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ORIGINAL RESEARCH

Safety of Once-Daily Oxymetazoline HCl Ophthalmic Solution, 0.1% in Patients with Acquired Blepharoptosis: Results from Four Randomized, Double-Masked Clinical Trials

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Purpose: An oxymetazoline 0.1% ophthalmic solution was recently approved for treatment of acquired blepharoptosis in adults. This study's objective was to evaluate the safety profile of oxymetazoline 0.1% when administered once daily for 14–84 days.

Patients and Methods: Pooled analysis examined safety outcomes from four randomized, double-masked, placebo-controlled clinical trials conducted at 6, 16, 27, and 35 sites, respectively, in the United States. In total, 568 participants with acquired blepharoptosis were evaluated. Median age was 66 years and 74.8% of participants were female. Overall, 375 participants self-administered oxymetazoline 0.1% to both eyes once/day and 193 self-administered placebo (vehicle) daily. Treatment-emergent adverse event (TEAE) rates, severity, and causality were evaluated in the overall population and within participant subgroups defined based on age, race, and ethnicity. Vital signs and ophthalmic findings were evaluated at predefined study visits. Patient-reported treatment tolerability was recorded at study end.

Results: TEAE incidence was similar among participants using oxymetazoline 0.1% (31.2%) or vehicle (30.6%). Nearly all TEAEs were mild-to-moderate, and most were not suspected of being treatment related. Serious TEAEs occurred in four participants receiving oxymetazoline 0.1% and one participant receiving vehicle. Nine and two participants in the oxymetazoline 0.1% and vehicle groups, respectively, discontinued due to a TEAE. Ocular TEAEs occurring in ≥2% of participants receiving oxymetazoline 0.1% were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, and corneal vital dye staining, with none occurring in >3.5% of participants. TEAE rates were similar across subgroups based on age, race, and ethnicity. No clinically significant mean changes in vital signs or ophthalmologic findings occurred, and >98% of participants rated oxymetazoline 0.1% as causing no/mild discomfort.

Conclusion: Once-daily oxymetazoline 0.1% was safe and well tolerated in participants with acquired blepharoptosis when used for 14–84 days. Safety did not appear to differ based on age, race, or ethnicity.

Keywords: adrenergic agonist, adverse event, eye drop, intraocular pressure, Müller's muscle, pupil, topical

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Plain Language Summary

Acquired blepharoptosis is a common condition of the upper eyelid. It is characterized by drooping of one or both eyelids, which affects the appearance of the eyes and can also impair the superior (upper) visual field and negatively impact daily activities. A solution of oxymetazoline 0.1%, used as a once-daily eye drop, recently became available for the

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treatment of acquired blepharoptosis in adults, making it the first drug approved for this condition (previously, surgery was the only effective treatment option). The efficacy and safety of oxymetazoline 0.1% have been studied in four clinical trials ranging in duration from 14 to 84 days. This analysis examined data from all four studies to provide a comprehensive evaluation of the safety of oxymetazoline 0.1% when used once daily in both eyes. In total, we evaluated 375 participants who used oxymetazoline 0.1% and 193 participants who used placebo (vehicle solution). Overall rates of unwanted adverse events were similar between the comparator groups. In addition, most events reported were mild and unrelated to treatment, and serious or severe events were rare. Adverse event rates were also found to be similar across participant groups defined based on age, race, and ethnicity. Oxymetazoline 0.1% did not cause any meaningful changes in ocular measures such as intraocular pressure and pupil diameter, and finally, the vast majority of participants indicated that oxymetazoline 0.1% use was associated with either no or only mild discomfort. These results provide important insights about oxymetazoline 0.1% and support a favorable safety profile.

Introduction

Blepharoptosis is a common condition of the upper eyelid, for which treatment options have been relatively limited. In addition to affecting the appearance of the eyes, drooping of the eyelids can impair the superior visual field.[1–4] The eyelid is raised primarily by the levator palpebrae superioris (levator), which receives input from the oculomotor nerve and inserts, via its aponeurosis, onto the anterior surface of the superior tarsal plate. Remaining lift is provided by the superior tarsal (Müller's) muscle, which receives sympathetic innervation from the superior ganglionic chain and inserts onto the superior tarsal plate.[5–9]

Acquired forms of blepharoptosis are typically classified based on underlying cause.[5,9–12] In a series of 251 surgical patients, aponeurotic blepharoptosis (due to stretching, dehiscence, or detachment of the levator muscle complex that is typically age-related) was the most common form of the condition,[10] a finding consistent with evidence showing increasing blepharoptosis prevalence with age.[13–15]

The standard of care for acquired blepharoptosis is surgical intervention targeting the levator, Müller's muscle, and levator aponeurosis.[5,16,17] Surgery is effective in improving eyelid elevation, superior visual field function, and quality-of-life measures,[16,18–20] but it also presents complication risks. These range from short-term concerns (bleeding, swelling, infection) that typically heal in the weeks post-procedure, to more persistent complications (lagophthalmos, exposure keratopathy) requiring further intervention.[5] Surgery can also have variable cosmetic outcomes, resulting in asymmetry, eyelid crease abnormalities, or over- or under-correction.[5] In a series of 1519 surgical patients, revision was required in 8.7% of cases, with over/under-correction identified as the leading causes for revision.[21]

The use of pharmacologic agents targeting α-adrenergic receptors, which are expressed on Müller's muscle,[22–24] has been described, with some evidence of eyelid elevation with topical phenylephrine, apraclonidine, brimonidine, or naphazoline.[25–33] The evidence for these agents is limited to short-term use, however, and their practical applications are limited, given their side effect profiles. For example, side effects of chronic apraclonidine use can include decreased visual acuity, allergic dermatitis, and dry mouth.[34–36]

Oxymetazoline HCl ophthalmic solution, 0.1% (oxymetazoline [1 mg/mL, equivalent to 0.9 mg oxymetazoline base/mL]; Upneeq®, RVL Pharmaceuticals, Inc., Bridgewater, NJ) was recently approved for the treatment of acquired blepharoptosis. The active chemical entity is the α-adrenergic agonist oxymetazoline, which has been used as a topical treatment for nasal decongestion (0.05% solution)[37,38] and reduction of ocular hyperemia (0.025% solution).[39,40] Application of oxymetazoline 0.1% to the eye is believed to stimulate α-adrenergic receptors on Müller's muscle,[22–24] resulting in contraction and eyelid elevation.

