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ORIGINAL RESEARCH

A Multicenter Randomized Double-Masked Study Comparing Preservative-free Brimonidine Tartrate Ophthalmic Solution 0.025% with LUMIFY® 0.025% for Ocular Redness in Adults

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ABSTRACT

***Introduction*:** Ocular redness is common, can affect quality of life, and can be relieved by short-term use of topical adrenergic receptor (AR) agonists. Brimonidine tartrate ophthalmic solution 0.025% (LUMIFY® 0.025%) is the first α2-AR-selective agonist approved for ocular redness. The preservative benzalkonium chloride (BAK) maintains ophthalmic solution sterility, reducing the risk of ocular infections, but may cause symptoms of ocular surface disease (OSD) in some patients. A BAK-free formulation of LUMIFY 0.025% (BTOS-PF 0.025%) could offer a solution for BAK-sensitive patients.

***Methods*:** This randomized, active-controlled, multicenter study aimed to establish non-inferior efficacy of BTOS-PF 0.025% to LUMIFY 0.025% and compare safety. Randomized participants received either formulation instilled as a single drop four times daily, for 4 weeks. The primary endpoint was investigator-assessed ocular redness at 5, 15, 30, 60, 90, 120, 180, and 240 min post-instillation at visit 1 (day 1). Eight hierarchical secondary endpoints included additional post-instillation timepoints at visit 1 and visits 2 and 3 (days 14 and 28), and participant-assessed redness.

***Results*:** BTOS-PF 0.025% was statistically non-inferior to LUMIFY 0.025% for ocular redness reduction across the eight timepoints at visit 1. Efficacy for both formulations was seen as early as 1 min and up to 8 h post-instillation. BTOS-PF 0.025% performed similarly to LUMIFY 0.025%

Prior Presentation: This study was presented in poster form at the AOA, ARVO, EuDEC and TFOS congresses in 2024.

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after 14 and 28 days, rebound redness rates were low and similar, and total clearance of ocular redness and participant-evaluated redness were similar. The safety profile of both formulations was similar, with no severe or serious ocular events.

Conclusions: BTOS-PF 0.025% was non-inferior to LUMIFY 0.025% in reducing ocular redness in adults, was well-tolerated, and offers an alternative topical solution, without loss of efficacy or compromised safety, for patients who prefer a preservative-free formulation or are at increased risk of OSD.

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT05360784. Date of registration: 29 April 2022.

Keywords: Brimonidine; Benzalkonium chloride; Brimonidine tartrate ophthalmic solution 0.025%; Hyperemia; LUMIFY; Ocular redness; Patient preference; Preservative-free; Vasoconstriction

Key Summary Points

Why carry out this study?

Ocular redness is a common condition with cosmetic and comfort-related impacts; current treatments like LUMIFY® 0.025% contain benzalkonium chloride (BAK), a preservative associated with ocular surface disease (OSD) in sensitive individuals.

There is an unmet need for a preservative-free formulation that maintains efficacy while avoiding potential BAK-related side effects, particularly in patients with pre-existing ocular surface conditions or on multiple eye medications.

The study aimed to determine whether a novel preservative-free formulation of brimonidine tartrate ophthalmic solution 0.025% (BTOS-PF 0.025%) is non-inferior to LUMIFY 0.025% in reducing ocular redness in adults, while also assessing the safety of the new formulation.

What was learned from the study?

BTOS-PF 0.025% offers a comparably effective preservative-free alternative formulation to BAK-containing LUMIFY 0.025%, without compromising safety, addressing a key unmet need in ocular redness management.

These findings support the broader use of preservative-free ocular therapeutics, particularly for patients sensitive to preservatives or at increased risk of OSD.

INTRODUCTION

Ocular redness is a common ophthalmic complaint caused by inflammation, most often of the conjunctiva, which leads to blood vessel dilation [1–3]. Environmental irritants can trigger ocular redness and, while potentially asymptomatic, it can be associated with reduced quality of life due to discomfort or cosmetic concerns [1–3]. Topical, over-the-counter (OTC) ophthalmic vasoconstrictors can temporarily relieve ocular vasocongestion by acting on α-adrenergic receptors (ARs), with current guidance to avoid chronic use and consult a doctor if redness persists beyond 72 h or worsens [1, 3, 4].

Brimonidine tartrate ophthalmic solution 0.025% (LUMIFY® 0.025%) is the first selective α2-AR agonist approved to treat ocular redness [1]. As an α2-AR-selective agonist, brimonidine tartrate exerts a greater constrictive effect on conjunctival venules, versus arterioles, in contrast with other ophthalmic vasoconstrictors that are α1- or mixed α1/α2-AR agonists [5, 6]. At 0.025%, brimonidine achieves a significant reduction in redness for up to 8 h after instillation, without the characteristic tachyphylaxis and/or ocular rebound redness typically associated with α1- or α1/α2-AR agonists. Its specific action may also contribute to its distinct safety profile [1, 5–7].

Maintaining the sterility of topical ophthalmic medications is necessary to reduce the risk of vision-threatening infections, and most regulatory bodies have required preservatives in multidose formulations since the 1970s [8, 9].

Benzalkonium chloride (BAK) is a preservative used in the majority of ophthalmic pharmaceuticals that acts as a non-specific antiseptic detergent to prevent colonization by Gram-positive and -negative bacteria, as well as fungi, with established efficacy against common pathogens [10, 11].

There is broad evidence of an association between BAK exposure and symptoms indicative of ocular surface disease (OSD) [8, 12]. The symptoms of OSD range from subclinical to severe, with evidence of a BAK exposure threshold for their onset based on total daily BAK exposure (drops per day or number of instilled BAK-containing medications) and/or prolonged use [8, 9, 12]. Indeed, most available clinical data on the impact of BAK exposure on OSD are from patients with glaucoma receiving long-term, multidose treatment, with at least one BAK-containing medication per day [8, 10]. Studies reporting no difference in ophthalmic clinical measures between BAK-containing and BAK-free formulations are based on short-term follow-up, so are more reflective of the intended use of topical anti-redness medications [1, 4, 8, 10].

Preservative-free ophthalmic solutions can avoid potential BAK-associated complications, especially for patients with pre-existing eye irritation or who are already using multiple topical medications [9, 11]. A BAK-free LUMIFY formulation (brimonidine tartrate ophthalmic solution, preservative free [BTOS-PF] 0.025%) could offer effective ocular decongestion in an alternative preparation to facilitate physician choice according to patient sensitivity or preference.

