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# Randomized, controlled, phase 2 trial of povidone-iodine/ dexamethasone ophthalmic suspension for treatment of adenoviral conjunctivitis

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# Randomized, Controlled, Phase 2 Trial of Povidone-Iodine/Dexamethasone Ophthalmic Suspension for Treatment of Adenoviral Conjunctivitis

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• PURPOSE: To evaluate the efficacy/safety of an ophthalmic suspension of povidone-iodine (PVP-I) 0.6% and dexamethasone 0.1% in patients with acute adenoviral conjunctivitis.

• DESIGN: Multicenter, randomized, vehicle-controlled, double-masked trial.

• METHODS: Adults with a positive Rapid Pathogen Screening Adeno-Detector Plus test were randomized 1:1:1 to PVP-I 0.6%/dexamethasone 0.1%, PVP-I 0.6%, or vehicle, bilaterally 4 times daily for 5 days (days 1-5). Patients were evaluated on days 3, 6, and 12 (+1-day window). Efficacy measures included clinical resolution and adenoviral eradication.

• RESULTS: Overall, 144 patients were included in the efficacy analysis (PVP-I/dexamethasone, n = 48; PVP-I, n = 50; vehicle, n = 46). The proportion of patients with clinical resolution (primary study eye with last observation carried forward [LOCF]) at the day 6 visit was higher with PVP-I/dexamethasone (31.3%) than with vehicle (10.9%; $P = .0158$) and PVP-I (18.0%; $P$ = nonsignificant). The proportion with adenoviral eradication (primary study eye with LOCF) was higher with PVP-I/dexamethasone than with vehicle at the day 3 (35.4% vs 8.7%; $P = .0019$) and day 6 (79.2% vs 56.5%; $P = .0186$) visits and vs PVP-I (day 3 visit, 32.0%; day 6 visit, 62.0%; each $P$ = nonsignificant). Treatment-emergent adverse events (AEs) occurred in 69.0% (vehicle), 62.7% (PVP-I), and 53.4% (PVP-I/dexamethasone) of patients in the safety dataset. Discontinuation owing to AEs occurred in 37 patients (vehicle, n = 16; PVP-I, n = 12; PVP-I/dexamethasone, n = 9).

• CONCLUSION: PVP-I/dexamethasone appeared safe and well tolerated, and significantly improved clinical resolution and adenoviral eradication in patients with acute adenoviral conjunctivitis. (Am J Ophthalmol 2018;194:7–15. © 2018 Shire, Lexington, MA, USA. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

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ACUTE CONJUNCTIVITIS IS A COMMON CONDITION, estimated to affect approximately 6 million people each year in the United States.[1] Viruses and bacteria are the most common pathogens associated with acute infectious conjunctivitis, with adenoviruses considered to be the most frequent cause of viral conjunctivitis.[2] Adenoviral conjunctivitis can cause significant discomfort and lost productivity. Although mostly self-limiting, in some cases it can lead to complications from long-term immune-mediated sequelae.[3] Adenoviruses are nonenveloped viruses that are relatively resistant to disinfection,[4] and adenoviral conjunctivitis is more contagious than other forms of conjunctivitis owing in part to adenoviruses being able to survive in a desiccated state for several weeks at room temperature.[5]

No medications are currently approved for the treatment of adenoviral conjunctivitis, and treatment is mostly supportive. A novel topical ophthalmic suspension of povidone-iodine (PVP-I) 0.6% and dexamethasone 0.1% is under clinical investigation, and has the potential to treat both the viral and inflammatory components of adenoviral conjunctivitis as well as immune-related sequelae such as subepithelial infiltrates. Dexamethasone is a potent, well-tolerated corticosteroid[6,7] routinely used as a topical ophthalmic antiinflammatory agent.[8,9] PVP-I is an antiseptic used in ophthalmology and general surgery.[10–12]

The combination of PVP-I and dexamethasone in various formulations has been studied in several preclinical and early-stage clinical trials. These include a study using a rabbit model of adenoviral keratoconjunctivitis, in which treatment with PVP-I 0.4%/dexamethasone 0.1% resulted in significantly improved clinical scores and significantly reduced viral titers compared with control treatments.[13] In an open-label trial of 6 patients with acute conjunctivitis who were positive for adenovirus by the Rapid Pathogen Screening Adeno-Detector test, clinical resolution and reduction of viral titer occurred within 5 days of treatment with PVP-I 0.4%/dexamethasone 0.1% 4 times daily (QID).[14] In a randomized controlled trial of 122 patients