The efficacy of once-daily oxymetazoline 0.1% administration was examined in two randomized, double-masked, placebo-controlled, 6-week Phase 3 clinical trials in individuals with acquired blepharoptosis. These studies demonstrated a significant effect of oxymetazoline 0.1%, with improvement of superior visual field deficits and upper eyelid elevation at predefined time points (treatment days 1 and 14).[41] Safety was also evaluated over the 42-day treatment period in these studies, revealing similar treatment-emergent adverse event (TEAE) rates with oxymetazoline 0.1% and vehicle, and few treatment-related ocular TEAEs.[41]

Oxymetazoline 0.1% has been evaluated in two additional randomized, double-masked, placebo-controlled trials: a 2-week Phase 1/2a proof-of-concept study and a 12-week safety study. This analysis provides an in-depth evaluation of the safety of once-daily oxymetazoline 0.1% administration for 14–84 days by combining results

from all four oxymetazoline 0.1% efficacy and safety trials, with an emphasis on TEAEs in the overall population and participant subgroups defined based on age, race, and ethnicity, as well as ophthalmic assessments and tolerability.

Materials and Methods

Studies

All studies had a randomized, double-masked, placebo-controlled design, and were conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice and International Council for Harmonisation guidelines. Protocols and informed consent forms were approved by a central Institutional Review Board (Alpha IRB, San Clemente, CA) prior to initiation. All participants completed written informed consent. Participant information and data were handled per Health Insurance Portability and Accountability Act provisions. The studies enrolled n=46 (6 sites [NCT01848041]), n=140 (16 sites [NCT02436759]), n=164 (27 sites [NCT03565887]), and n=234 (35 sites [NCT03536949]) participants, respectively. Data were pooled given consistency in study design, inclusion/exclusion criteria, treatment, and safety endpoints. Rationale, methodology, results, and conclusions are reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines.

In all studies, participants were randomized 2:1 to self-administer oxymetazoline 0.1% or placebo (vehicle) daily to both eyes, for the entire study period (Table 1). Randomization schemes were created by an independent biostatistician using a block design. Participants, investigators, staff, and study management personnel were masked to the identity of treatment until after final database lock.

Participants

Key inclusion criteria were age ≥9 (studies RVL-1201-202, RVL-1201-203) or ≥18 years (studies RVL-1201-001, RVL-1201-201), presence of acquired blepharoptosis, defined by Marginal Reflex Distance 1 (MRD-1) ≤2.5 mm (study RVL-1201-001) or ≤2.0 mm (phase 3 studies), and superior visual field deficit (assessed via Humphrey Visual Field Test in study RVL-1201-001 and Leicester Peripheral Field Test (LPFT) in studies RVL-1201-201 and RVL-1201-202) in at least one eye. There was no superior visual field criterion in the 12-week study (RVL-1201-203). Individuals were excluded if they had pseudoptosis, congenital blepharoptosis, Marcus Gunn jaw-winking syndrome, Horner syndrome, mechanical blepharoptosis, myasthenia gravis, substantial dermatochalasis, or history of blepharoptosis surgery or periocular neurotoxin injection <3 months pre-enrollment. Potential participants were also excluded if, at screening, they had resting heart rate (HR) outside of the normal range (defined as 60–100 beats per minute [bpm] in studies RVL-1201-001 and RVL-1201-201, and 50–110 bpm in studies RVL-1201-202 and RVL-1201-203) or hypertension (defined as diastolic blood pressure (DBP) >105 mmHg in studies RVL-1201-001 and RVL-1201-201, and DBP > 105 mm Hg or systolic blood pressure (SBP) >220 mmHg in studies RVL-1201-202 and RVL-1201-203). The phase 1/2a study (RVL-1201-001) excluded individuals with advanced arteriosclerotic disease, history of myocardial infarction, angina, arrhythmia, or irregular pulse, as well as individuals using a beta blocker within 14 days preceding screening. The remaining studies excluded individuals with advanced arteriosclerotic disease and history of cerebrovascular accident. Notably, hypertension was the most common non-ocular medical history finding in the pooled population (50.4% and 48.2% of participants in the oxymetazoline 0.1% and vehicle groups, respectively).

Safety

Efficacy endpoints evaluated in the 6-week studies have been previously described.[41] In all studies, TEAEs were recorded from screening to completion and classified per the Medical Dictionary for Regulatory Activities (MedDRA). TEAE severity, causality, and relationship to discontinuation, were assessed by investigators. Serious TEAEs were defined as TEAEs that were life-threatening, medically significant, or resulted in death, persistent or significant disability/incapacity, or inpatient hospitalization/prolongation of hospitalization. Investigators provided detailed narratives for any serious TEAE or TEAE leading to discontinuation.

