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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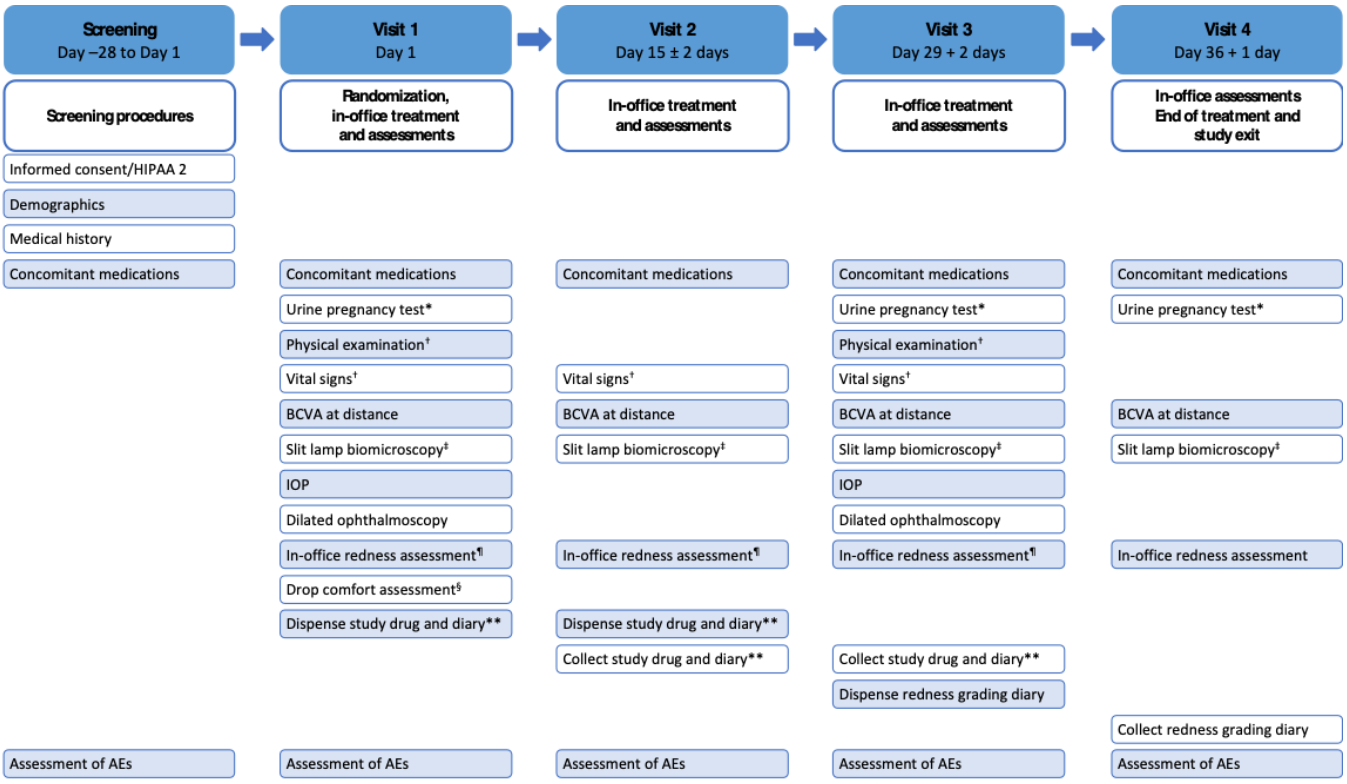
Supplementary Material

Figure S1: Study design.



Informed consent was required before performing any study-related procedure. If medication washout was necessary, informed consent was obtained prior to Visit 1; if there was no washout period, the screening visit and Visit 1 occurred on the same day. *For females of childbearing potential, including all females who had experienced menarche and had not experienced menopause (as defined by amenorrhea for >12 consecutive months) or had not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). †Physical examination included general health, and examination of head, eyes, ears, nose and throat, and recording of any other comments; vital signs (resting blood pressure and pulse) were collected with body weight at Visits 1 and 3 and without body weight at Visit 2. ‡Evaluated before and after study drug instillation at Visits 1, 2, and 3. ¶At Visit 1, the investigator evaluated ocular redness prior to study drug instillation and at 1 (+0.5), 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), 240(+15), 360(+15), and 480(+15) minutes post-study drug instillation; at Visit 2 and 3, the investigator evaluated ocular redness prior to study drug instillation and at approximately 1 and 5 minutes post-instillation. §Participants assessed comfort at instillation,

and at 30 seconds and 1 minute post-instillation, using a 0–10-unit scale for each eye at Visit 1; participants also selected comfort descriptor terms from a pre-determined list at 3 minutes post-instillation at Visit 1. **Performed by the unmasked designee.

AE, adverse event; BCVA, best-corrected visual acuity; HIPAA, Health Insurance Portability and Accountability Act; IOP, intraocular pressure.

Table S1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• ≥18 years of age at the time of giving informed consent; either gender; and any race or ethnicity
• Provided written informed consent and signed the Health Insurance Portability and Accountability Act form
• Willing and able to follow all instructions and attend all study visits
• A history of vasoconstrictor (redness relief drops) use within the last 6 months, or a desire to use OTC vasoconstrictors for redness relief
• Able to self-administer eye drops satisfactorily or with a care provider routinely available for this purpose[a]
• If female and of childbearing potential:[b]
  ○ Willing to have urine pregnancy testing performed at Visit 1 (must be negative) and at exit visit
  ○ Not lactating
  ○ Willing to use at least one medically accepted form of birth control[c] for at least 14 days before the first dose of study drug (Visit 1), throughout the study, and for 1 month after the last dose of study drug
	• Pregnant, nursing, or planning a pregnancy within the study period
	• Known contraindications or sensitivity to any of the study drug(s) or their components, or any other medications required by the protocol
	• Ocular surgical intervention within 3 months prior to screening or during the study, and/or a history of refractive surgery within the past 6 months
	• Presence of an active ocular infection (bacterial, viral, or fungal) or positive history of an ocular herpetic infection at any visit
	• Use of any of the following disallowed medications during the period indicated prior to screening and for the duration of the study:[e]
	  ○ Any topical ophthalmic agent, including artificial tear products, eye whiteners (eg, vasoconstrictors), ocular decongestants, ocular antihistamines, ocular corticosteroids, dilating drops (excluding dilated ophthalmoscopy exam at Visit 1), and contact lenses, ≤5 days prior to baseline and for the duration of the study
	  ○ Systemic antihistamines or decongestants <7 days prior to baseline and for the duration of the study

• If male and with female partner of childbearing potential, willing to use at least 1 medically acceptable form of birth control[d] • If necessary, a calculated best-corrected visual acuity of ≥0.3 logMAR in each eye, as measured by ETDRS • A baseline (Visit 1) investigator-assessed redness score >1 unit in both eyes on the 0–4-unit scale of the Investigator Ocular Redness Scale • Stable ocular health (defined as no ocular conditions requiring therapy or surgical intervention) during the study	○ Systemic corticosteroids or cancer chemotherapy, and/or any systemic medications that, in the opinion of the investigator, may confound study data, or interfere with study participation: <14 days prior to baseline and for the duration of the study • Significant illness that could compromise study participation, in the opinion of the investigator (currently active or within 7 days of beginning study drug) • Concurrent use of an investigational drug or device during the study period (anticipated or within 30 days of beginning study drug) • Ocular or systemic condition or situation that, in the opinion of the investigator, could put the participant at increased risk, confound study data, or interfere significantly with their study participation • Planned surgery (ocular or systemic) during the study period or within 30 days after the study period • Currently breastfeeding or planning to breastfeed during the study period, or a female who was currently pregnant, was planning a pregnancy, or had a positive urine pregnancy test at Visit 1 • Diagnosis of ocular hypertension or glaucoma at Screening

	• Symptoms that, in the opinion of the investigator, were associated with COVID-19 or been in contact with someone diagnosed with COVID-19 in the last 14 days

[a]If eyedrops were to be administered by a care provider, or alternative, then they were present at Visit 1 to administer eye drops in-office. [b]Women considered capable of becoming pregnant included all females who had experienced menarche and had not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). [c]Acceptable forms of birth control were true abstinence (when this was in line with the preferred and usual lifestyle of the participant), spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of male partner at least 3 months before the first dose of study drug (Visit 1). [d]Acceptable forms of birth control were true abstinence (when this was in line with the preferred and usual lifestyle of the participant) or vasectomy ≥3 months before the first dose of study drug (Visit 1); without a vasectomy, the participant must have used condoms with spermicidal agent ≥14 days before the first dose of study drug (Visit 1) and for 1 month after the last dose of the study drug (Visit 3). [e]Any ophthalmic medications were discontinued before study start to not confound either the safety or the efficacy results, meaning that participants were ineligible and would not be enrolled if they had active dry eye disease that required treatment, such as artificial tears.

EDTRS, Early Treatment Diabetic Retinopathy Study; logMAR, Logarithm of the Minimum Angle of Resolution; OTC, over-the-counter.