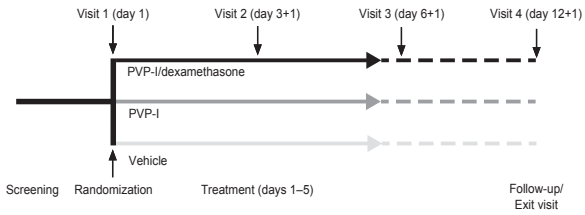


**FIGURE 1. Study design. PVP-I = povidone-iodine.**

with a clinical diagnosis of presumed viral conjunctivitis, ocular administration of PVP-I 0.4%/dexamethasone 0.1% QID significantly reduced the duration of conjunctivitis compared with patients receiving artificial tears.[15] More recently, in a randomized controlled trial of 74 patients with adenoviral keratoconjunctivitis, patients treated with PVP-I 1.0%/dexamethasone 0.1% experienced significantly faster improvement of clinical signs than control groups, with near-complete recovery in 5-7 days and almost-complete viral eradication (92% reduction) by the fifth day of treatment.[16]

In this multicenter phase 2 randomized controlled study, we evaluated the efficacy and safety of an ophthalmic suspension of PVP-I 0.6% and dexamethasone 0.1% for the treatment of acute adenoviral conjunctivitis in adults.

## METHODS

• **STUDY DESIGN:** This was a multicenter, randomized, double-masked, parallel-group, active- and vehicle-controlled phase 2 study conducted in India. Patients were randomized 1:1:1 to PVP-I 0.6%/dexamethasone 0.1% ophthalmic suspension, PVP-I 0.6% alone, or vehicle. One drop of study medication was applied to each eye QID for 5 days. The first dose was administered in the office on day 1 (visit 1), with office visits for efficacy and safety evaluations on day 3 (visit 2), day 6 (visit 3), and day 12 (visit 4), with a +1-day window allowed (Figure 1). The study treatments were provided as sterile, preserved suspensions or solutions in 10-mL amber glass bottles with separate sterile dropper tips for topical ophthalmic administration. Compliance with treatment was assessed by review of dosing diaries provided to the patients. Any patient who missed >20% of doses during a given dosing period was considered noncompliant during that dosing period.

The study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The trial protocol and its amendments, informed consent form, and subject diary instructions were approved by ethics committees at all participating sites prior to study initiation; a list of the independent ethics committees can be found at Clinical Trials Registry India (http://ctri.nic.in/Clinicaltrials/login.php) using the trial search keyword "FST100." All patients provided written informed consent. The trial was registered at ClinicalTrials.gov (identifier NCT01470664).

• **PATIENTS:** All patients were recruited from eye clinics in India. Eligible patients were adults (≥18 years) who had a best-corrected visual acuity (BCVA) of 0.60 logarithm of the minimum angle of resolution (logMAR) or better in each eye. In addition, patients were required to have signs of adenoviral conjunctivitis within 5 days of visit 1, a positive Rapid Pathogen Screening Adeno-Detector Plus test (Rapid Pathogen Screening Inc, Sarasota, Florida, USA) at visit 1, a diagnosis of suspected acute adenoviral conjunctivitis in ≥1 eye, and a watery conjunctival discharge score of ≥1 and bulbar conjunctival redness score of ≥1 (both on a 0-3 scale, where 0 = absent/normal, 1 = mild, 2 = moderate, and 3 = severe).

Exclusion criteria included pregnancy or nursing; known sensitivity to any of the components of the investigational drugs; presence of an ocular infection or inflammation other than acute adenoviral conjunctivitis; intraocular pressure (IOP) steroid responders or those with a history of glaucoma or elevated IOP > 21 mm Hg; or history of recurrent corneal erosion syndrome or those with clinically significant optic nerve defects, active ulcerative keratitis, autoimmune disease, uncontrolled systemic disease, or debilitating disease. Use of contact lenses, investigational devices, and the following medications were prohibited during the study: antivirals, corticosteroids (except for stable use of inhaled/nasal corticosteroids and topical steroids [not including around the eye]), or any other topical ophthalmic solutions (including investigational or diagnostic products).

• **EFFICACY ASSESSMENTS:** The following efficacy endpoints were included: (1) a composite endpoint of clinical resolution (absence [score = 0] of watery conjunctival discharge and bulbar conjunctival redness) and adenoviral eradication (negative cell culture immunofluorescence assay [CC-IFA]) in the study eye; (2) the individual measurement of clinical resolution or adenoviral eradication; (3) expanded clinical cure (both watery conjunctival discharge and bulbar conjunctival redness scores of 0 or 1); and (4) global clinical score (sum of bulbar conjunctival redness and watery conjunctival discharge scores, total score 0-6). Crossover infection was also recorded, based on an increase in the global clinical score of the fellow eye, where the fellow eye was defined according to the clinically worse study eye definition (see Statistical Analyses). All fellow eyes were eligible for assessment of crossover infection, regardless of the global clinical score at baseline.

