

# SAFETY AND EFFICACY OF OFLOXACIN (0.3%), PREDNISOLONE (ACETATE 0.2%), AND TETRAHYDROZOLINE HYDROCHLORIDE (0.4%) COMBINATION EYE DROPS IN PATIENTS WITH BACTERIAL CONJUNCTIVITIS A PHASE IV, OPEN-LABEL STUDY

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## ABSTRACT

**Background:** Adding anti-inflammatory and decongestant agents to antibiotics may mitigate the inflammation and symptoms of bacterial conjunctivitis until bacterial eradication occurs. We performed this study to investigate the safety and efficacy of ofloxacin, prednisolone, and tetrahydrozoline hydrochloride combination (Loxtra™ eye drops) in bacterial conjunctivitis.

**Materials and Methods:** Fifty patients with clinically confirmed bacterial conjunctivitis were enrolled in this study. For seven days, each patient self-administered Loxtra™ eye drops (ofloxacin 3 mg, prednisolone 2 mg, and tetrahydrozoline 0.4 mg). Clinical safety and efficacy outcomes were assessed at the end of the follow-up period.

**Result:** At the end of study (EOS) visit, 100%, 98%, and 100% of patients who used Loxtra™ eye drops achieved  $\geq$  one grade reduction in conjunctival discharge, ocular itching, and conjunctival redness scores. Compared to baseline values, we recorded significant reductions ( $p < 0.05$ ) in the mean conjunctival discharge, ocular itching, and conjunctival redness scores by the first follow-up and EOS visits (after 3 and 7 days, respectively). The overall therapeutic response at the EOS visit was “Much Improved” for 100% of subjects. Regarding safety, only one patient experienced a severe headache. The adverse event was non-serious and related to the study drug. Otherwise, no adverse events were recorded.

**Conclusion:** Loxtra™ eye drops demonstrated high safety and efficacy in treating patients with bacterial conjunctivitis and ameliorating their symptoms. Therefore, we recommend this product for clinical use in patients with bacterial conjunctivitis.

**Keywords:** Conjunctivitis; Ofloxacin; Prednisolone; Tetrahydrozoline Hydrochloride

## 1.0 Introduction

Bacterial conjunctivitis is a common, inflammatory ocular condition, caused by infection with various organisms, such as *Streptococcus pyogenes*, *Staphylococcus aureus*, *Neisseria gonorrhea*, and *H. Influenza* (Høvdning, 2008). It is usually manifested by ocular discharge, foreign body sensation, itching, and conjunctival redness (Leibowitz, 2000). In developed countries, bacterial conjunctivitis is estimated to account for 1 to 4% of all general practitioner consultations (Dart, 1986; McDonnell, 1988). Bacterial conjunctivitis is often self-limited, and clinical cure usually occurs in one to two weeks in >60% of patients. However, using antibiotics can increase the speed of recovery and improve the rates of early clinical and microbiological remissions (Azar, Dhaliwal, Bower, Kowalski, & Gordon, 1996; Sheikh, Hurwitz, van Schayck, McLean, & Nurmatov, 2012).

The choice of optimal antibiotic for this condition is affected by the method of administration, safety and clinical outcomes (Høvdning, 2008). Ofloxacin is a broad spectrum, bactericidal, a fluoroquinolone antibiotic that exerts its pharmacological action by interfering with bacterial DNA (Smythe & Rybak, 1989). In an in-vitro study, the antimicrobial effect of ofloxacin against ocular bacterial isolates was superior or equal to that of several antibiotics, including norfloxacin, tobramycin, gentamicin, and chloramphenicol (Osato et al., 1989). Another study by Block et al. showed that ciprofloxacin, ofloxacin, and tetracycline were the most effective against bacterial conjunctivitis, even in conditions caused by resistant *Streptococcus Pneumonia* and *H. Influenza* (Block et al., 2000). Therefore, ofloxacin is recommended and is available in several commercial formulations for bacterial conjunctivitis.

Prednisolone is a synthetic corticosteroid that inhibits prostaglandins synthesis and thereby, inhibits macrophage migration, capillary dilatation and edema, and fibrin deposition (Thompson & Lippman, 1974). Tetrahydrozoline hydrochloride is a sympathomimetic agent with an alpha-adrenergic activity that induces vasoconstriction, and therefore, acts as a conjunctival decongestant (Abelson, Yamamoto, & Allansmith, 1980). Clinical studies have shown that tetrahydrozoline gives prompt relief (for 1-4 hrs.) from ocular and nasal congestion (MENDER, 1959; NEISTADT, 1955). Adding prednisolone and tetrahydrozoline to an antibiotic may be useful to reduce the inflammation and mitigate the symptoms until bacterial eradication occurs.