Vital signs, intraocular pressure (IOP), pupil diameter, Snellen visual acuity (VA), corneal fluorescein staining, slit lamp exam, and ophthalmoscopy and fundus exam were monitored in all studies, at predefined study visits (Figure 1). Common post-instillation time points across at least two studies and included in the pooled safety analysis were as follows: HR and blood pressure (treatment days 1 [2 and 8 hours], 14 [0, 2, and 8 hours], and 42); IOP (treatment day 42); Snellen VA (treatment days 1 [8 hours], 14 [0 and 8 hours], and 42); pupil diameter (treatment days 1 [2 hours], 14 [2 hours], and 42); corneal

Table 1 Participant Disposition, Demographics, Treatment Exposure, and Compliance, by Treatment Group

	Oxymetazoline 0.1% (n=375)	Vehicle (n=193)
Participants completing all study visits, n (%)	356 (94.9)	188 (97.4)
Compliance with treatment, mean (SD)[a]		
Phase 3 studies (n=358 once-daily oxymetazoline 0.1%; n=178 once-daily vehicle)	98.5 (11.81)	97.1 (9.11)
Phase 1/2a study (n=15 once-daily oxymetazoline 0.1%; n=15 vehicle)	97.3 (5.55)	97.1 (6.77)
Treatment exposure, mean days (SD)	56.4 (24.01)	56.4 (24.02)
Age (years)		
Mean (SD)	63.9 (13.78)	62.9 (14.45)
Median	67.0	65.0
Min, Max	13, 92	14, 90
Age group, n (%)		
9–17 years	2 (0.5%)	2 (1.0%)
18–50 years	54 (14.4%)	32 (16.6%)
51–64 years	103 (27.5%)	60 (31.1%)
65–75 years	147 (39.2%)	69 (35.8%)
>75 years	69 (18.4%)	30 (15.5%)
Sex, n (%)		
Female	290 (77.3%)	135 (69.9%)
Male	85 (22.7%)	58 (30.1%)
Race, n (%)		
White	329 (87.7%)	170 (88.1%)
Black	30 (8.0%)	16 (8.3%)
Asian	12 (3.2%)	7 (3.6%)
American Indian	2 (0.5%)	0
Pacific Islander	2 (0.5%)	0
Ethnicity, n (%)		
Not Hispanic/Latino	317 (84.5%)	162 (83.9%)
Hispanic/Latino	58 (15.5%)	31 (16.1%)

Notes: Data from N=568 participants enrolled in four oxymetazoline 0.1% clinical trials ranging in duration from 14 to 84 days, and randomized to self-administer oxymetazoline 0.1% once daily or vehicle. Includes participants from two phase 3 efficacy studies 42 days in duration with data previously reported by Slonim et al 2020.[41] In the 2-week phase 1/2a study (RVL-1201-001), participants self-administered a single drop of oxymetazoline 0.1% once daily, oxymetazoline 0.1% twice daily, or vehicle twice daily, to both eyes, and study visits occurred at screening and treatment days 1, 7, and 14. In the phase 3 trials, oxymetazoline 0.1% or vehicle was self-administered as a single drop once daily, in both eyes, for the duration of the study. As previously described, in the 6-week phase 3 efficacy studies (RVL-1201-201 and RVL-1201-202), study visits occurred at screening and days 1, 14, and 42.[41] In the phase 3 safety study (RVL-1201-203), study visits occurred at screening and days 1, 14, 42, and 84. [a]Compliance corresponds to the percentage of opened vials returned relative to the number of vials that should have been used during the treatment period.
Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.

fluorescein staining (treatment days 1 [8 hours], 14 [8 hours], and 42); slit lamp exam (treatment days 1 [8 hours], 14 [0 and 8 hours], and 42); ophthalmoscopy and fundus exam (treatment day 42). Patient-reported treatment tolerability was recorded at the end of each study (final visit/early termination), using a 4-point scale.

Participants randomized to once-daily oxymetazoline 0.1% treatment or vehicle were included in the safety analysis, with grouping determined on an as-treated basis. In addition to the total population, TEAEs were examined in subgroups defined post hoc, based on data collected at screening. Subgroups were defined by age (9–17, 18–50, 51–64, 65–75, >75 years), race (white, non-white), and ethnicity (Hispanic/Latino, Not Hispanic/Latino). TEAE incidences are presented as number of participants and percentages within each treatment and participant subgroup. Continuous variables are presented as mean (SD). Statistical testing was not performed given that the pooled population was not powered to reliably detect statistical differences in safety signals between treatment groups.