This study aims to establish that the efficacy of BTOS-PF 0.025% is non-inferior to LUMIFY 0.025% for treating ocular redness in adults, and to compare the safety of these two formulations.

METHODS

Study Design and Population

This was a multicenter, double-masked, randomized, active-controlled, parallel-group, efficacy and safety study in healthy adults with ocular redness, treated for 4 weeks. The study enrolled participants at six clinical sites, based on the inclusion and exclusion criteria summarized in Supplementary Table S1. These criteria included history of use, or desire to use, OTC topical vasoconstrictors for the relief of ocular redness, ability to administer eye drops, and consideration of relevant medical and non-medical conditions and concomitant treatments (including artificial tears); these criteria were specified as part of the study protocol to optimize patient safety and prevent confounding. Participants with ophthalmic conditions requiring treatment that could not be discontinued, such as active dry eye disease requiring topical ocular lubricants, were ineligible for the study. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines, the principals of Good Clinical Practice, and applicable local regulatory requirements. The study protocol, informed consent form, and other information provided to participants, and all appropriate amendments were properly reviewed and approved by an Institutional Review Board (Alpha IRB, 1001 Avenida Pico, San Clemente, CA, USA).

Participants attended five scheduled study visits: Screening (day −28 to day 1), visit 1 (baseline; day 1), visit 2 (enrollment; day 15 ± 2 days), visit 3 (day 29 + 2 days), and visit 4 (day 36 + 1 day; Supplementary Fig. S1). At visit 1, a computer-generated randomization schedule assigned eligible participants 1:1 to receive either BTOS-PF 0.025% or LUMIFY 0.025%; participants also received a diary and their first dose of study drug at this visit. Supplementary Fig. S1 describes the full schedule of visits during the study.

Study Interventions

A single drop of the assigned study treatment was instilled into each eye (bilaterally). After the initial in-office administration, the dosing regimen for both BTOS-PF 0.025% and LUMIFY 0.025% was four times daily (QID), approximately 4 h apart, for a duration of 4 weeks. A trained technician performed the instillation,

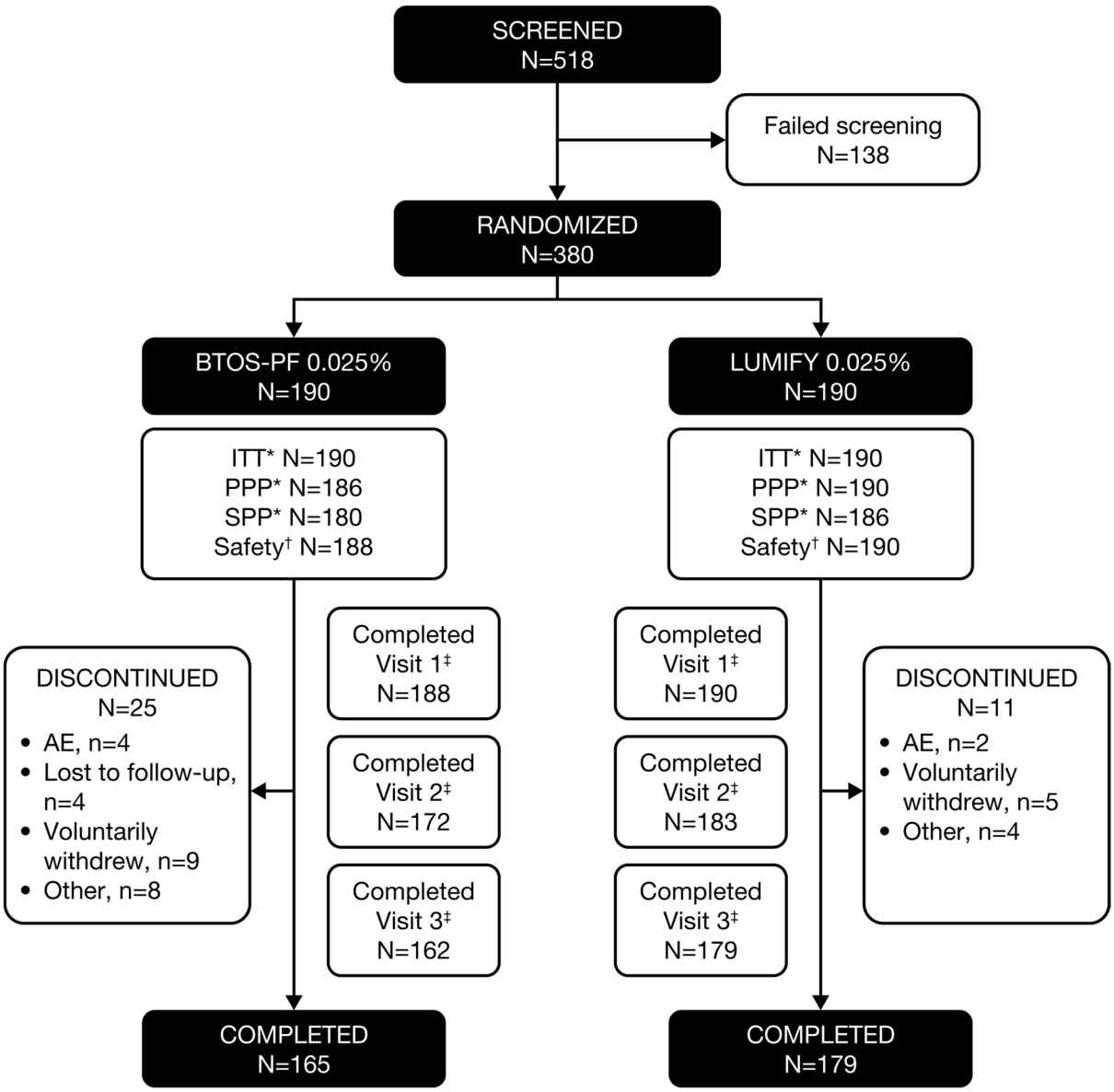

Fig. 1 Participant disposition. *The ITT population included all randomized participants; the PPP population included participants in the ITT who did not have significant protocol deviations likely to affect the primary endpoint analysis; and the SPP population included participants in the ITT who did not have significant protocol deviations likely to affect the secondary endpoints and analyses. †The safety population included all randomized participants who received at least one dose of study drug. ‡For each visit, a participant who had a pre-dose and a post-dose measure for the primary endpoint was defined to have completed the visit. *AE* adverse event, *BTOS-PF* brimonidine tartrate ophthalmic solution, preservative free, *ITT* intent-to-treat, *PPP* primary per-protocol, *SPP* secondary per-protocol