Several clinical trials have tested the efficacy of different antibiotics in selected bacterial conjunctivitis patients (Rietveld et al., 2005; Rose et al., 2005); however, whether the results of these trials would apply to the general population remains questionable. We performed this phase IV study to investigate the safety and efficacy of ofloxacin, prednisolone, and tetrahydrozoline hydrochloride combination, available commercially as Loxtra<sup>TM</sup> eye drops in bacterial conjunctivitis.

## 2.0 Materials and Methods

### 2.1. Patient selection

This study enrolled male and female patients with a confirmed bacterial conjunctivitis diagnosis who were between 12 and 65 years of age and had ocular itching and conjunctival redness scores  $\geq 2$  and conjunctival discharge score  $\geq 1$  (based on a three-point assessment scale). The diagnoses of enrolled patients were made clinically. Patients were instructed to avoid wearing contact lenses or use any other medication for their ocular condition during the study period (starting three days before administration of Loxtra™ eye drops), and only those who agreed to these precautions were enrolled. We excluded pregnant, breastfeeding females, patients with hypersensitivity to any of the study product components, those with all viral conjunctivitis and corneal infections, and patients who had ocular surgeries within the past six months. We recorded no patient withdrawal from this study due to serious adverse effects or protocol violations.

### 2.2. Treatments

The study lasted for a total of 10 days. Following a three-day screening period, Subjects self-administered/instilled one drop into the conjunctival sac of the eye(s) four times daily for up to 7 study days. Each 1 ml of Loxtra™ eye drops contains 3 mg of ofloxacin, 2 mg of prednisolone, and 0.4 mg of tetrahydrozoline. We monitored the compliance of the patients to the study treatment using self-reported diaries. All other medications for bacterial conjunctivitis were prohibited except for rescue medications that were only allowed upon the investigator's discretion. Rescue medications included systemic antihistaminics with short-acting half-lives, such as chlorpheniramine, promethazine, and diphenhydramine.

### 2.3. Study outcomes

We used several endpoints to assess the efficacy of the investigated product. The primary efficacy outcome was the proportion of patients who achieved clinical cure of bacterial conjunctivitis, detected as absence (grade 0) of conjunctival discharge at EOS visit. Secondary efficacy endpoints included the percentage of patients who had one grade reduction in the ocular itching and conjunctival redness scores (each based on a four-point scoring system from 0 to 3). Moreover, a scale from 0 to 2 was used to assess the overall therapeutic response in which 0=no improvement, 1=improved, and 2=much improved. The total symptoms and signs score (TSSS) for each subject was obtained by adding the values of each symptom and signs divided by the total number of them.

Regarding safety, we recorded the incidence and severity of adverse events (AEs). A serious AE was defined as an event that follows drug administration and ends in mortality, life-threatening or disabling event, or hospitalization. The methods of recording these events involved self-reporting by patients or elucidation by the investigator during history taking and physical examination during follow-up visits.

## 2.4. Statistical analysis

We enrolled a total sample size of 50 subjects, assuming that 50% of subjects would achieve clinical cure at the first follow-up visit. All statistical analyses were conducted on the SPSS software (IBM, Chicago, Illinois, USA). To test the significance of the difference in assessment scores between baseline and study follow-up visits, we used the dependent student's t-test. Moreover, we used the Chi  $\chi^2$  to demonstrate any significant difference in the proportions of subjects experiencing improvement after treatment.

## 3.0 Result

### 3.1 Patients characteristics at baseline

Table 1: Subject baseline demography and disease characteristics

Subjects' characteristics	Baseline values
<b>Gender</b>	
Male, n (%)	29 (58%)
Female, n (%)	21 (42%)
<b>Age</b> (Mean $\pm$ SD, in year)	36.75 (10.9)
<b>Weight</b> (Mean $\pm$ SD, in kg)	73.3 (12.3)
<b>BMI</b> (Mean $\pm$ SD, in kg/cm <sup>2</sup> )	26.79 (3.95)
<b>Race</b>	
Caucasian, n (%)	50 (100%)
<b>Medical History</b>	
No, n (%)	50 (100%)
<b>Mucopurulent discharge grade</b>	
Mean $\pm$ SD	1.76 (0.66)
Grade 1, n (%)	18 (36%)
Grade 2, n (%)	26 (52%)
Grade 3, n (%)	6 (12%)
<b>Ocular Itching Assessment Score</b>	
Mean $\pm$ SD	2.26 (0.44)
Grade 2, n (%)	37 (74%)
Grade 3, n (%)	13 (26%)
<b>Conjunctival Redness Assessment Score</b>	
Mean $\pm$ SD	2.18 (0.39)
Grade 2, n (%)	41 (82%)
Grade 3, n (%)	9 (18%)