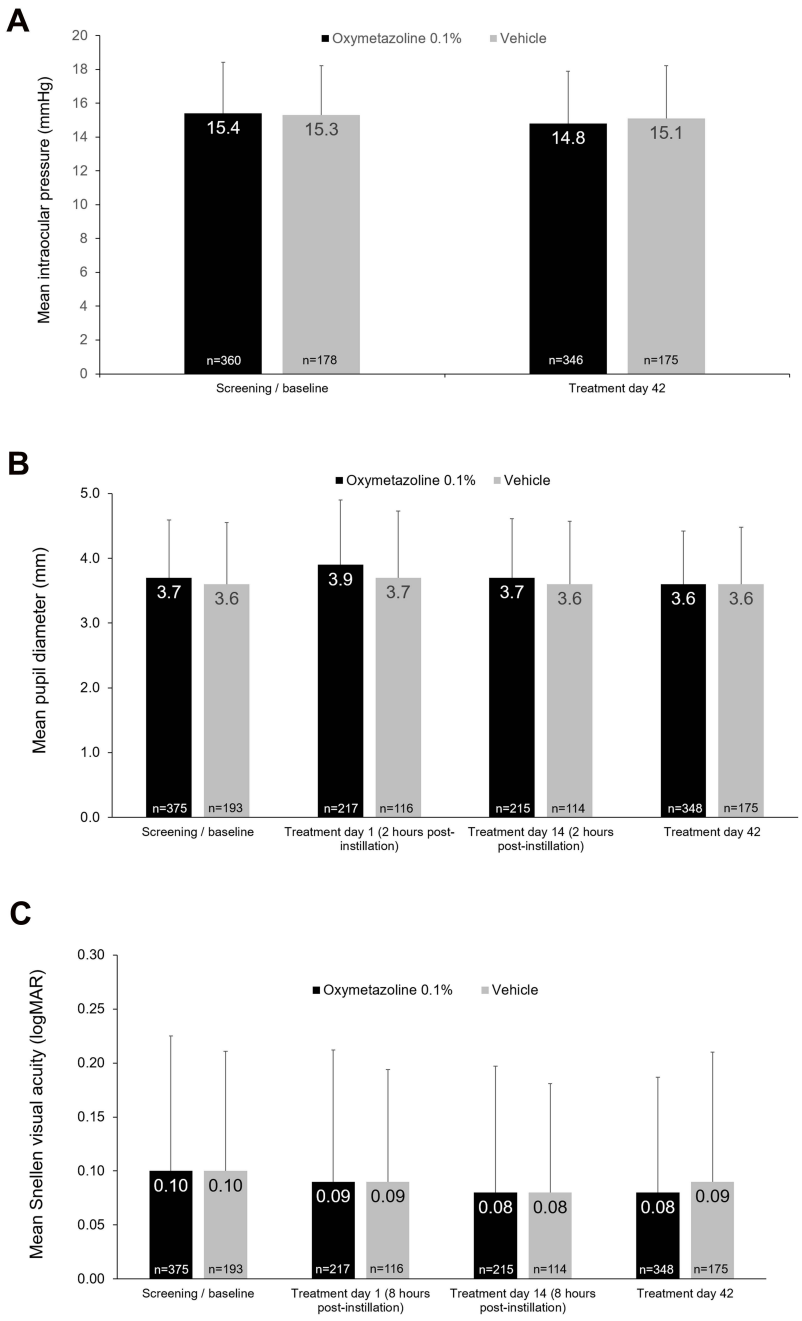

Figure 1 Mean ± standard deviation (**A**) intraocular pressure (IOP), (**B**) pupil diameter, and (**C**) Snellen visual acuity (VA) at selected time points. Results shown are for OD. Data from N=568 participants enrolled in four oxymetazoline 0.1% clinical trials ranging in duration from 14 to 84 days, except IOP, which presents data from N=538 participants enrolled in three phase 3 trials ranging in duration from 42 to 84 days. Includes data from participants from two phase 3 efficacy studies 42 days in duration with data previously reported by Slonim et al 2020.[41] In the phase 1/2a study, pupil diameter and Snellen VA were evaluated at screening and on treatment days 1 and 14, and IOP was evaluated at screening and on treatment days 7 and 14. As previously reported, in the phase 3 efficacy trials, pupil diameter and Snellen VA were evaluated at all study visits, and IOP was evaluated at screening and on treatment day 42. In the phase 3 safety trial, pupil diameter and Snellen VA were evaluated at all study visits, and IOP was evaluated at baseline/screening and on treatment days 42 and 84.

Results

Population

Safety analysis included 375 participants treated with oxymetazoline 0.1% once daily in both eyes, and 193 participants who received vehicle (Table 1). Overall, 94.9% and 97.4% of participants receiving oxymetazoline 0.1% and vehicle, respectively, completed all study visits. Most participants in both treatment groups were >50 years old (oxymetazoline 0.1%: 85.1%; vehicle: 82.4%) and the majority were female (oxymetazoline 0.1%: 77.3%; vehicle: 69.9%). Similarly,

most participants were white (oxymetazoline 0.1%: 87.7%; vehicle: 88.1%) and identified their ethnicity as Not Hispanic/Latino (oxymetazoline 0.1%: 84.5%; vehicle: 83.9%). Treatment compliance was >97% in both treatment groups, across phase 1/2a and phase 3 studies. Mean treatment exposure was 56.4 days in both groups.

Adverse Events

Overall TEAE incidences were similar for the participants treated with oxymetazoline 0.1% (31.2% (n=117 participants)) and vehicle (30.6% (n=59 participants)) (Table 2). There were no apparent differences in TEAE rate with oxymetazoline 0.1% in participant subgroups defined based on age, race, or ethnicity. TEAE incidence ranged from 29.6% to 34.0% in the age groups examined (excluding the 9–17 years group, which included 2 participants/treatment group). Similarly, TEAE rates in the oxymetazoline 0.1% group were 30.4% among white participants, 37.0% among non-white participants, 20.7% among Hispanic/Latino participants, and 33.1% among non-Hispanic/Latino participants (Table 2).

Nine participants receiving oxymetazoline 0.1% and two participants receiving vehicle had a TEAE that led to discontinuation from the study. In the oxymetazoline 0.1% group, TEAEs resulting in study withdrawal and suspected of being treatment-related were single instances of mild eyelid edema, mild instillation site pain and headache, mild ocular discomfort, mild allergic blepharitis, moderate conjunctival hyperemia and dry eye, and mild eye irritation. Other, non-treatment-related TEAEs leading to discontinuation in the oxymetazoline 0.1% group were single instances of mild glare and moderate migraine, moderate upper limb fracture, and moderate eye irritation and ocular hyperemia. In the vehicle group, withdrawal from the study was reported for one participant with mild iritis and a second participant with moderate lower gastrointestinal hemorrhage (neither suspected of being treatment-related). Given the infrequency of discontinuation due to a TEAE, it is difficult to discern any potential difference across patient subgroups, however the data suggest similar rates across participants based on age and race (Table 2). There were no deaths during any study, and serious TEAEs were reported in four participants (1.1%) treated with oxymetazoline 0.1% and one participant (0.5%) receiving vehicle. All serious TEAEs were non-ocular, not suspected of being treatment-related by the site investigator, and were resolved (brief narratives in Table 3).

The most common TEAEs, regardless of severity and causality, are summarized in Table 4. No TEAE occurred in >3.5% of participants in either treatment group. TEAEs in the Eye Disorders System Organ Class (SOC) occurred in 74 (19.7%) and 26 (13.5%) participants in the oxymetazoline 0.1% and vehicle groups, respectively. TEAEs reported for ≥2.0% of participants in either treatment group were: punctate keratitis (oxymetazoline 0.1%: n=13 (3.5%); vehicle: n=4 (2.1%)), conjunctival hyperemia (oxymetazoline 0.1%: n=11 (2.9%); vehicle: n=1 (0.5%)), dry eye (oxymetazoline 0.1%: n=9 (2.4%); vehicle: n=1 (0.5%)), blurred vision (oxymetazoline 0.1%: n=8 (2.1%); vehicle: n=0), instillation site pain (oxymetazoline 0.1%: n=8 (2.1%); vehicle: n=0), corneal vital dye staining (oxymetazoline 0.1%: n=8 (2.1%); vehicle: n=4 (2.1%)), and headache (oxymetazoline 0.1%: n=8 (2.1%); vehicle: n=2 (1.0%)).

Cardiovascular TEAEs were uncommon. Among the 375 participants in the oxymetazoline 0.1% treatment group, there was one event each (0.5%) of bradycardia and tachycardia, both of which were mild in severity and judged to be unrelated to treatment. A TEAE of hypertension was reported for 3/375 participants (0.8%) in the oxymetazoline 0.1% group, as well as 2/193 participants (1.0%) in the vehicle group. This TEAE was judged to be unrelated to treatment in all 3 participants in the oxymetazoline 0.1% group and 1 of 2 participants in the vehicle group. Hypertension was mild in 2 participants in the oxymetazoline 0.1% group and severe in the other (a 56-year-old female with a history of hypertension), and mild and moderate in one participant each in the vehicle group. A TEAE of increased DBP that was mild, and judged to be unrelated to treatment, occurred in one participant (0.3%) receiving oxymetazoline 0.1%, and one participant in the vehicle group had a TEAE of atrial fibrillation (moderate in severity, unrelated to treatment).

Among participants with ≥1 reported TEAE, 95.7% in the oxymetazoline 0.1% group and 100% in the vehicle group had a maximum TEAE intensity of mild or moderate (Table 5). Across all participant subgroups, 20.7% to 24.6% of participants receiving oxymetazoline 0.1% had a maximum TEAE intensity of mild (23.5% overall). In the oxymetazoline 0.1% group, the proportion of participants with a TEAE of moderate intensity ranged from 5.8% to 7.4% across age subgroups (excluding the 9–17 group). A TEAE of moderate intensity occurred in 5.5%

Table 2 Summary of Treatment-Emergent Adverse Events (TEAEs)

		Oxymetazoline 0.1% (n=375)	Vehicle (n=193)
Participants reporting any TEAE, n (%)	Overall	117 (31.2%)	59 (30.6%)
	Age group, n (%)		
	9–17 Years (n=2/2)[a]	1 (50.0%)	2 (100.0%)
	18–50 Years (n=54/32)	16 (29.6%)	5 (15.6%)
	51–64 Years (n=103/60)	35 (34.0%)	14 (23.3%)
	65–75 Years (n=147/69)	44 (29.9%)	24 (34.8%)
	>75 Years (n=69/30)	21 (30.4%)	14 (46.7%)
	Race, n (%)		
	White (n=329/170)	100 (30.4%)	55 (32.4%)
	Non-white (n=46/23)	17 (37.0%)	4 (17.4%)
	Ethnicity, n (%)		
	Not Hispanic/Latino (n=317/162)	105 (33.1%)	51 (31.5%)
	Hispanic/Latino (n=58/31)	12 (20.7%)	8 (25.8%)
Participants reporting any TEAE leading to discontinuation from study, n (%)	Overall	9 (2.4%)	2 (1.0%)
	Age group, n (%)		
	9–17 Years (n=2/2)	0	0
	18–50 Years (n=54/32)	2 (3.7%)	1 (3.1%)
	51–64 Years (n=103/60)	2 (1.9%)	0
	65–75 Years (n=147/69)	4 (2.7%)	0
	>75 Years (n=69/30)	1 (1.4%)	1 (3.3%)
	Race, n (%)		
	White (n=329/170)	8 (2.4%)	2 (1.2%)
	Non-white (n=46/23)	1 (2.2%)	0
	Ethnicity, n (%)		
	Not Hispanic/Latino (n=317/162)	9 (2.8%)	0
	Hispanic/Latino (n=58/31)	0	2 (6.5%)
Participants reporting any serious TEAE, n (%)	Overall	4 (1.1%)	1 (0.5%)
	Age group, n (%)		
	9–17 Years (n=2/2)	0	0
	18–50 Years (n=54/32)	0	0
	51–64 Years (n=103/60)	2 (1.9%)	0
	65–75 Years (n=147/69)	1 (0.7%)	0
	>75 Years (n=69/30)	1 (1.4%)	1 (3.3%)
	Race, n (%)		
	White (n=329/170)	4 (1.2%)	1 (0.6%)
	Non-white (n=46/23)	0	0
	Ethnicity, n (%)		
	Not Hispanic/Latino (n=317/162)	4 (1.3%)	0
	Hispanic/Latino (n=58/31)	0	1 (3.2%)

Notes: Data from N=568 participants enrolled in four oxymetazoline 0.1% clinical trials ranging in duration from 14 to 84 days. Includes participants from two phase 3 efficacy studies 42 days in duration with data previously reported by Slonim et al 2020.[41] [a]For each participant subgroup, (n=x/y) represents the number participants receiving oxymetazoline 0.1% and vehicle, respectively.

Abbreviation: TEAE, treatment-emergent adverse event.

Table 3 Summary of Serious Treatment-Emergent Adverse Events (TEAEs)

Serious TEAE (MedDRA Preferred Term)	Treatment Group	Details
Arthralgia	Oxymetazoline 0.1%	• 62-year-old white female with a history of hip replacement who developed arthralgia in the same hip • Severe, not suspected of being treatment-related and resolved following revision surgery; completed study

Cerebrovascular accident[a]	Oxymetazoline 0.1%	• 86-year-old white male with a history of hypertension
		• Vital signs at predefined study visits:
		  • Treatment day 1 (baseline): HR: 80 bpm, SBP: 138 mmHg, DBP: 80 mmHg
		  • Treatment day 1 (8 hours post-dose): HR: 74 bpm; SBP: 140 mmHg; DBP: 90 mmHg
		  • Treatment day 14 (pre-dose): HR: 78 bpm; SBP: 144 mmHg; DBP: 80 mmHg
		  • Treatment day 14 (8 hours post-dose): HR: 78 bpm; SBP: 160 mmHg; DBP: 88 mmHg
		  • End of study: HR: 74 bpm; SBP: 148 mmHg; DBP: 80 mmHg
		• Mild, not suspected of being treatment-related, and was resolved; completed study

Hyperparathyroidism[a]	Oxymetazoline 0.1%	• 73-year-old white female hospitalized for elective parathyroidectomy due to a history of hyperparathyroidism • Severe, not suspected of being treatment-related, and resolved after surgery; completed study
Nephrolithiasis	Oxymetazoline 0.1%	• 63-year-old white female • Severe, not suspected of being treatment-related, and considered resolved with sequelae following hospitalization and right-sided ureteroscopic laser lithotripsy and stone removal, and right-sided retrograde pyelogram and stent placement; completed study
Lower gastrointestinal hemorrhage[a]	Vehicle	• Occurred in an 83-year-old white female • Moderate, not suspected of being treatment-related, and resolved after hospitalization and treatment; withdrawn from study

Notes: Data from N=568 participants enrolled in four oxymetazoline 0.1% clinical trials ranging in duration from 14 to 84 days. Includes participants from two phase 3 efficacy studies 42 days in duration with data previously reported by Slonim et al 2020. [a]Serious TEAE in a participant enrolled in 6-week phase 3 efficacy trial and previously noted in Slonim et al 2020.[41]

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; MedDRA, Medical Dictionary for Regulatory Activities; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event.

(n=18/329) of white participants and 13.0% (n=6/46) of non-white participants receiving oxymetazoline 0.1%. No Hispanic/Latino participant had a moderate TEAE.

Five participants (1.3%) in the oxymetazoline 0.1% group and none in the vehicle group had a TEAE that was judged to be severe (Table 5). All severe TEAEs were non-ocular, and included the incidences of hyperparathyroidism, arthralgia, and nephrolithiasis noted in Table 3. Additionally, a 53-year-old white female had TEAEs of viral infection and secondary dehydration, and a 56-year-old white female had a TEAE of hypertension, judged to be severe. The latter individual had a medical history of hypertension. On day 14, the participant's SBP and DBP increased from baseline (151/92 mmHg) to 170/105 mmHg. The TEAE was resolved, and at end of study, SBP and DBP were 156 and 97 mmHg, respectively. HR did not change from baseline. No severe TEAE was suspected of being treatment-related by the site investigator.

Most TEAEs were not suspected of being treatment-related. Among the 117 participants receiving oxymetazoline 0.1% and reporting a TEAE, 47/117 (40.2%) had ≥1 event suspected of being treatment-related (vs 15/59 participants (25.4%) receiving vehicle). Treatment-related TEAE rates were similar across age, race, and ethnicity subgroups, though rates were low in the relatively small Hispanic/Latino ethnicity group (Table 5). Overall, 28 (7.5%) participants in the oxymetazoline 0.1% group and 8 (4.1%) participants in the vehicle group had a TEAE in the Eye Disorder SOC that was judged to be treatment-related. The TEAEs in this category most commonly judged to be treatment-related in the oxymetazoline 0.1% group were conjunctival hyperemia and dry eye (both n=6 (1.6%)), and punctate keratitis, blurred vision, and eye

Table 4 Most Common Treatment-Emergent Adverse Events (TEAEs; Occurring in >1% of Patients in Either Treatment Arm)

TEAE, by SOC and MedDRA Preferred Term, n (%)	Oxymetazoline 0.1% (n=375)	Vehicle (n=193)
Eye disorders	74 (19.7%)	26 (13.5%)
Punctate keratitis	13 (3.5%)	4 (2.1%)
Conjunctival hyperemia	11 (2.9%)	1 (0.5%)
Dry eye	9 (2.4%)	1 (0.5%)
Vision blurred	8 (2.1%)	0
Eye irritation	4 (1.1%)	0
Eye pruritus	1 (0.3%)	3 (1.6%)
General disorders and administration site conditions	13 (3.5%)	4 (2.1%)
Instillation site pain	8 (2.1%)	0
Instillation site complication	1 (0.3%)	3 (1.6%)
Infections and infestations	16 (4.3%)	13 (6.7%)
Nasopharyngitis	3 (0.8%)	3 (1.6%)
Upper respiratory tract infection	3 (0.8%)	3 (1.6%)
Investigations	9 (2.4%)	6 (3.1%)
Vital dye staining cornea present	8 (2.1%)	4 (2.1%)
Nervous system disorders	11 (2.9%)	4 (2.1%)
Headache	8 (2.1%)	2 (1.0%)

Notes: TEAEs were coded by SOC and Preferred Term in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Data from N=568 participants enrolled in four oxymetazoline 0.1% clinical trials ranging in duration from 14 to 84 days. Includes participants from two phase 3 efficacy studies 42 days in duration with data previously reported by Slonim et al 2020.[41]

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

irritation (all n=3 (0.8%)). Among these TEAEs in the vehicle group, n=1 incidence of dry eye (0.5%) was treatment-related. No other TEAE in this category was treatment-related in >0.3% of participants receiving oxymetazoline 0.1%. In the vehicle group, the only TEAE in this category judged to be related to treatment in ≥1.0 of participants was increased lacrimation (n=2 (1.0%)). Other treatment-related TEAEs occurring in ≥1.0% of participants in either group were instillation site pain (oxymetazoline 0.1%: n=8 (2.1%); vehicle: n=0), instillation site complication (oxymetazoline 0.1%: n=1 (0.3%); vehicle: n=3 (1.6%)), and corneal vital dye staining (oxymetazoline 0.1%: n=6 (1.6%); vehicle: n=3 (1.6%)).

Vital Signs and Ophthalmic Endpoints

There were no clinically significant mean post-baseline changes in HR, SBP, or DBP in either treatment group. Mean change from baseline HR on day 42 in the oxymetazoline 0.1% and vehicle groups was 0.6 (8.26) bpm and 0.7 (7.36) bpm, respectively. Mean change from baseline SBP on day 42 in the oxymetazoline 0.1% and vehicle groups was −0.9 (12.43) mmHg and −2.2 (14.29) mmHg, respectively, and mean change in DBP at the same time point was −0.5 (8.18) mmHg in the oxymetazoline 0.1% group and −1.4 (8.42) mmHg in the vehicle group.

No clinically significant shifts from baseline were noted for IOP, pupil diameter, or Snellen VA in either treatment group (Figure 1). Evaluating phase 3 study participants, mean OD IOP was 15.4 (3.03) mmHg at screening and 14.8 (3.10) mmHg on day 42 in the oxymetazoline 0.1% group, and 15.3 (2.93) mmHg at screening and 15.1 (3.13) mmHg on day 42 with vehicle. Mean OD Snellen VA was 0.10 (0.125) LogMAR at baseline and 0.08 (0.107) LogMAR on day 42 in the oxymetazoline 0.1% group and 0.10 (0.111) LogMAR at baseline and 0.09 (0.120) LogMAR on day 42 with vehicle. Mean pupil diameter did not differ from baseline at any time point evaluated. Mean OD pupil diameter was 3.7 (0.89) mm at baseline and 3.6 (0.82) mm on day 42 in the oxymetazoline 0.1% group, and 3.6 (0.95) mm at baseline and 3.6 (0.88) on day 42 with vehicle. Results in OS were similar. Results for corneal fluorescein staining, slit lamp examination, and dilated ophthalmoscopy suggested no differences between treatment groups.

Tolerability

At the end of the 14-day study, all participants receiving once-daily oxymetazoline 0.1% or vehicle rated treatment as causing no discomfort. At the end of the 6-week studies, 95.5%, 3.0%, and 1.5% of participants receiving oxymetazoline 0.1% rated treatment as causing no discomfort, mild discomfort, and moderate discomfort, respectively. Among participants receiving vehicle, 99.0% and 1.0% rated treatment as causing no discomfort and mild discomfort, respectively. No participants rated either treatment as causing severe discomfort after 6 weeks' use. At the end of the 12-week study, 92.0% and 8.0% of participants receiving oxymetazoline 0.1% rated treatment as causing no discomfort or mild discomfort, respectively. Corresponding numbers with vehicle were and 93.4% and 6.6%. No participant rated either treatment as causing moderate or severe discomfort after 12 weeks' use.

Discussion

The data from four randomized, double-masked, placebo-controlled clinical studies support the safety of

Table 5 Relationship to Treatment and Severity of Treatment-Emergent Adverse Events (TEAEs)

		Oxymetazoline 0.1% (n=375)	Vehicle (n=193)
Participants reporting maximum TEAE severity of MILD, n (%)[a]	Overall	88 (23.5%)	41 (21.2%)
	Age group, n (%)		
	9–17 Years (n=2/2)[b]	0	2 (100.0%)
	18–50 Years (n=54/32)	12 (22.2%)	3 (9.4%)
	51–64 Years (n=103/60)	25 (24.3%)	11 (18.3%)
	65–75 Years (n=147/69)	34 (23.1%)	17 (24.6%)
	>75 Years (n=69/30)	17 (24.6%)	8 (26.7%)
	Race, n (%)		
	White (n=329/170)	77 (23.4%)	37 (21.8%)
	Non-white (n=46/23)	11 (23.9%)	4 (17.4%)
	Ethnicity, n (%)		
	Not Hispanic/Latino (n=317/162)	76 (24.0%)	36 (22.2%)
	Hispanic/Latino (n=58/31)	12 (20.7%)	5 (16.1%)
Participants reporting maximum TEAE severity of MODERATE, n (%)	Overall	24 (6.4%)	18 (9.3%)
	Age group, n (%)		
	9–17 Years (n=2/2)	1 (50.0%)	0
	18–50 Years (n=54/32)	4 (7.4%)	2 (6.3%)
	51–64 Years (n=103/60)	6 (5.8%)	3 (5.0%)
	65–75 Years (n=147/69)	9 (6.1%)	7 (10.1%)
	>75 Years (n=69/30)	4 (5.8%)	6 (20.0%)
	Race, n (%)		
	White (n=329/170)	18 (5.5%)	18 (10.6%)
	Non-white (n=46/23)	6 (13.0%)	0
	Ethnicity, n (%)		
	Not Hispanic/Latino (n=317/162)	24 (7.6%)	15 (9.3%)
	Hispanic/Latino (n=58/31)	0	3 (9.7%)
Participants reporting maximum TEAE severity of SEVERE, n (%)[c]	Overall	5 (1.3%)	0
	Age group, n (%)		
	9–17 Years (n=2/2)	0	0
	18–50 Years (n=54/32)	0	0
	51–64 Years (n=103/60)	4 (3.9%)	0
	65–75 Years (n=147/69)	1 (0.7%)	0
	>75 Years (n=69/30)	0	0
	Race, n (%)		
	White (n=329/170)	5 (1.5%)	0
	Non-white (n=46/23)	0	0
	Ethnicity, n (%)		
	Not Hispanic/Latino (n=317/162)	5 (1.6%)	0
	Hispanic/Latino (n=58/31)	0	0

(*Continued*)

Table 5 (Continued).

		Oxymetazoline 0.1% (n=375)	Vehicle (n=193)
Participants reporting ≥1 TEAE suspected of being treatment-related, n (%)	Overall	47 (12.5%)	15 (7.8%)
	Age group, n (%)		
	9–17 Years (n=2/2)	0	0
	18–50 Years (n=54/32)	9 (16.7%)	0
	51–64 Years (n=103/60)	14 (13.6%)	5 (8.3%)
	65–75 Years (n=147/69)	17 (11.6%)	6 (8.7%)
	>75 Years (n=69/30)	7 (10.1%)	4 (13.3%)
	Race, n (%)		
	White (n=329/170)	39 (11.9%)	14 (8.2%)
	Non-white (n=46/23)	8 (17.4%)	1 (4.3%)
	Ethnicity, n (%)		
	Not Hispanic/Latino (n=317/162)	45 (14.2%)	15 (9.3%)
	Hispanic/Latino (n=58/31)	2 (3.4%)	0

Notes: Data from N=568 participants enrolled in four oxymetazoline 0.1% clinical trials ranging in duration from 14 to 84 days. Includes participants from two phase 3 efficacy studies 42 days in duration with data previously reported by Slonim et al 2020.[41] [a]Mild TEAE = discomfort but no disruption of normal daily activity; Moderate TEAE = discomfort sufficient to cause interference with normal daily activity; Severe TEAE = discomfort that is incapacitating, resulting in inability to perform normal activities. [b]For each participant subgroup, (n=x/y) represents the number participants receiving oxymetazoline, 0.1% and vehicle, respectively. [c]All TEAEs assessed as severe were non-ocular and all were judged to be non-treatment related by site investigators.

Abbreviation: TEAE, treatment-emergent adverse event.

once-daily oxymetazoline 0.1% for 14–84 days. Further, the data reveal similar TEAE rates, severity, and relationship to treatment, across participant subgroups based on age, race, and ethnicity, though a larger patient sample is required to comprehensively evaluate safety with respect to these factors. While ocular TEAEs tended to be treatment-related more frequently among participants receiving oxymetazoline 0.1%, these were uncommon overall. Only instillation site pain (all events mild) was judged to be treatment-related in >2% of participants receiving oxymetazoline 0.1%. Further, the low incidences of severe (1.3%) or serious (1.1%) TEAEs, and TEAEs leading to discontinuation (2.4%) are encouraging. The effect of oxymetazoline 0.1% on ophthalmic measures was minimal, and participant evaluations revealed that once-daily oxymetazoline 0.1% use caused little or no discomfort.

Oxymetazoline is thought to act via α-adrenergic receptors on Müller's muscle,[22–24] resulting in muscle contraction and eyelid elevation. This muscle remains intact and functional in the most common form of acquired blepharoptosis (aponeurotic),[9,10] and it is a common surgical target.[16,42,43] Functional studies demonstrate that oxymetazoline is a full α_2 agonist and a partial α_1 agonist, with an approximately 5-fold greater affinity for α_2.[44,45] Within the α_1 receptor subgroup, oxymetazoline has been shown to have a higher affinity for α_{1A} vs α_{1B}, and weak affinity for the α_{1D} subtype.[46] The in vivo pharmacology of oxymetazoline 0.1% remains to be fully elucidated, however it is possible that receptor selectivity may contribute to the observed safety profile. Tachyphylaxis is common with prolonged use of α_1-selective or mixed α_1/α_2 agents, and the mechanism of this phenomenon is thought to be a reduced α_1-adrenergic receptor response.[45] Improvement in upper eyelid elevation has been shown with naphazoline, a mixed α_1/α_2 agonist,[45] but so has tachyphylaxis with repeated daily dosing.[32] Similarly, rebound effects of ocular decongestants are also thought to occur via an α_1-dependent mechanism.[45] Following administration of phenylephrine, which is α_1-selective,[45] patients can experience clinically significant pupil dilation.[47] In comparison, there was a negligible effect on pupil diameter with oxymetazoline 0.1% and no reports of a TEAE of mydriasis in the present studies. Similarly, there were no documented cases of tachyphylaxis over 14–84 days of treatment with oxymetazoline 0.1%. Chronic use of oxymetazoline 0.05% nasal spray can cause tachyphylaxis and rebound congestion,[48,49] thus making investigation of this question essential in future studies.

The molecular targets of oxymetazoline, α-adrenergic receptors, are widely expressed in smooth muscle and blood vessels of the eye, in structures including the conjunctiva, iris-ciliary structures, and aqueous outflow tract,[50] which may in part explain the occurrence of ocular TEAEs such as punctate keratitis, conjunctival hyperemia, and dry eye in participants using oxymetazoline 0.1%. It is also noteworthy that dry eye, punctate keratitis, and conjunctival hyperemia were among the most commonly reported ocular history findings in the pooled population (reported for 43.8%, 5.8%, and 5.3% of participants, respectively), suggesting general susceptibility to corneal irritation or sensitivity. A 0.026% topical oxymetazoline solution has been shown to transiently reduce tear volume and flow,[51] and while these tear parameters were not evaluated in the oxymetazoline 0.1% clinical trials, it is possible that some transient effects on tear volume may have contributed to the observed ocular TEAEs.

Occurrences of blurred vision and instillation site pain with oxymetazoline 0.1% were transient and mild. A single event of mild transient instillation site pain led to discontinuation of a 77-year-old participant with a history of dry eye. This event had resolved without intervention on the day of discontinuation. Sympathomimetic agents such as oxymetazoline can be associated with transient mydriasis and acute angle closure glaucoma (of which blurred vision is a sign) in patients with narrow angle glaucoma. The oxymetazoline 0.1% trials, however, excluded individuals with a history of closed/narrow angle glaucoma (unless patent peripheral iridotomy had been performed >3 months prior to enrollment). Further, as shown in Figure 1, there were no significant shifts from baseline in pupil diameter observed with oxymetazoline 0.1% use. Thus, any potential mechanism of transient blurring of vision requires further investigation. It is possible that some instances of transient blurred vision with oxymetazoline 0.1% may have been related to the presence of hypromellose, a viscoelastic polymer that is commonly included in ophthalmic solutions.

Conclusions

While limited with respect to duration of oxymetazoline 0.1% use (14–84 days), these findings further support the potential clinical utility of this non-surgical therapeutic agent. Longer-duration studies including larger numbers of patients will be needed to evaluate the ocular and systemic safety of oxymetazoline 0.1% in clinical practice, and future studies into the efficacy and safety of this agent in pediatric or congenital blepharoptosis patients may provide further insight into its broader utility. While no direct comparison has been made between oxymetazoline 0.1% and surgery, the low rates of treatment-related ocular TEAEs suggest that for some patients with acquired blepharoptosis, particularly those with mild or moderate eyelid droop, this pharmacologic option may, in addition to being efficacious,[41] offer a desirable safety profile.

Data Sharing Statement

The authors do not intend to share individual deidentified study participant data.

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