Table S2: Sensitivity analyses for the primary and secondary endpoints

Primary endpoints	Secondary endpoints
• Primary efficacy analysis repeated on the ITT population with observed data only • No single or multiple imputations were performed	• Secondary efficacy analyses repeated on the SPP population using the same imputation strategy as the primary efficacy endpoint
• Primary efficacy analysis repeated on the ITT population where all the missing redness scores and redness scores on or after prohibited medication use were imputed using the worst (highest) ocular redness score • No multiple imputations were performed	• Secondary efficacy analyses repeated on the ITT population where redness scores after intercurrent events (including missing scores and scores during prohibited medication use) were not imputed
• Primary efficacy analysis was repeated on the ITT population where all the missing redness scores and redness scores on or after prohibited medication use in the BTOS-PF 0.025% group were imputed using the worst (highest) ocular redness score and the LUMIFY 0.025% group were imputed using the best (lowest) ocular redness scores • No multiple imputations were performed	• Secondary efficacy analyses repeated on the SPP population where redness scores after intercurrent events (including missing scores and scores during prohibited medication use) were not imputed
• Primary efficacy analysis repeated on the PPP population with observed data only • No single or multiple imputations were performed	
• Primary efficacy analysis repeated on the per-protocol population using the same imputation strategy as used in the primary efficacy endpoint	

• Primary efficacy analysis repeated on the ITT population where all the missing values and redness scores on or after prohibited medication use were imputed using a regression-based multiple imputation strategy • No single imputations were performed	
• Primary efficacy analysis repeated on the ITT population where all the missing values and redness scores on or after prohibited medication use were imputed using multiple imputations with MNAR assumption by searching for the tipping point (shift value causing the final test result to be reversed from non-inferior to inferior) • Tipping point analysis was performed at each of the primary efficacy timepoints (5, 15, 30, 60, 90, 120, 180, and 240 minutes post-instillation) • Shift range and size was determined when executing the analysis	

BTOS-PF, brimonidine tartrate ophthalmic solution-preservative free; ITT, intent-to-treat; MNAR, missing not at random; PPP, primary per-protocol; SPP, secondary per-protocol.

Table S3: Hierarchy of secondary endpoint analyses

Hierarchy position	Secondary endpoint
1	Change from **pre-instillation ocular redness score evaluated by the investigator** at **1 minute** after study drug instillation (0–4-unit scale, allowing half-unit increments) at **Visit 1**
2	Change from **pre-instillation ocular redness score evaluated by the investigator** at **1 minute** after study drug instillation (0–4-unit scale, allowing half-unit increments) at **Visit 2**
3	Change from **pre-instillation ocular redness score evaluated by the investigator** at **5 minutes** after study drug instillation (0–4-unit scale, allowing half-unit increments) at **Visit 2**
4	Change from **pre-instillation ocular redness score evaluated by the investigator** at **1 minute** after study drug instillation (0–4-unit scale, allowing half-unit increments) at **Visit 3**
5	Change from **pre-instillation ocular redness score evaluated by the investigator** at **5 minutes** after study drug instillation (0–4-unit scale, allowing half-unit increments) at **Visit 3**
6	Change from **pre-instillation ocular redness score evaluated by the investigator** at **360 minutes** after study drug instillation (0–4-unit scale, allowing half-unit increments) at **Visit 1**
7	Change from **pre-instillation ocular redness score evaluated by the investigator** at **480 minutes** after study drug instillation (0–4-unit scale, allowing half-unit increments) at **Visit 1**
8	**Ocular redness score evaluated by the participant** as captured in the **dosing diary throughout the treatment period** (0–4-unit scale, NOT allowing half-unit increments)

Table S4: Summary of treatment-related TEAEs

SOC **PT**	**BTOS-PF 0.025%, n (%)** **(n=188)**	**LUMIFY 0.025%, n (%)** **(n=190)**
Any treatment-related TEAE	**9 (4.8%)**	**13 (6.3%)**
Any treatment-related non-ocular TEAE	**0**	**1 (0.5%)**
Infections and infestations	0	1 (0.5%)
Tooth infection	0	1 (0.5%)
Investigations	0	1 (0.5%)
Blood glucose increased	0	1 (0.5%)
Any treatment-related ocular TEAE	**9 (4.8%)**	**12 (6.3%)**
Eye disorders	2 (1.1%)	4 (2.1%)
Conjunctival hyperemia	1 (0.5%)	4 (2.1%)
Eye pain	1 (0.5%)	0
Photophobia	0	0
Dry eye	0	1 (0.5%)
Eye irritation	0	1 (0.5%)
Eyelid margin crusting	0	1 (0.5%)
Miosis	0	1 (0.5%)
Visual acuity reduced	0	1 (0.5%)
General disorders and administration site conditions	7 (3.7%)	8 (4.2%)
Instillation site pain	5 (2.7%)	6 (3.2%)

Instillation site pruritus	2 (1.1%)	0
Instillation site foreign body sensation	0	2 (1.1%)

Treatment-related TEAEs include TEAEs that were recorded with a relationship “related” by the investigator. 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.