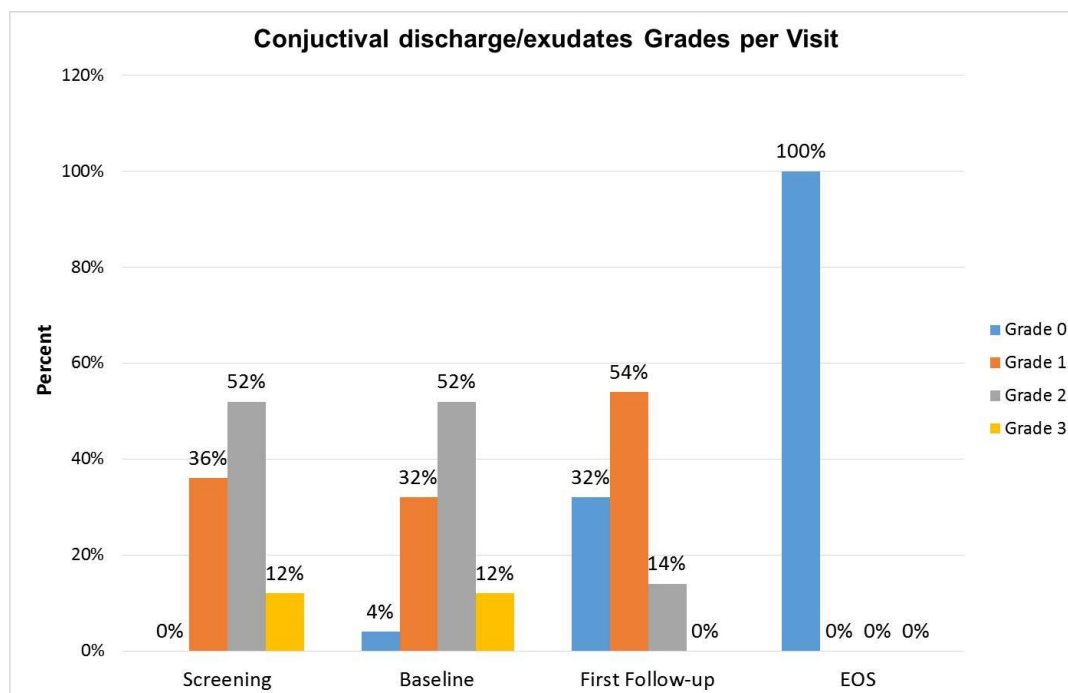
(Data are either frequency (Percentage) or mean  $\pm$  standard deviation)

We enrolled 50 patients following a three-day screening process; all of them completed the required study visits. The majority of enrolled patients were males (29; 58%), and the mean

age was  $36.75 \pm 10.9$  years. The mean discharge, itching, and redness scores at baseline were  $1.76 \pm 0.66$ ,  $2.26 \pm 0.44$ , and  $2.18 \pm 0.39$ , respectively. Only 6, 13, and 9 patients had severe discharge, itching, and redness, respectively. Compliance was 100 percent in 100% of participants on Day 3 then 98% by Day 7. One Subject had 70 percent compliance at Day 7. Details on baseline data of enrolled patients are illustrated in Table 1.

### 3.2 Efficacy Outcomes

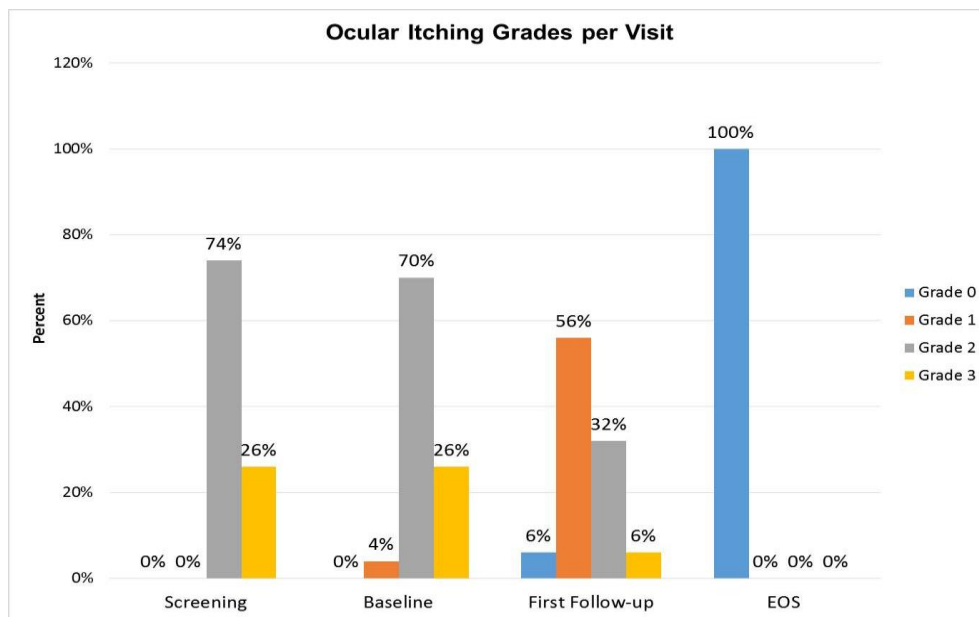
#### 3.2.1 Conjunctival Discharge/Exudates (Primary Outcome)