• **SAFETY ASSESSMENTS:** Safety was the primary endpoint of this trial. Safety measures included slit-lamp biomicroscopy (including nondilated fundus examination), BCVA, urine pregnancy test, and adverse events (AEs). Tolerability was

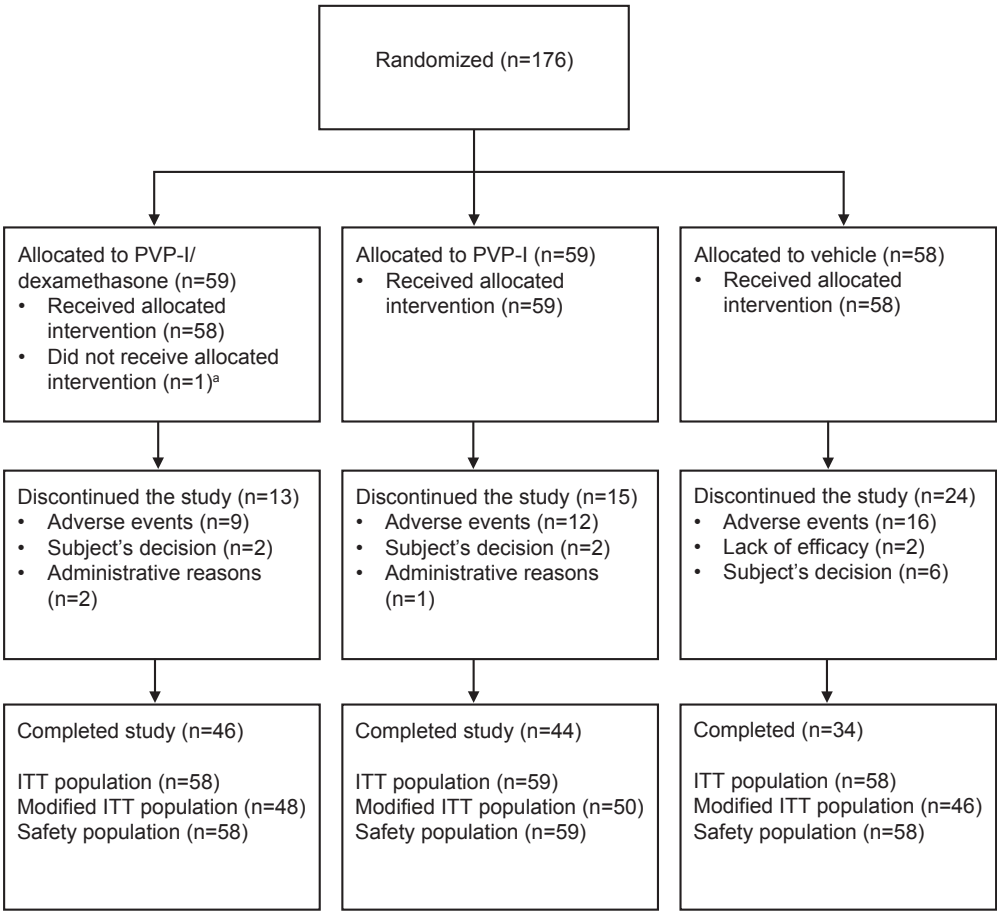


**FIGURE 2. Patient disposition. [a]One patient was randomized but did not receive study treatment; this patient discontinued at visit 1 (subject decision) and was excluded from all analysis populations. ITT = intent-to-treat; PVP-I = povidone-iodine.**

**TABLE 1.** Demographic Characteristics (Intent-to-Treat Population)

| | PVP-I/Dexamethasone N = 58 | PVP-I N = 59 | Vehicle N = 58 | All Patients N = 175 |
|---|---|---|---|---|
| Age, mean (SD), years | 33.7 (12.3) | 35.1 (11.0) | 34.6 (13.3) | 34.5 (12.2) |
| Sex, n (%) | | | | |
| Male | 39 (67.2) | 40 (67.8) | 37 (63.8) | 116 (66.3) |
| Female | 19 (32.8) | 19 (32.2) | 21 (36.2) | 59 (33.7) |
| Race, n (%) | | | | |
| Asian | 58 (100) | 59 (100) | 58 (100) | 175 (100) |

PVP-I = povidone-iodine.

measured by assessment of drop comfort at the day 1 visit by the patient upon instillation (administered by a designated staff member), and at 1 and 2 minutes after instillation using a 0-10 scale (0 = very comfortable, 10 = very uncomfortable). IOP was not measured during the study.

• **STATISTICAL ANALYSES:** The efficacy analysis was conducted on the modified intent-to-treat (mITT) population, a subset of the ITT population (randomized patients who received ≥1 dose of study medication) who had positive CC-IFA results in ≥1 eye at day 1, watery conjunctival discharge and bulbar conjunctival redness scores ≥1 in the same eye at day 1, and ≥1 follow-up visit. All analyses except crossover infection were conducted using the primary study eye, defined as the eye with a positive CC-IFA at day 1 or, if both/neither were infected, the eye

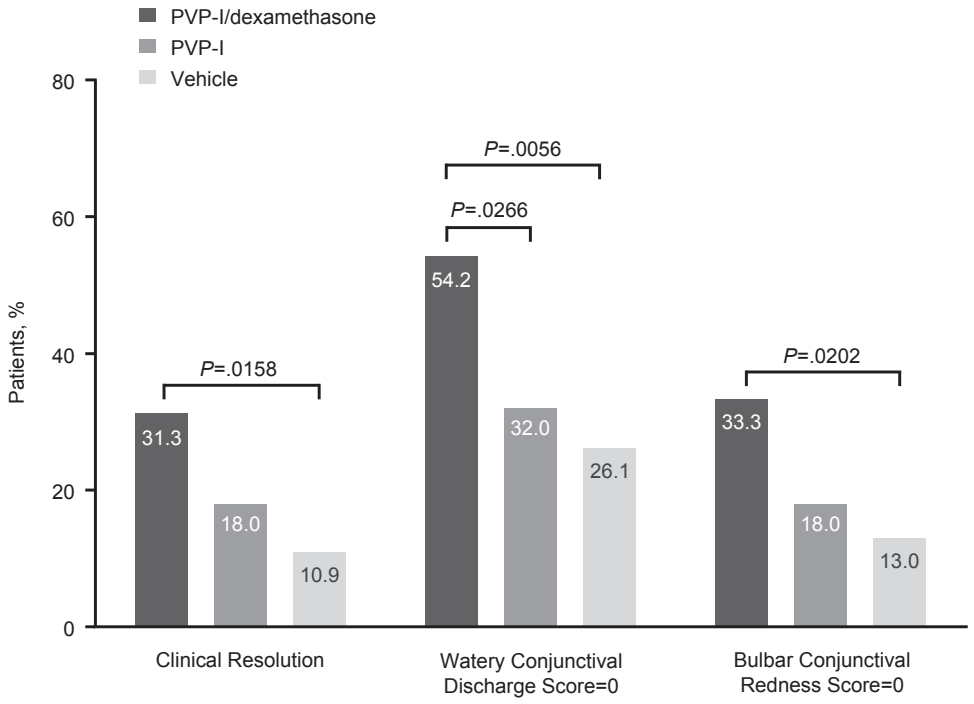


**FIGURE 3. Clinical resolution, watery conjunctival discharge, and bulbar conjunctival redness at day 6 (+1-day window; modified intent-to-treat population with last observation carried forward, primary study eye). Clinical resolution was defined as the absence (score = 0) of both watery conjunctival discharge and bulbar conjunctival redness. Watery conjunctival discharge and bulbar conjunctival redness were scored on a scale of 0 (absent/normal) to 3 (severe). Only statistically significant *P* values (< .05) are shown; all other comparisons between treatment groups were nonsignificant. PVP-I = povidone-iodine.**

with the highest global clinical score. If both eyes had the same score, the right eye was the study eye. Analysis of the crossover infection data was conducted using the clinically worse study eye definition (eye with the highest global clinical score at baseline or, if both eyes had the same global clinical score at baseline, the right eye). The nonstudy eye was designated as the fellow eye.

Binary efficacy endpoints were compared between treatment arms using Pearson $\chi^2$ or Fisher exact tests (in the case of expected counts < 5); change from baseline in global clinical score and raw score were compared between treatment arms using the 2-sample *t* test, at the 2-sided .05 significance level with missing data imputed by last observation carried forward (LOCF). Formal sample size calculations were not performed, as this trial was a proof-of-concept study. However, a sample size of 160 evaluable patients (approximately 53-54 per treatment arm) was deemed reasonable to assess safety and provide information for powering future studies.

## RESULTS

• **STUDY POPULATION:** The study was conducted between December 17, 2012 and May 23, 2014. A total of 176 patients were randomized, and 124 completed the study (Figure 2). The safety and ITT populations included 175 patients. The mITT population included 144 patients. The mean (standard deviation) age across all patients in the ITT population was 34.5 (12.2) years. Two thirds of patients were male (66.3%) and all were Asian (Table 1).

Three patients in the vehicle group and 1 patient in the PVP-I/dexamethasone group were recorded as noncompliant with dosing.

Serotype data were available for 18 patients (6 in the PVP-I/dexamethasone group, 5 in the PVP-I group, and 7 in the vehicle group), most of whom had serotype data across multiple visits. Of these, 17 patients had the D8 serotype in both eyes. At visits 1 and 2, 1 patient in the vehicle arm had the B3 serotype in the fellow eye and the D8 serotype in the study eye.

• **CLINICAL RESOLUTION:** After 5 days of treatment (day 6 visit), the proportion of patients with clinical resolution in the primary study eye was significantly higher in the PVP-I/dexamethasone group (31.3% [15/48]) compared with the vehicle group (10.9% [5/46], $P = .0158$), and numerically higher compared with the PVP-I group (18.0% [9/50], $P =$ nonsignificant [NS]) (Figure 3). At the day 6 visit, a greater proportion of patients also had complete resolution of the individual signs with PVP-I/dexamethasone compared with vehicle ($P = .0056$ for discharge, $P = .0202$ for redness) or

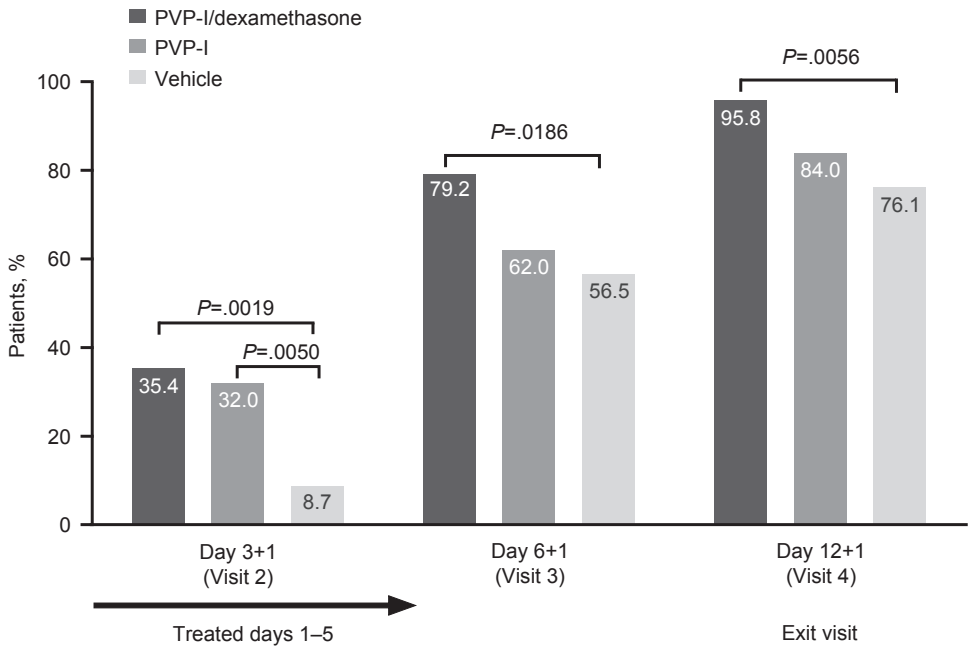


**FIGURE 4. Adenoviral eradication at days 3, 6, and 12 (+1-day window; modified intent-to-treat population with last observation carried forward, primary study eye). Adenoviral eradication was defined as a negative cell culture immunofluorescence assay result. Only statistically significant *P* values (< .05) are shown; all other comparisons between treatment groups were nonsignificant. PVP-I = povidone-iodine.**

PVP-I ($P = .0266$ for discharge, $P$ = NS for redness). No patients had clinical resolution at the day 3 visit. By the day 12 visit, 62.5% of patients (30/48) treated with PVP-I/dexamethasone, 62.0% (31/50) treated with PVP-I, and 45.7% (21/46) treated with vehicle had clinical resolution ($P$ = NS between treatment groups).

• **ADENOVIRAL ERADICATION:** After 5 days of treatment (day 6 visit), the proportion of patients with adenoviral eradication in the primary study eye was significantly greater following treatment with PVP-I/dexamethasone (79.2% [38/48]) compared with vehicle (56.5% [26/46], $P = .0186$), and numerically greater compared with PVP-I (62.0% [31/50], $P$ = NS) (Figure 4). Adenoviral eradication with PVP-I/dexamethasone was evident as early as at the day 3 visit, and remained statistically significantly greater compared with vehicle at the day 12 visit.

The proportion of patients at the day 6 visit with both adenoviral eradication and clinical resolution was significantly greater in the PVP-I/dexamethasone group (31.3% [15/48]) than in the vehicle group (6.5% [3/46]; $P = .0023$), and numerically greater than in the PVP-I group (18.0% [9/50], $P$ = NS) (Figure 5).

• **EXPANDED CLINICAL CURE:** The proportion of patients achieving expanded clinical cure with PVP-I/dexamethasone was significantly greater compared with vehicle at all visits (day 3 visit, 35.4% [17/48] vs 8.7% [4/46], $P = .0019$; day 6 visit, 77.1% [37/48] vs 43.5% [20/46], $P = .0009$; day 12 visit, 95.8% [46/48] vs 71.7% [33/46], $P = .0014$), and compared with PVP-I at the day 6 visit (77.1% [37/48] vs 52.0% [26/50], $P = .0096$). The proportion of patients with expanded clinical cure was also numerically greater following treatment with PVP-I/dexamethasone than with PVP-I at the day 3 visit (35.4% [17/48] vs 18.0% [9/50], $P$ = NS) and day 12 visit (95.8% [46/48] vs 84.0% [42/50], $P$ = NS). The proportion of patients with expanded clinical cure in the PVP-I group was not significantly different from that in the vehicle group at all visits.

• **GLOBAL CLINICAL SCORE:** Reductions from baseline in the global clinical score were significantly greater following treatment with PVP-I/dexamethasone compared with vehicle at all visits (mean change from baseline: day 3 visit, –1.7 vs –0.9, $P = .0097$; day 6 visit, –3.6 vs –2.1, $P = .0002$; day 12 visit, –4.3 vs –3.5, $P = .0468$), and at the day 3 and day 6 visits compared with PVP-I (day 3 visit, –1.7 vs –1.1, $P = .0370$; day 6 visit, –3.6 vs –2.6, $P = .0057$; day 12 visit, –4.3 vs –4.1, $P$ = NS). The proportion of patients in the PVP-I/dexamethasone group with any improvement from baseline in global clinical score was significantly greater than with vehicle at all visits (day 3 visit, 81.3% vs 56.5%, $P = .0095$; day 6 visit, 97.9% vs 76.1%, $P = .0015$; day 12 visit, 100% vs 87.0%, $P = .0115$), and significantly greater than PVP-I at the day 3 (81.3% vs 60.0%, $P = .0212$) and day 6 (97.9% vs 82.0%, $P = .0158$) visits.

At all visits, compared with vehicle, a significantly greater proportion of patients in the PVP-I/dexamethasone group

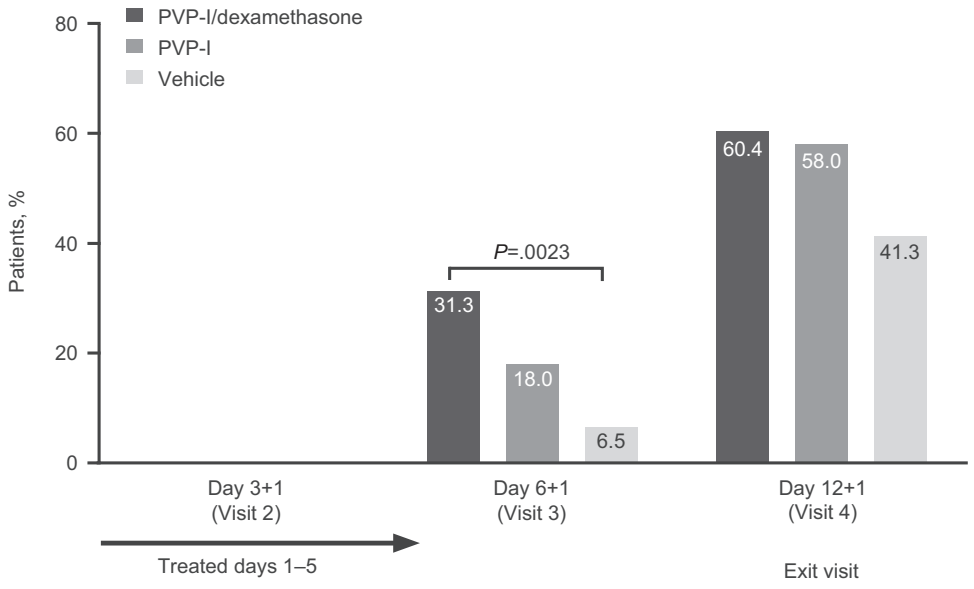


**FIGURE 5. Both adenoviral eradication and clinical resolution at days 3, 6, and 12 (+1-day window; modified intent-to-treat population with last observation carried forward, primary study eye). Adenoviral eradication was defined as a negative cell culture immunofluorescence assay result. Clinical resolution was defined as the absence (score = 0) of both watery conjunctival discharge and bulbar conjunctival redness. Only statistically significant *P* values (< .05) are shown; all other comparisons between treatment groups were nonsignificant. PVP-I = povidone-iodine.**

**TABLE 2.** Crossover Infection (Intent-to-Treat Population With Last Observation Carried Forward)

| | PVP-I/Dexamethasone N = 58 | PVP-I N = 59 | Vehicle N = 58 |
|---|---|---|---|
| Visit 2 | 7 (12.1) | 17 (28.8) | 9 (15.5) |
| Visit 3 | 11 (19.0) | 16 (27.1) | 15 (25.9) |
| Visit 4 | 9 (15.5) | 7 (11.9) | 8 (13.8) |

PVP-I = povidone-iodine.

Values are n (%).

Crossover infection to a patient's fellow eye was a binary variable (yes/no) based on an increase in the global clinical score (sum of watery conjunctival discharge and bulbar conjunctival redness) in the fellow eye.

had either a ≥2-point reduction from baseline in the global clinical score (day 3 visit, 70.8% vs 39.1%, $P = .002$; day 6 visit, 91.7% vs 58.7%, $P = .0002$; day 12 visit, 100% vs 76.1%, $P = .0003$) or a ≥50% reduction (day 3 visit, 39.6% vs 6.5%, $P = .0002$; day 6 visit, 85.4% vs 43.5%, $P < .0001$; day 12 visit, 97.9% vs 71.7%, $P = .0004$). The reduction from baseline in global clinical score in the PVP-I/dexamethasone arm was also statistically superior to that in the PVP-I arm at the day 3 and day 6 visits for both a ≥2-point reduction (day 3 visit, 70.8% vs 48.0%, $P = .0215$; day 6 visit, 91.7% vs 70.0%, $P = .0067$) and a ≥50% reduction (day 3 visit, 39.6% vs 20.0%, $P = .0337$; day 6 visit, 85.4% vs 58.0%, $P = .0027$). At the day 6 visit, a significantly greater proportion of patients in the PVP-I/dexamethasone group, compared with vehicle or PVP-I alone, had a ≥3-point reduction (75.0% vs 43.5%, $P = .0019$ vs vehicle; 75.0% vs 54.0%, $P = .0301$ vs PVP-I) or ≥4-point reduction (58.3% vs 28.3%, $P = .0033$ vs vehicle; 58.3% vs 34.0%, $P = .0157$ vs PVP-I) from baseline. At all visits, none of the global clinical score endpoints in the PVP-I group were significantly different from those in the vehicle group.

• **CROSSOVER INFECTION:** The majority of patients in each treatment group did not meet the definition of crossover infection at each visit (Table 2).

• **SAFETY:** Overall, 61.7% of patients (108/175) experienced 281 treatment-emergent AEs (TEAEs). The proportion of patients with TEAEs was highest in the vehicle group (69.0% [40/58]), followed by the PVP-I group (62.7% [37/59]) and the PVP-I/dexamethasone group (53.4% [31/58]). The majority of TEAEs were mild in severity, no serious AEs were reported, and no TEAEs were suspected of being related to study treatment. Thirty-seven patients withdrew owing to AEs (PVP-I/dexamethasone, n = 9/58 [15.5%]; PVP-I, n = 12/59 [20.3%]; vehicle, n = 16/58 [27.6%]). The majority of TEAEs were ocular, with only 3 nonocular TEAEs reported by 2 patients (headache reported by 1 PVP-I-treated patient, and nasopharyngitis and cough reported by 1 vehicle-treated patient). The most frequently reported

**TABLE 3.** Ocular Treatment–Emergent Adverse Events Occurring in ≥5% of Any Treatment Group (Safety Population)

| Event, N (%) | PVP-I/Dexamethasone N = 58 | PVP-I N = 59 | Vehicle N = 58 | All Patients N = 175 |
|---|---|---|---|---|
| Corneal infiltrates | 11 (19.0) | 18 (30.5) | 12 (20.7) | 41 (23.4) |
| Punctate keratitis | 13 (22.4) | 16 (27.1) | 11 (19.0) | 40 (22.9) |
| Eyelid edema | 7 (12.1) | 16 (27.1) | 12 (20.7) | 35 (20.0) |
| Conjunctivitis | 5 (8.6) | 10 (16.9) | 11 (19.0) | 26 (14.9) |
| Conjunctivitis viral | 6 (10.3) | 4 (6.8) | 6 (10.3) | 16 (9.1) |
| Conjunctival edema | 2 (3.4) | 4 (6.8) | 9 (15.5) | 15 (8.6) |
| Conjunctival disorder | 1 (1.7) | 6 (10.2) | 4 (6.9) | 11 (6.3) |
| Visual acuity reduced | 2 (3.4) | 5 (8.5) | 4 (6.9) | 11 (6.3) |
| Conjunctival follicles | 3 (5.2) | 5 (8.5) | 3 (5.2) | 11 (6.3) |
| Keratitis | 2 (3.4) | 1 (1.7) | 3 (5.2) | 6 (3.4) |
| Eye pain | 2 (3.4) | 0 | 4 (6.9) | 6 (3.4) |
| Meibomian gland dysfunction | 3 (5.2) | 0 | 2 (3.4) | 5 (2.9) |

PVP-I = povidone-iodine.

ocular TEAEs were corneal infiltrates, punctate keratitis, eyelid edema, and conjunctivitis. Most events occurred more frequently in the PVP-I and vehicle groups than in the PVP-I/dexamethasone group (Table 3).

There were no safety concerns raised in any of the clinical examinations (including BCVA and slit-lamp biomicroscopy). Mean drop comfort scores upon instillation were similar among all treatment groups and were 2 or 3 on a scale from 0 (very comfortable) to 10 (very uncomfortable).

## DISCUSSION

THE RESULTS OF THIS STUDY INDICATE THAT AN ophthalmic suspension of PVP-I 0.6% and dexamethasone 0.1% is safe and well tolerated for the treatment of acute adenoviral conjunctivitis. Outcomes for PVP-I 0.6%/dexamethasone 0.1% showed statistical superiority compared with vehicle for clinical resolution, adenoviral eradication, expanded clinical cure, and multiple parameters of global clinical score. Trends to improvement relative to PVP-I alone were also observed. The outcomes for the PVP-I group did not show statistical superiority to vehicle, with the exception of adenoviral eradication at the day 3 visit.

Adenoviral conjunctivitis typically lasts 14-21 days.[17] In our study, the number of patients with complete adenoviral eradication was significantly higher in the PVP-I/dexamethasone group than in the vehicle group as early as the day 3 visit, while the number of patients with both adenoviral eradication and clinical resolution was significantly higher in the PVP-I/dexamethasone group than in the vehicle group at the day 6 visit. No patients achieved clinical resolution at the day 3 visit, but at this time point, 70.8% of patients in the PVP-I/dexamethasone group had a reduction from baseline of ≥2 points (out of a maximum total score of 6) in the global clinical score compared with 39.1% in the vehicle group. A smaller proportion (35.4%) of patients treated with PVP-I/dexamethasone demonstrated adenoviral eradication at the day 3 visit, suggesting that patients receiving this treatment should be counseled to continue to take precautions for ≥6 days to prevent spread of the infection. Overall, these results suggest that PVP-I/dexamethasone may be effective at quickly eradicating the virus and improving clinical signs, which could benefit quality of life and minimize the spread of infection. A rapid improvement of conjunctivitis is also expected to have a positive socioeconomic impact because patients are able to return to school or work sooner.

PVP-I/dexamethasone appeared to be safe and well tolerated in this study, with a lower proportion of patients in the PVP-I/dexamethasone group (53.4%) experiencing TEAEs than in the vehicle (69%) or PVP-I (62.7%) groups. There were no serious AEs during the study, no TEAEs were suspected of being related to study treatment, and the majority of TEAEs in each treatment group were mild in severity. In addition, the drop tolerability of PVP-I 0.6%/dexamethasone 0.1% was acceptable, with drop comfort scores similar to those in the vehicle group. This is noteworthy because drop comfort is a component of ocular tolerability, and ocular discomfort can influence patient preference and treatment compliance.[18]

A study that used the adenovirus type 5/New Zealand rabbit ocular model showed that corticosteroids alone can increase viral replication and the duration of viral shedding.[19] However, results from the present study and others[14–16] suggest that PVP-I/dexamethasone does not increase or prolong viral shedding, with adenoviral eradication observed from day 3 through day 12 in our study. In addition, rapid adenoviral eradication and clinical resolution with PVP-I/dexamethasone should ensure that the

duration of treatment is short, thus lowering the risk of steroid-related side effects. Overall, the PVP-I/dexamethasone antiseptic-steroid combination appears to have a virucidal effect and also mitigates the secondary immune response (which can lead to more serious ocular sequelae), thereby accelerating the resolution of associated clinical signs.

The differential diagnosis of conjunctivitis can be difficult because different forms of the condition (bacterial, viral, allergic) present similar symptoms.[20] Misdiagnosis of bacterial conjunctivitis can occur in up to 50% of cases,[21] which often results in inappropriate antibiotic treatment. PVP-I has broad-spectrum antimicrobial action that includes bacteria, viruses, and fungi.[22] Bactericidal activity has been demonstrated in vitro for PVP-I alone[10,23] and for PVP-I 0.4%/dexamethasone 0.1%, which in 1 study killed 99.9% of common ocular pathogens (methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Candida albicans*) within 15 seconds of exposure.[24] PVP-I/dexamethasone therefore has the potential to mitigate the negative effects of misdiagnosis. In addition, PVP-I/dexamethasone could avoid unnecessary use of antibiotics and reduce the potential of developing antibiotic resistance,[25,26] which has not been observed following multiple topical applications of PVP-I alone.[27] Infectious conjunctivitis caused by herpes simplex virus (HSV) is also difficult to differentiate from adenoviral conjunctivitis.[28] Although less common than adenovirus, HSV keratitis is the most common cause of infectious corneal blindness in developed countries.[28] PVP-I has been demonstrated in vitro to have virucidal activity against HSV at concentrations as low as 0.1%.[23,29] This study provides useful data on the efficacy and safety of PVP-I/dexamethasone, especially since there are few published results from randomized controlled trials of topical drug therapies for adenoviral conjunctivitis. The results from our study are consistent with results from studies of different PVP-I/dexamethasone formulations.[13–16] A phase 2 pilot study (NCT01461954) conducted in Brazil has also investigated the safety and efficacy of PVP-I 0.6%/dexamethasone 0.1% compared with vehicle for the treatment of clinically suspected acute viral conjunctivitis, and showed trends toward efficacy; however, too few patients with confirmed adenoviral conjunctivitis were enrolled to deliver meaningful results.

A strength of our study is that viral culture was used to confirm infection with adenovirus. A limitation of this study is that it was conducted only in adults; further studies are needed to evaluate the safety and efficacy of PVP-I/dexamethasone in children. As this was a single-country study, future studies are needed in other populations and regions and on a broader range of adenoviral serotypes.

In conclusion, these findings suggest that PVP-I 0.6%/dexamethasone 0.1% is a promising option for the treatment of acute adenoviral conjunctivitis. Phase 3 studies are ongoing to further evaluate PVP-I/dexamethasone for the treatment of adenoviral conjunctivitis (NCT02998541 and NCT02998554), and for the treatment of bacterial conjunctivitis (NCT03004924). The advantages of PVP-I/dexamethasone could include mitigation of the negative effects of misdiagnosis and consequent reduction of the costs and risks associated with unnecessary antibiotic prescriptions.

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