Table 1 Baseline participant demographics and characteristics

	BTOS-PF 0.025% (*N* = 190)	LUMIFY 0.025% (*N* = 190)	All participants (*N* = 380)
Age (years)			
Mean (SD)	58.4 (14.65)	59.5 (14.76)	59.0 (14.70)
Range	20–83	19–87	19–87
< 65 years, *n* (%)	114 (60.0%)	106 (55.8%)	220 (57.9%)
≥ 65 years, *n* (%)	76 (40.0%)	84 (44.2%)	160 (42.1%)
Sex, *n* (%)			
Male	48 (25.3%)	65 (34.2%)	113 (29.7%)
Female	142 (74.7%)	125 (65.8%)	267 (70.3%)
Undifferentiated	0	0	0
Childbearing potential, *n* (%)			
Yes	26 (18.3%)	26 (20.8%)	52 (19.5%)
No	116 (81.7%)	99 (79.2%)	215 (80.5%)
Race, *n* (%)			
American Indian or Alaska	1 (0.5%)	4 (2.1%)	5 (1.3%)
Asian	2 (1.1%)	3 (1.6%)	5 (1.3%)
Black or African American	46 (24.2%)	43 (22.6%)	89 (23.4%)
White	138 (72.6%)	138 (72.6%)	276 (72.6%)
Multiple race[a]	3 (1.6%)	1 (0.5%)	4 (1.1%)
Unknown	0	1 (0.5%)	1 (0.3%)
Ethnicity, *n* (%)			
Hispanic or Latino	12 (6.3%)	17 (8.9%)	29 (7.6%)
Non-Hispanic or non-Latino	178 (93.7%)	173 (91.1%)	351 (92.4%)
Iris color (OU), *n* (%)[b]			
Black	2 (1.1%)	8 (4.2%)	10 (2.6%)
Blue	50 (26.3%)	55 (28.9%)	105 (27.6%)
Brown	84 (44.2%)	82 (43.2%)	166 (43.7%)
Hazel	31 (16.3%)	25 (13.2%)	56 (14.7%)
Green	22 (11.6%)	20 (10.5%)	42 (11.1%)
Gray	1 (0.5%)	0	1 (0.3%)

N numbers represent the number of participants in the given treatment arm for the population being analyzed; percentages are based on the number of participants with a given treatment for the population

BTOS-PF brimonidine tartrate ophthalmic solution, preservative free, *OU* both eyes, *SD* standard deviation

[a]Multiple race was marked if participants had two races selected on electronic case report forms

[b]Values for iris color were the same for right and left eyes

in-office, at visit 1, visit 2, and visit 3. An additional visit (visit 4) occurred 7 days after participants discontinued treatment at the end of the study.

Study Objectives and Assessments

The primary objective was to demonstrate that the efficacy of BTOS-PF 0.025% is non-inferior to LUMIFY 0.025% for treating ocular redness in adults; the secondary objective was to compare the safety of BTOS-PF 0.025% and LUMIFY 0.025%.

Efficacy was assessed at visits 1, 2, and 3; safety was assessed at all visits and patient-reported tolerability was self-evaluated by each participant at visit 1. Participants used their diaries to document QID dosing of their study drug and personal perception of ocular redness, and indicate compliance. The full schedule of assessments and visits for this study are described in Supplementary Fig. S1.

Primary Efficacy Endpoint Evaluation

The primary efficacy endpoint was investigator-assessed ocular redness score before study drug instillation and at 5, 15, 30, 60, 90, 120, 180, and 240 min after instillation at visit 1. Ocular redness was graded in half-unit increments on a 0–4-unit photographic scale (Ora™ Calibra Ocular Redness Scale), with 0 corresponding to no redness and 4 to extremely severe redness (large, numerous, dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, and involves the entire vessel bed). Use of this scale has been recently reported [7, 13]. Redness reduction was analyzed as a comparative reduction in hyperemia between BTOS-PF 0.025% and LUMIFY 0.025%, rather than evaluating absolute reduction in redness for each product.

Secondary Efficacy Endpoint Evaluation

Eight secondary endpoints were evaluated, including investigator-assessed change in pre-instillation ocular redness score at 1, 360, and 480 min after study drug instillation at visit 1, and 1 and 5 min after study drug instillation at both visits 2 and 3. Participant-assessed ocular redness score (0–4-unit scale, not allowing half-unit increments) was recorded in the at-home diary, for each of the four doses instilled on each day of the treatment period (score before instillation and 2 min post-instillation), and was an additional secondary endpoint.

Supportive Efficacy Evaluation

Supportive efficacy endpoints were total clearance of ocular redness (investigator-assessed redness score of 0) at each post-instillation timepoint at each visit (1 min to 480 min post-instillation at visit 1, and 1 min and 5 min post-instillation at visits 2 and 3), and mean ocular redness score at all visit 1 timepoints from 1 to 480 min.

Safety Evaluation

Safety assessments included adverse events (AEs; reported, elicited, and observed), physical examination and vital signs, best-corrected visual acuity (BCVA), intraocular pressure (IOP), dilated ophthalmoscopy, biomicroscopy, and ocular rebound redness (increase of ≥ 1 unit in mean ocular redness score in the follow-up period compared with baseline at visit 1). Investigators documented AEs at all study visits; treatment-emergent AEs (TEAEs) were AEs that occurred or worsened on or after the first dose of the study drug, but were not necessarily related to study treatment.

Participants assessed drop tolerability using two approaches: comfort score on a 0–10 scale (0 = very comfortable–10 = very uncomfortable) at 30 s and 1 min post-instillation on visit 1, and by completing a drop comfort descriptor questionnaire (selecting three comfort descriptor terms from a predetermined list) at 3 min post-instillation visit 1.

Statistical Analyses

The target sample size was 183 participants per treatment group to provide approximately 90% power to demonstrate non-inferiority of BTOS-PF 0.025% to LUMIFY 0.025% at all eight post-instillation timepoints at visit 1 (based on a two-sample t test and assuming a non-inferiority limit of 0.22 units, mean difference of 0 units, and a common standard deviation of 0.50 units with one-sided alpha of 0.025).

Four analysis populations were included in the study: the intent-to-treat (ITT) population included all randomized participants; the primary and secondary per-protocol populations included patients in the ITT who did not have significant protocol deviations likely to affect the primary or secondary endpoint analyses, respectively; and the safety population included all randomized participants who received ≥ 1 dose of study drug.

Primary analyses were performed for the ITT population, based on summary statistics for the pre-dose ocular redness score and each of the post-dose timepoints. BTOS-PF 0.025% was compared with LUMIFY 0.025% for each of the eight timepoints at visit 1 using two-sided 95% confidence intervals around the difference between mean ocular redness scores (BTOS-PF 0.025% minus LUMIFY 0.025%). To demonstrate non-inferiority of BTOS-PF 0.025% to LUMIFY 0.025%, the upper confidence limit around the mean difference between redness scores at each timepoint must not exceed the pre-determined non-inferiority limit of 0.22 units. Sensitivity analyses were performed on primary endpoint data and are described in Supplementary Table S2. Secondary efficacy endpoints were evaluated hierarchically for statistical non-inferiority (Supplementary Table S2).

Safety parameters were reviewed to compare BTOS-PF 0.025% with LUMIFY 0.025%, according to the treatment received by each participant in the safety population. Change from baseline in slit-lamp biomicroscopy, IOP, BCVA, and vital signs were reported by treatment group. Ocular rebound redness was summarized separately, by treatment, using descriptive statistics; assessments performed by eye were summarized for each eye separately. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) terms, with separate summaries for ocular and non-ocular AEs.

Drop comfort scores were summarized with continuous descriptive statistics at visit 1, by treatment group; the scores were averaged over both eyes and summarized.

RESULTS

The study enrolled 380 healthy adults (the ITT population); after screening and randomization, 190 participants were allocated to each treatment group. The primary per-protocol population included 376 participants (BTOS-PF 0.025%, $n = 186$; LUMIFY 0.025%, $n = 190$) and the safety population included 378 participants (BTOS-PF 0.025%, $n = 188$; LUMIFY 0.025%, $n = 190$). Figure 1 summarizes the participant disposition for the study.

Compliance was high across all participants in the ITT and safety populations (95.7 and 97.4%, respectively) and similar for both treatment groups (96.8 and 97.9% for the BTOS-PF 0.025% and LUMIFY 0.025% groups, respectively). Mean (standard deviation) treatment exposure was 28.5 (5.67) days and similar for both treatment arms: 28.0 (6.83) days for the BTOS-PF 0.025% group and 29.0 (4.17) days for the LUMIFY 0.025% group.

Participant mean age was 59 years, with a range of 19–87 years; 160 participants (42.1%) were ≥ 65 years of age.

Demographic characteristics are shown in Table 1 and were comparable between the two study groups, except for black iris color and gender. In the BTOS-PF 0.025% group, 2/190 participants had black iris color (1.1%); in the LUMIFY 0.025% group, 8/190 had black iris color (4.2%). There were 142 female and 48 male participants in the BTOS-PF 0.025% group (47.7 and 25.3%, respectively); the LUMIFY 0.025% group included 125 female and 65 male participants (65.8 and 34.2%, respectively). The proportion of females to males enrolled in the study overall was greater (70.3 and 29.7%, respectively). Concomitant use of any ocular

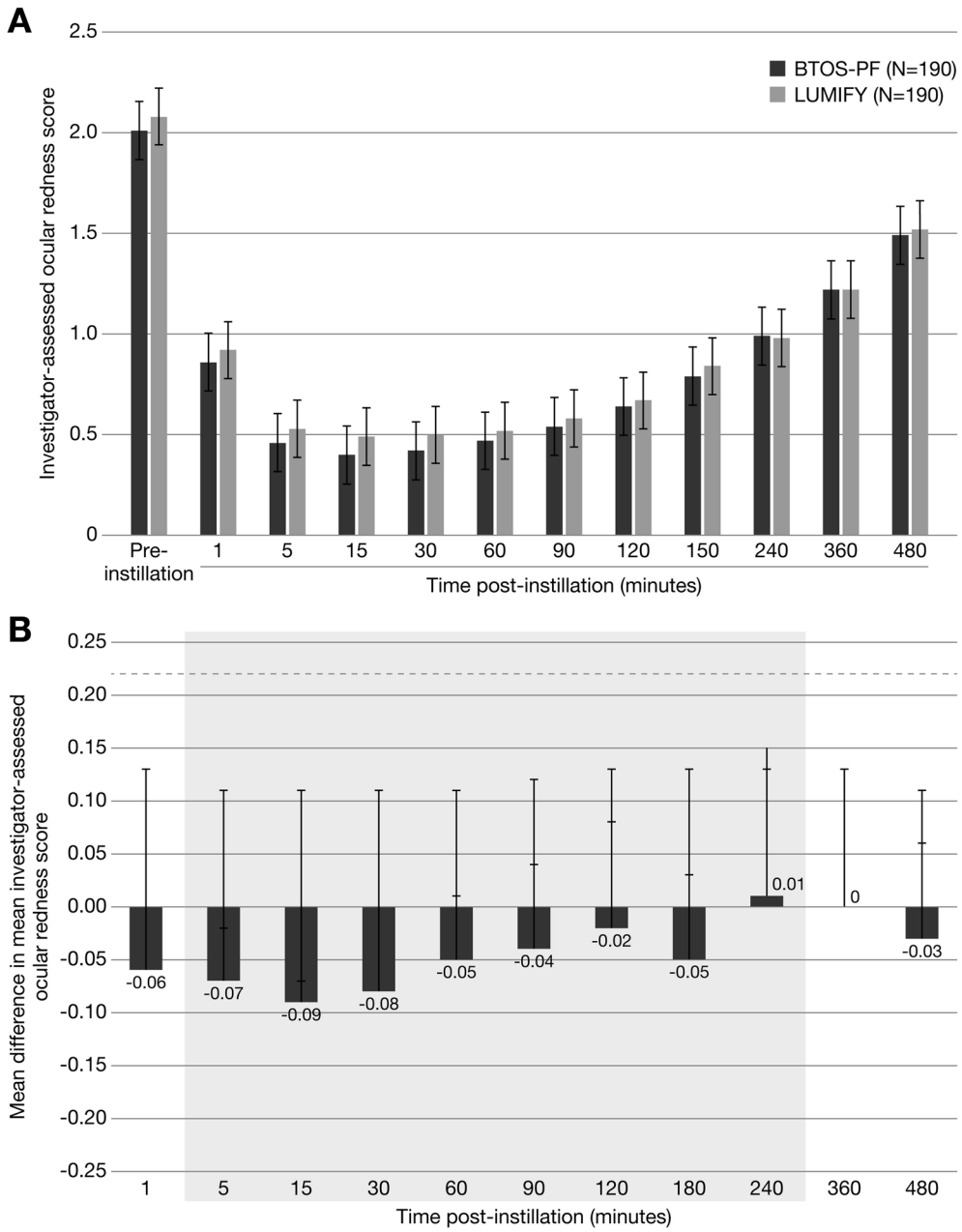

Fig. 2 **A** Change in mean ocular redness score from pre-instillation at visit 1. **B** Mean difference in ocular redness score between BTOS-PF 0.025% and LUMIFY 0.025% at visit 1. **A** Ocular redness was graded by the investigator on a scale from 0 to 4 in half-unit increments, where 0 corresponds to no redness and 4 corresponds to extremely severe redness. *Error bars* indicate the standard error of the mean score; missing data due to lack of efficacy or AEs were imputed using worst observation carried forward method (MNAR assumption). **B** Mean difference in investigator-assessed ocular redness score was assessed using a two-sample *t* test to compare BTOS-PF 0.025% ($n = 190$) and LUMIFY 0.025% ($n = 190$) using multiple imputation methodology (ITT population). *Error bars* indicate the two-sided 95% CI, with the *dotted line* indicating the predetermined non-inferiority limit of 0.22; the table states the upper and lower 95% CI values for each timepoint, with *bold numbers* highlighting upper-limit values less than 0.22; and *gray shading* indicates timepoints that were analyzed for statistical non-inferiority as part of the primary endpoint analysis. *AE* adverse event, *BTOS-PF* brimonidine tartrate ophthalmic solution, preservative free, *CI* confidence interval, *ITT* intent-to-treat, *MNAR* missing not at random

medication was similar between the treatment groups (8.9 and 11.6% of participants in the BTOS-PF 0.025% and LUMIFY 0.025% groups, respectively), and all instances of artificial tears and topical ocular decongestants were discontinued prior to randomization and study drug instillation.

Ocular medical history was comparable between treatment groups. All participants except one had a history of ocular redness (379/380 participants; $n = 190$ in the BTOS-PF 0.025% group and $n = 189$ in the LUMIFY 0.025% group). Other common ocular disorders included a history of dry eye in 184 participants (48.4%), cataract in 218 (57.4%), and vitreous detachment in 91 (23.9%) participants. The occurrence of the most common eye disorders was similar for both treatment groups: 50.5 and 46.3% of participants in the BTOS-PF 0.025% and LUMIFY 0.025% groups, respectively had dry eye, 29.5 and 31.6%, respectively, had cataract, and 22.6 and 25.3%, respectively, had vitreous detachment.

Primary Efficacy

The primary efficacy endpoint was investigator-assessed ocular redness score at eight timepoints from 5 to 240 min after study drug instillation at visit 1. Baseline (pre-installation) scores were comparable for the BTOS-PF 0.025% and LUMIFY 0.025% groups, and all mean post-instillation values were comparable at each of the eight timepoints, with mean differences between the treatment groups ranging from −0.09 to 0.01 units (Fig. 2a).

At all of the primary efficacy endpoint timepoints, the upper confidence limit around the mean difference in ocular redness between BTOS-PF 0.025% and LUMIFY 0.025% did not exceed the pre-determined non-inferiority limit of 0.22 (Fig. 2b), indicating that BTOS-PF 0.025% was statistically non-inferior to LUMIFY 0.025% for the reduction of ocular redness and that the study had met its primary endpoint. Sensitivity analyses were consistent with the primary analysis as the upper confidence limit around the mean difference did not exceed the pre-determined non-inferiority limit.

Secondary and Supporting Efficacy

Change in mean ocular redness score at 1 min and 5 min post-instillation for visits 1, 2, and 3, as appropriate, is presented in Fig. 3. Change in pre-installation ocular redness was comparable between treatment groups for the first three secondary endpoints in the hierarchy (1 min post-instillation at visit 1, 1 min post-instillation at visit 2, and 5 min post-instillation at visit 2).

Mean difference between the BTOS-PF 0.025% group and LUMIFY 0.025% group for the first three secondary endpoints in the hierarchy ranged from −0.03 to 0.01 units and met the non-inferiority criteria, as the upper confidence limit around the mean difference did not exceed the pre-determined non-inferiority limit of 0.22 (Table 2). For these three secondary endpoints, the BTOS-PF 0.025% group was statistically non-inferior compared with the LUMIFY 0.025% group.

For the remaining investigator-rated ocular redness hierarchical secondary endpoints (1 min and 5 min post-instillation at visit 3, 360 min post-instillation at visit 1, and 480 min post-instillation at visit 1; Supplementary Table S3), the mean change from pre-instillation in ocular rebound redness between treatment groups was 0.05–0.10 units. While the later visit 1 timepoints and those at visit 3 supported the primary efficacy non-inferiority findings (upper confidence limits 0.21 for 360 min post-instillation and 0.16 for 480 min post-instillation; Fig. 2b), no statistical inference was applied to these data as the prior secondary endpoint in the hierarchy did not meet the non-inferiority criteria (upper confidence limits of 0.24 and 0.23 for 1 min and 5 min post-instillation on visit 3, respectively; Table 2). The results of the sensitivity analyses were consistent with the original analysis of these investigator-assessed secondary endpoints.

Although participant-assessed ocular redness scores and changes from pre-instillation ocular redness values were similar between treatment groups, with upper confidence limits < 0.19, no statistical inference was applied because the prior hierarchical endpoint did not meet the non-inferiority criteria.

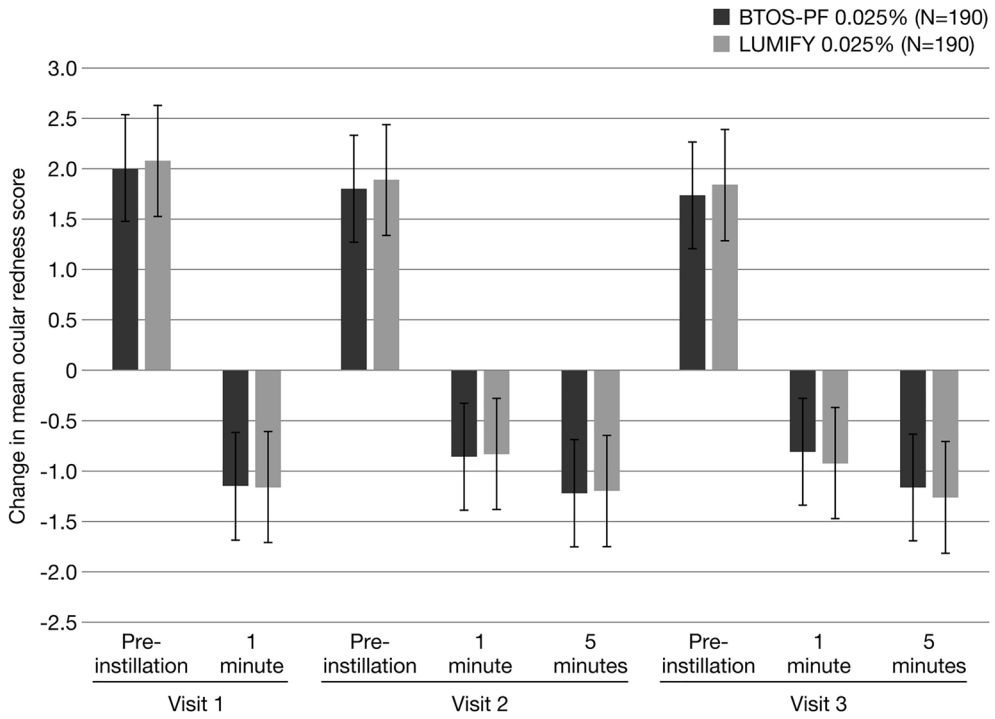

Fig. 3 Change in mean ocular redness score at 1 min and 5 min from pre-instillation. Ocular redness was graded by the investigator on a scale from 0 to 4 in half-unit increments, where 0 corresponds to no redness and 4 corresponds to extremely severe redness. Missing data due to lack of efficacy or AEs were imputed using worst observation carried forward method (MNAR assumption). *Error bars* indicate the standard error of the mean score. *AE* adverse event, *BTOS-PF* brimonidine tartrate ophthalmic solution, preservative free, *MNAR* missing not at random

A similar percentage of participants in the BTOS-PF 0.025% and LUMIFY 0.025% groups achieved total clearance of ocular redness, supporting primary and secondary endpoint findings. At visit 1, there was no significant difference between treatment groups in the number of participants achieving total clearance at any of the 11 timepoints from 1 to 480 min post-instillation; at 480 min post-instillation, two participants from each treatment group had total clearance of ocular redness. While not statistically significant, the percentage of patients with total clearance of ocular redness was numerically greater for the BTOS-PF 0.025% group than for the LUMIFY 0.025% group at the majority of timepoints from visit 1 to visit 3 (Table 3).

Safety

The overall safety profile of BTOS-PF 0.025% was favorable and similar to LUMIFY 0.025% (Tables 4 and 5). A total of 48 TEAEs were reported for 37/188 participants (19.7%) in the BTOS-PF 0.025% group, and 61 TEAEs reported for 39/190 participants (20.5%) in the LUMIFY 0.025% group. Ten TEAEs in the BTOS-PF 0.025% group and 15 in the LUMIFY 0.025% group were considered treatment-related and occurred in nine and 13 participants, respectively (Supplementary Table S4).

Occurrence of ocular TEAEs was similar in both treatment groups: 20 ocular TEAEs occurred in 16 participants (8.5%) in the BTOS-PF 0.025% group, and 21 ocular TEAEs occurred in 20 (10.5%) participants in the LUMIFY 0.025% group (Table 5). Eye disorders were reported in eight participants (8.5%) in the BTOS-PF 0.025%

Table 2 Mean difference in ocular redness score at 1 min and 5 min from pre-instillation

Treatment/timepoint	BTOS-PF 0.025% (*N* = 190) Mean (SE)	LUMIFY 0.025% (*N* = 190) Mean (SE)	Mean difference[a] (SE)	Two-sided 95% CI[a]	Hierarchy
Visit 1 (day 1)					
Pre-instillation	2.01 (0.040)	2.08 (0.042)			
1-min change from pre-instillation	− 1.15 (0.050)	− 1.16 (0.051)	0.01 (0.072)	**(− 0.13, 0.15)**	1
Visit 2 (day 15)					
Pre-instillation	1.80 (0.049)	1.89 (0.053)			
1-min change from pre-instillation	− 0.86 (0.048)	− 0.83 (0.046)	− 0.03 (0.067)	**(− 0.16, 0.10)**	2
5-min change from pre-instillation	− 1.22 (0.049)	− 1.20 (0.051)	− 0.02 (0.071)	**(− 0.16, 0.12)**	3
Visit 3 (day 29)					
Pre-instillation	1.74 (0.049)	1.84 (0.052)			
1-min change from pre-instillation	− 0.81 (0.049)	− 0.92 (0.044)	0.11 (0.066)	(− 0.01, 0.24)	4
5-min change from pre-instillation	− 1.16 (0.052)	− 1.26 (0.047)	0.09 (0.070)	(− 0.04, 0.23)	5

BTOS-PF brimonidine tartrate ophthalmic solution, preservative free, *CI* confidence interval, *SE* standard error

[a]Mean difference in investigator-assessed ocular redness score was assessed using a two-sample *t* test to compare BTOS-PF 0.025% (*n* = 190) and LUMIFY 0.025% (*n* = 190) using multiple imputation methodology. Bold text indicates timepoints that achieved statistical non-inferiority as part of the hierarchical secondary endpoint analysis

group and 12 (6.3%) participants in the LUMIFY 0.025%; general disorders and administration site conditions were reported for eight participants in both the BTOS-PF 0.025% and LUMIFY 0.025% groups (4.3 and 4.2%, respectively). Infections and infestations were only reported in participants receiving BTOS-PF 0.025% (three patients with hordeolum, 1.6%).

Most TEAEs were mild in severity. One participant in the LUMIFY 0.025% group experienced a serious and severe non-ocular TEAE of sepsis, which was considered severe, unexpected, and not related to study drug. One participant in the BTOS-PF 0.025% group reported ocular TEAEs of conjunctival hyperemia and eye pain, which were considered moderate in severity and related to study drug. None of the ocular events were considered severe or serious.

Four participants in the BTOS-PF 0.025% group and two participants in the LUMIFY 0.025% group discontinued the study due to a TEAE. None of these events were considered related to study treatment and all were considered mild, apart from one moderate incidence of COVID-19 in a patient in the BTOS-PF 0.025% group. None of the events leading to discontinuation were considered serious, and all patients had either recovered/resolved or were recovering/resolving at the time of data analysis.

No safety concerns resulted from of any of the clinical examinations (BCVA, slit-lamp biomicroscopy, IOP, and ocular rebound redness), and there were no changes in vital signs or physical examination findings leading to concern in either the BTOS-PF 0.025% group or LUMIFY 0.025% group.

Rates of ocular rebound redness were low and similar between treatment groups: three (1.8%) participants in the BTOS-PF 0.025% group and one (0.6%) participant in the LUMIFY 0.025% group experienced ocular rebound redness.