(Fig.1: Changes in grades of conjunctival discharge/exudates from visit 1 to End of study visit)

The mean conjunctival discharge score dropped from  $1.76 \pm 0.66$  at baseline to  $0.82 \pm 0.66$  at first follow-up visit ( $p < 0.001$ ) and to  $0.0 \pm 0.0$  by EOS visit ( $p < 0.001$ ). By the first follow-up visit, 12%, 82%, and 6% of patients achieved zero, one, and two grades' reduction in the conjunctival discharge score, respectively. Therefore, 88% of patients achieved  $\geq 1$  grade reduction in conjunctival discharge score. By the EOS visit, 36%, 52%, and 12% of patients achieved one, two, and three grades' reduction in the conjunctival discharge score, respectively. Therefore, 100% of patients achieved  $\geq 1$  grade reduction in conjunctival discharge score (Figure 1).

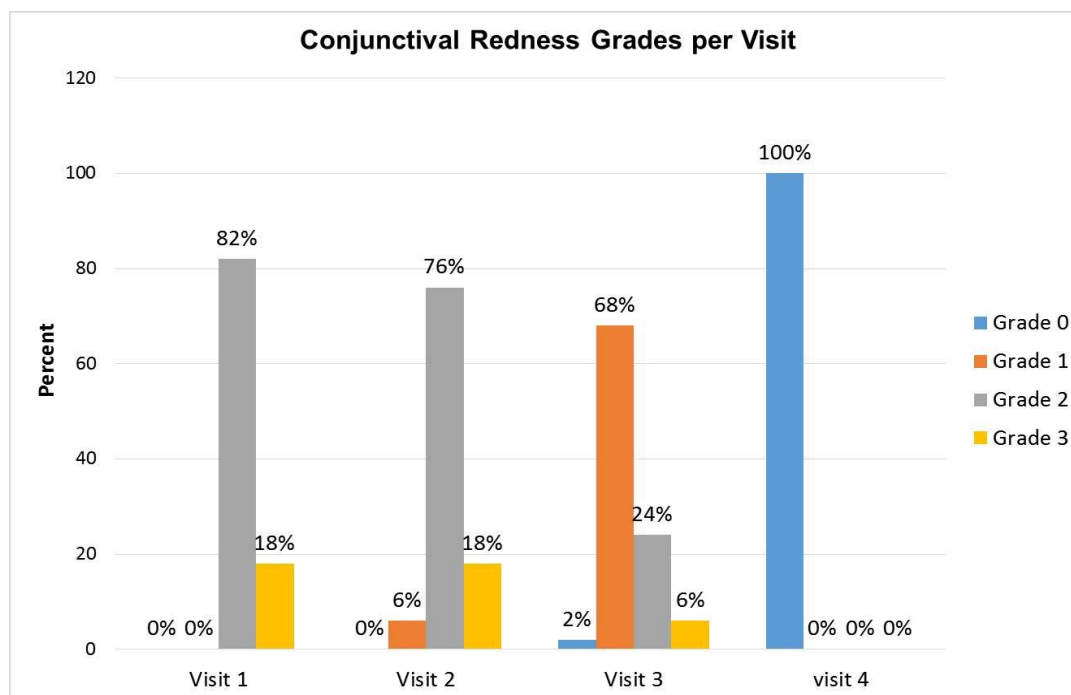
### 3.2.2 Ocular itching



(Fig.2: Changes in grades of the ocular assessment score from visit 1 to End of study visit)

We recorded a significant reduction in the mean ocular itching score from  $2.26 \pm 0.44$  at baseline to  $1.38 \pm 0.70$  at first follow-up visit ( $p < 0.001$ ) and to  $0.0 \pm 0.0$  by EOS visit ( $p < 0.001$ ). By the first follow-up visit, 18%, 76%, and 6% of patients achieved zero, one, and two grades' reduction in the ocular itching score, respectively. Therefore, 82% of patients achieved  $\geq 1$  grade reduction in ocular itching score. By the EOS visit, 2%, 0%, 74%, and 26% of patients achieved zero, one, two, and three grades' reduction in the ocular itching score, respectively. