical medication or antibiotic for the treatment of blepharitis or Meibomian gland disease, contact lens use, current ocular infection, inflammation or allergic conjunctivitis, history of herpetic keratitis, LASIK surgery, use of glaucoma medications, or ocular surgery in the preceding 6 months. Women who were pregnant and nursing were excluded from participation. The use of artificial tears or eye lubricants was allowed.

Study design

After signing an informed consent, eligible subjects with DED were enrolled and assigned to one of four treatment groups. The investigational product was supplied as a sterile liquid solution in four concentrations: 0.125%, 0.25%, 0.4%, and 0.6%. Assignment to treatment group was done sequentially starting with 0.125% until 10 subjects were enrolled, repeating the process for increasing doses until a total of 40 subjects were enrolled. Each eye was counted as one subject. Subjects were instructed to apply one drop twice daily, approximately 12 h apart, for 12 weeks. Subjects who required more relief from ocular irritation were instructed to continue use of non-prescription eye lubricants, administered at least 1 h before or after ALG-1007. Patients returned for evaluation 1 week after the baseline visit, then every 2 weeks until the end of the 12-week study period.

Outcome measures

Exploratory outcome measures included change from baseline (CFB) in TBUT, total ocular staining score, change in lissamine conjunctival staining, change in fluorescein corneal staining, and change in subject-reported symptoms using visual analog scale (VAS). The primary safety assessment was the occurrence of ocular and non-ocular drug-related adverse events (AEs). Subjects were questioned regarding the occurrence of symptoms, including blurring of vision, ocular irritation, burning, stinging, itching, foreign body (FB) sensation, irritation, photophobia, and pain. Other safety assessments were slit-lamp findings. Slit-lamp examination was performed to look for conjunctival edema, conjunctival congestion, conjunctival discharge, corneal edema, corneal endothelial changes, anterior chamber cells, anterior chamber flare, anterior synechiae, posterior synechiae, iris atrophy, iris nodules, and iris neovascularization. Exploratory outcome and safety measures were assessed at each follow-up visit.

Statistical methods

No formal hypothesis testing was performed since this was a Phase I exploratory clinical study. Efficacy analysis was performed on the modified intent-to-treat population (mITT), which included all randomized subjects who received at least one dose of study drug and had at least one follow-up visit. The study sample size was based on establishing a reasonable number of subjects to provide adequate safety and efficacy information to proceed to the next phase of clinical development. Descriptive statistics were used to tabulate and summarize study outcomes. Continuous variables were described according to sample size, mean ± standard deviation (SD), median, minimum, and maximum. Discrete variables and AEs were summarized according to frequencies and percentages.

Dry eye data from 11 patients and 20 eyes were analyzed; 6 patients were treated with 0.125% solution, and 5 with 0.60% solution. Symptom scores on burning, itching, discomfort, dryness, photophobia, FB sensation, and pain from baseline and week 12 were analyzed. Intervening weeks were measured but not analyzed. An overall symptom score was derived by calculating the CFB and averaging the seven individual symptom changes. A CFB was also calculated for the four other measures taken: TBUT, SICCA, cornea staining, and conjunctiva staining.

For each endpoint, analysis of variance (ANOVA), with repeated measures for bilaterally treated eyes, was used to assess dose difference in two treatment groups, 0.125% and 0.6%. In addition to the test of treatment effect, the CFB for each dose was examined separately to determine if a significant CFB had occurred.

RESULTS

Participants

The study was conducted for a duration of approximately 6 months between April 18 (first visit of the first subject) and November 16 (last exam of the last subject), 2018. Forty eyes (subjects) from 21 patients were randomized equally into four treatment groups. All 40 subjects completed the study and were included in the safety population, mITT population, and per protocol population.

Baseline characteristics [Table 1] were similar between treatment groups. All subjects were of Armenian descent, with 17 males and 23 females. Age ranged from 25 to 79 years, with a mean (SD) of 48.7 (6.4). Only three subjects reported
Lindstrom, et al.: Safety and efficacy of ALG-1007 in dry eye disease

Baseline assessments [Table 2] showed a TBUT mean (SD) of 3.8 (0.85). TBUT was comparable among the four treatment groups; three of the four groups had a mean TBUT of 3.9 while the fourth group (0.25%) had a mean TBUT of 3.6. The overall SICCA total ocular staining score average (SD) was 5.1 (1.92). SICCA score varied among the treatment groups; the group that received 0.125% had a baseline mean SICCA score of 3.4, which is the lowest score among the four groups; the group that received 0.6% had a baseline mean SICCA score of 6.2, which is the highest score among the four groups. Scores for the seven symptoms in the VAS questionnaire also varied across the treatment groups [Table 3]; 0.25% treatment arm had the highest baseline scores in four out of seven of the symptoms (burning, itching, FB sensation, and discomfort); 0.4% treatment arm had the highest baseline score for dryness; 0.6% treatment arm had the highest baseline score for photophobia; and 0.125% treatment arm had the highest baseline score for pain. Subjects in 0.6% treatment arm reported no itching or pain at baseline.

Safety assessments

AEs

No serious AEs were noted in any of the treatment groups through the 12-week study. None of the subjects reported...
Slit-lamp findings

One subject in 0.4% treatment group presented with mild (+1) conjunctival discharge during visit 3 (week 2); this was resolved by the next visit. Two subjects in 0.4% treatment group presented with mild (+1) lid erythema through day 0 to week 2; this was self-limited and resolved by week 4. None of the subjects developed lid edema, conjunctival edema/congestion, corneal edema/endothelial changes, anterior chamber cells/flare, anterior/posterior synechia, or iris atrophy/nodules/neovascularization.

Correlations between variables

The change symptom intercorrelations were generally positive and strong, justifying a collapsing into a single scale. The Cronbach’s coefficient alpha was 0.75 for the composite scale, indicating good consistency within the 7 items.

The composite symptom score correlated negatively with TBUT and positive with the staining measures, as expected. However, only TBUT and SICCA were statistically significant.

Exploratory efficacy outcomes

**TBUT**

All four treatment groups demonstrated an increase in TBUT [Figure 2]. About 0.6% treatment group demonstrated an increasing trend in TBUT as early as 2 weeks after the baseline visit; this was sustained for 12 weeks. In contrast, TBUT reached a peak at 8 weeks for 0.4% group and at 10 weeks for 0.125% group. The ANOVA model which compared baseline values to week 12 values showed that both the subjects given the lowest dose and the subjects given the highest dose showed a significant difference in mean TBUT CFB from baseline. The increase in 0.6% treatment group was significantly greater compared to 0.125% treatment group.

**SICCA total ocular staining score**

Similar decreasing trends were seen in the corneal fluorescein stain score [Figure 3], nasal conjunctival lissamine green stain score [Figure 4], temporal conjunctiva lissamine green stain score [Figure 5], and total ocular stain score [Figure 6] for all concentrations of ALG-1007. At the end of the 12-week study, the highest tested dose (0.6%) produced the lowest cornea, nasal conjunctiva, temporal conjunctiva, and total ocular stain scores. Like TBUT, the decreasing trend in both nasal and temporal conjunctival staining was first observed 2 weeks after the baseline visit in the two higher doses; the decreasing trend in corneal staining was first observed 2 weeks after the baseline visit in 0.6% group. The difference in the total ocular staining score between the lowest dose and the highest dose is shown in Figure 6. At the end of 12 weeks, the CFB in the group given 0.125% was -1.7; the CFB in the group given 0.6% was -5.3, representing a statistically significant difference based on ANOVA.

**VAS symptom index**

All the treatment groups demonstrated an improvement in the symptoms of the VAS present at baseline – burning, itching, FB sensation, discomfort, dryness, photophobia, and pain [Figure 7]. Pain and itching were not reported in any of the subjects in 0.6% treatment group at baseline or at any time during the study.

### Table 2: Baseline assessments.

<table>
<thead>
<tr>
<th>Treatment arm (%)</th>
<th>TBUT (SD)</th>
<th>Corneal staining</th>
<th>Nasal conjunctiva</th>
<th>Temporal conjunctiva</th>
<th>SICCA total ocular stain (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125</td>
<td>3.9 (0.76)</td>
<td>1.6</td>
<td>0.8</td>
<td>0.7</td>
<td>3.4 (1.84)</td>
</tr>
<tr>
<td>0.25</td>
<td>3.6 (1.18)</td>
<td>1.9</td>
<td>1.6</td>
<td>1.5</td>
<td>5.7 (2.11)</td>
</tr>
<tr>
<td>0.4</td>
<td>3.9 (0.81)</td>
<td>0.4</td>
<td>2.1</td>
<td>2.4</td>
<td>5.2 (1.48)</td>
</tr>
<tr>
<td>0.6</td>
<td>3.9 (0.66)</td>
<td>1.6</td>
<td>1.9</td>
<td>1.9</td>
<td>6.2 (1.03)</td>
</tr>
<tr>
<td>Overall</td>
<td>3.8 (0.85)</td>
<td>1.4 (0.93)</td>
<td>1.6 (0.81)</td>
<td>1.6 (0.90)</td>
<td>5.1 (1.92)</td>
</tr>
</tbody>
</table>

TBUT: Tear film breakup time, SD: Standard deviation

### Table 3: Baseline VAS.

<table>
<thead>
<tr>
<th>Treatment arm (%)</th>
<th>Burning</th>
<th>Itching</th>
<th>FBS</th>
<th>Discomfort</th>
<th>Dryness</th>
<th>Photophobia</th>
<th>Pain</th>
<th>Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125</td>
<td>51</td>
<td>32.2</td>
<td>66</td>
<td>62.2</td>
<td>66.1</td>
<td>28.8</td>
<td>30.5</td>
<td>48.1</td>
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<tr>
<td>0.25</td>
<td>69.2</td>
<td>44.2</td>
<td>86</td>
<td>79.6</td>
<td>57.3</td>
<td>44.5</td>
<td>25.2</td>
<td>58.0</td>
</tr>
<tr>
<td>0.4</td>
<td>47</td>
<td>4</td>
<td>22</td>
<td>70</td>
<td>74</td>
<td>18</td>
<td>24.8</td>
<td>37.1</td>
</tr>
<tr>
<td>0.6</td>
<td>60.3</td>
<td>0</td>
<td>61.3</td>
<td>59.1</td>
<td>63.1</td>
<td>63.6</td>
<td>0</td>
<td>43.9</td>
</tr>
</tbody>
</table>

FBS: Foreign body sensation
Figure 2: (a) Change in tear film breakup time (TBUT) mean absolute values. (b) Change in TBUT mean change from baseline.

Figure 3: (a) Change in cornea staining score mean absolute values. (b) Change in cornea staining score mean change from baseline.

Figure 4: (a) Change in nasal conjunctival staining mean absolute values. (b) Change in nasal conjunctival staining mean change from baseline.

Figure 5: (a) Change in temporal conjunctival staining mean absolute values. (b) Change in temporal conjunctival staining mean change from baseline.
Lindstrom, et al.: Safety and efficacy of ALG-1007 in dry eye disease

Figure 6: (a) Change in total ocular staining mean absolute values. (b) Change in total ocular staining mean change from baseline.

Figure 7: Change in visual analog scale (VAS) score, (a) 0.125%, (b) 0.25%, (c) 0.4%, and (d) 0.6% group.

Figure 8: Composite visual analog scale (VAS) score mean change from baseline.

Improvement in all symptoms was seen by week 2 in the group that received 0.6%. In comparison, this was not seen until week 4 in the group that received 0.125% [Figure 8]. All symptoms that were present at baseline in 0.6% group progressively decreased to a greater degree than the corresponding values in 0.125% group. Analysis of the 12-week VAS composite score CFB between 0.125% and 0.6% groups demonstrated a greater improvement achieved with the higher dose, a difference which was statistically significant based on ANOVA.

DISCUSSION

Subjects who received ALG-1007 demonstrated an improvement in both signs (TBUT and SICCA) and symptoms (VAS) of DED. This is theoretically due to the ability of ALG-1007 to regulate integrin αMβ2 and downgrade inflammation by interfering with the complement
CONCLUSION

The results of this exploratory study suggest that use of twice daily ALG-1007 ocular solution is safe and well-tolerated – even at the highest dose – with no severe AEs reported over the 12-week treatment and observation period. 0.6% ALG-1007 demonstrated the most robust improvements in TBUT, ocular staining, and dry eye symptoms.

Acknowledgments

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

Vicken Karageozian, John Park, Melvin Sarayba, Lisa Karageozian, Janine Aubel, and Hampar Karageozian are employees of Allegro Ophthalmics, LLC, and have equity or stocks. Richard Lindstrom, Eric Donnenfeld, and Edward Holland are consultants for Allegro Ophthalmics, LLC, and have equity or stocks.

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