Table 3 Total clearance of ocular redness

Treatment timepoint	BTOS-PF 0.025% ($N = 190$)		LUMIFY 0.025% ($N = 190$)		p value[a]
	m	Participants (%) with total clearance	*m*	Participants (%) with total clearance	
Visit 1					
1 min post-instillation	187	31 (16.6)	190	26 (13.7)	0.4330
5 min post-instillation	188	81 (43.1)	190	73 (38.4)	0.3561
15 min post-instillation	188	97 (51.6)	190	81 (42.6)	0.0809
30 min post-instillation	188	92 (48.9)	190	79 (41.6)	0.1507
60 min post-instillation	188	81 (43.1)	190	74 (38.9)	0.4135
90 min post-instillation	188	69 (36.7)	190	71 (37.4)	0.8933
120 min post-instillation	188	60 (31.9)	190	60 (31.6)	0.9441
180 min post-instillation	188	41 (21.8)	190	40 (21.1)	0.8579
240 min post-instillation	188	19 (10.1)	190	24 (12.6)	0.4395
360 min post-instillation	188	9 (4.8)	190	7 (3.7)	0.5943
480 min post-instillation	188	2 (1.1)	185	2 (1.1)	0.9871
Visit 2					
1 min post-instillation	172	32 (18.6)	183	18 (9.8)	0.0176
5 min post-instillation	172	61 (35.5)	183	52 (28.4)	0.1541
Visit 3					
1 min post-instillation	162	22 (13.6)	179	24 (13.4)	0.9629
5 min post-instillation	161	59 (36.6)	179	63 (35.2)	0.7807

N represents the total number of participants in the given treatment for the population being analyzed; percentages were based on m (number of subjects with non-missing ocular redness score at each timepoint). Total clearance defined as ocular redness score of 0, based on investigator assessment; ocular redness was graded by the investigator on a scale from 0 to 4 in half-unit increments, where 0 corresponds to no redness and 4 to extremely severe redness

BTOS-PF brimonidine tartrate ophthalmic solution, preservative free

[a]From a chi-squared test if sample size was at least 5; if less than 5, Fisher's exact test was used

Patient-Reported Tolerability

Tolerability was comparable between treatment groups. Mean patient-reported comfort scores were < 1 across all timepoints for both BTOS-PF 0.025% and LUMIFY 0.025% groups, and the most common first-word descriptors for each preparation were the same. For BTOS-PF 0.025% and LUMIFY 0.025%, "comfortable" (50.0 and 51.1%, respectively), "refreshing" (20.2 and 20%, respectively), and "cool" (14.4 and 11.6%, respectively) were the three most common first-word descriptors. Negative first-word descriptors were used to describe BTOS-PF 0.025% and LUMIFY 0.025% in < 7% of cases and included "burning" (5.3 and 6.8%, respectively), "filmy" (2.7 and 3.2%, respectively), and "stinging" (1.6 and 0.0%, respectively). No safety concerns were raised from tolerability assessments.

Table 4 Summary of non-ocular TEAEs (safety population)

SOC, *n* (%)	BTOS-PF 0.025% (*N* = 188)	LUMIFY 0.025% (*N* = 190)
Any non-ocular TEAEs	**23 (12.2%)**	**22 (11.6%)**
Infections and infestations	13 (6.9%)	13 (6.8%)
Investigations	4 (2.1%)	2 (1.1%)
Endocrine disorders	1 (0.5%)	1 (0.5%)
Gastrointestinal disorders	1 (0.5%)	3 (1.6%)
Metabolism and nutrition disorders	1 (0.5%)	1 (0.5%)
Musculoskeletal and connective tissue disorders	1 (0.5%)	2 (1.1%)
Skin and subcutaneous tissue disorders	1 (0.5%)	0
Blood and lymphatic system disorders	0	1 (0.5%)
Ear and labyrinth disorders	0	1 (0.5%)
General disorders and administration site conditions	0	1 (0.5%)
Renal and urinary disorders	0	1 (0.5%)
Respiratory, thoracic, and mediastinal disorders	0	2 (1.1%)
Vascular disorders	0	1 (0.5%)

N numbers in the table headers represent the total number of participants in the given treatment arm for the population being analyzed and were used as the denominator for calculating percentages. *N* numbers in each row represent the number of unique participants in the given category (a participant with multiple AEs within the same SOC or PT were only counted once in that SOC or PT). A TEAE is defined as an AE with a start date on or after the first dose of study drug or that worsened following administration of study drug treatment or study completion/discontinuation. AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. SOCs are sorted by descending frequency of BTOS-PF 0.025% participants

AE adverse event, *BTOS-PF* brimonidine tartrate ophthalmic solution, preservative free, *PT* preferred term, *SOC* system organ class, *TEAE* treatment-emergent adverse event

DISCUSSION

Ocular redness is a common ophthalmic complaint caused by inflammation, with triggers including environmental irritants [1–3]. Topical OTC ophthalmic vasoconstrictors can temporarily relieve the vasocongestion that leads to the appearance of ocular redness, with current guidance restricting their use to short-term [1, 3, 4]. LUMIFY 0.025% is an ophthalmic solution of brimonidine tartrate 0.025%, and is the first α2-AR-selective agonist approved to treat ocular redness [1, 6, 7].

Like most multidose topical ophthalmic preparations, LUMIFY 0.025% contains BAK as a preservative to prevent loss of sterility and reduce the risk of eye infections [8, 10, 11, 14]. While the antimicrobial effects of BAK are necessary in many scenarios, extended exposure to BAK-containing products should be avoided to reduce the risk of symptoms of OSD, particularly in patients who chronically use topical ophthalmic agents, or use more than one topical agent at any given time, leading to cumulative BAK exposure. A preservative-free LUMIFY 0.025% formulation (BTOS-PF 0.025%) could offer an alternative preparation to minimize or eliminate BAK exposure to benefit patients

Table 5 Summary of ocular TEAEs

SOC, *n* (%)	**BTOS-PF 0.025%, *n* (%) (*N* = 188)**	**LUMIFY 0.025%, *n* (%) (*N* = 190)**
Any ocular TEAEs	**16 (8.5%)**	**20 (10.5%)**
Eye disorders	8 (4.3%)	12 (6.3%)
Blepharospasm	1 (0.5%)	0
Conjunctival hemorrhage	1 (0.5%)	1 (0.5%)
Conjunctival hyperemia	1 (0.5%)	0
Eye pain	1 (0.5%)	0
Ocular hyperemia	1 (0.5%)	0
Photophobia	1 (0.5%)	0
Vision blurred	1 (0.5%)	0
Visual acuity reduced	1 (0.5%)	4 (2.1%)
Visual impairment	1 (0.5%)	1 (0.5%)
Blepharitis	0	1 (0.5%)
Dry eye	0	1 (0.5%)
Eye irritation	0	1 (0.5%)
Eye pruritus	0	1 (0.5%)
Eyelid margin crusting	0	1 (0.5%)
Miosis	0	1 (0.5%)
Punctate keratitis	0	1 (0.5%)
General disorders and administration site conditions	8 (4.3%)	8 (4.2%)
Instillation site pain	6 (3.2%)	6 (3.2%)
Instillation site pruritus	2 (1.1%)	0
Instillation site foreign body sensation	0	2 (1.1%)
Infections and infestations	3 (1.6%)	0
Hordeolum	3 (1.6%)	0

N numbers in the table headers represent the total number of participants in the given treatment arm for the population being analyzed and were used as the denominator for calculating percentages. *N* numbers in each row represent the number of unique participants in the given category (a participant with multiple AEs within the same SOC or PT were only counted once in that SOC or PT). A TEAE is defined as an AE with a start date on or after the first dose of study drug or that worsened following administration of study drug treatment or study completion/discontinuation. AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. SOCs are sorted by descending frequency of BTOS-PF 0.025% participants

AE adverse event, *BTOS-PF* brimonidine tartrate ophthalmic solution, preservative free, *PT* preferred term, *SOC* system organ class, *TEAE* treatment-emergent adverse event

with existing eye irritation or sensitivity, or who are already using daily topical ophthalmic preparations, as long as efficacy is maintained [8–11, 15].

In this randomized, active-controlled, multicenter study, we aimed to demonstrate that the efficacy of BTOS-PF 0.025% is non-inferior to LUMIFY 0.025% for treating ocular redness in adults. The design of the study evaluated redness reduction as comparative reductions in hyperemia with BTOS-PF 0.025% relative to LUMIFY 0.025%. The study met the primary endpoint, and BTOS-PF 0.025% was statistically non-inferior to LUMIFY 0.025% for the reduction of ocular redness across eight timepoints at the first instillation visit, from 5 to 240 min post-instillation. The study outcome assessments mirrored the pivotal trial of LUMIFY 0.025% for the reduction of ocular redness [7].

While not statistically significant, additional timepoints at visit 1 (1, 360, and 480 min post-instillation) were analyzed as secondary hierarchical endpoints and indicated that BTOS-PF 0.025% performed similarly to LUMIFY 0.025%, supporting the primary efficacy non-inferiority findings. Both formulations effectively reduced ocular redness from as early as 1 min post-instillation and up to 8 h post-instillation.

BTOS-PF 0.025% was non-inferior to LUMIFY 0.025% for the reduction of ocular redness at visit 2, and performed similarly at visit 3, although no statistical inference was made based on the hierarchical assessment of these endpoints. Other data collected at visits 2 and 3 indicated that BTOS-PF 0.025% performed similarly to LUMIFY 0.025% after 14 and 28 days of use; rates of ocular rebound redness were low and similar for BTOS-PF 0.025% and LUMIFY 0.025% during the study.

Results for the investigator-assessed total clearance of ocular redness also demonstrated that BTOS-PF 0.025% performed similarly to LUMIFY 0.025%. In addition, all self-reported ocular redness scores and change from pre-instillation ocular redness values were similar between treatment groups, although no statistical inferences were made from participant-evaluated redness data.

The overall safety profile of BTOS-PF 0.025% was favorable and similar to LUMIFY 0.025%, with no severe or serious ocular events, and most TEAEs were mild. The patient-reported tolerability of BTOS-PF 0.025% and LUMIFY 0.025% was comparable, with > 93% of participants choosing positive first-word descriptors overall, and the same words used for both preparations by similar proportions of participants.

Limitations of the study include the absence of statistical inference possible for all the secondary outcomes due to the preplanned hierarchical analysis. Although similar proportions of participants in the BTOS-PF and LUMIFY groups had dry eye at baseline, impact of baseline dry eye severity and lubricating drop use on redness response and/or tolerability assessments cannot be discounted. Further investigations, such as dedicated assessment of short-term effects and longer-term outcomes, including additional assessment visits after discontinuing treatment beyond 7 days, could be informative. Future subanalyses according to baseline age, sex, and dry eye severity could also be of interest, depending on the availability of a larger sample size.

CONCLUSIONS

The efficacy of BTOS-PF 0.025% was statistically non-inferior to LUMIFY 0.025% for the reduction of ocular redness in adults when administered QID for up to 1 month. The safety profile and tolerability of BTOS-PF 0.025% were favorable and similar to LUMIFY 0.025%, and ocular rebound redness was comparable and minimal.

BTOS-PF 0.025% offers an alternative topical treatment option for clinicians and their adult patients who prefer a preservative-free formulation to manage ocular redness. The findings from the study demonstrate that BTOS-PF 0.025% provides a preservative-free formulation without loss of efficacy or compromised safety when compared with the original BAK-containing medication.

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Data Availability. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Melissa Toyos is a clinical investigator, speaker and consultant for Bausch + Lomb and Mallinckrodt, a clinical investigator and consultant for Dompé and Sun Pharma, and a clinical investigator for Kala Pharmaceuticals, Glaukos and CBCC Global. Melinda DiVito is an employee of Bausch + Lomb Inc.; Patrick M. Vollmer is a clinical investigator and speaker for Bausch + Lomb; Elisabeth M. Messmer is a speaker for: Alcon, Bausch + Lomb, Bayer, Dompé, Fidia, GlaxoSmithKline, Novartis, OmniVision, Sanofi, Santen GmbH, Théa Pharma GmbH, TRB-Chemedica AG, Ursapharm, and Visufarma, and a consultant for: Alcon, Alfa Intes, DMG, Dompé, Kala, Novaliq, Novartis, Santen GmbH, Senju, Shire, Sifi, Sun, Théa Pharma GmbH, TRB-Chemedica AG, Viatris, and Visufarma. Selina McGee, Jared Peterson, Assem Patel, Guruprasad Pattar, David G. Evans, and Gina Wesley have nothing to disclose.

Ethical Approval. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines, the principals of Good Clinical Practice, and applicable local regulatory requirements. The study protocol, informed consent form, and other information provided to participants, and all appropriate amendments were properly reviewed and approved by an Institutional Review Board (Alpha IRB, 1001 Avenida Pico, San Clemente, CA 92673).

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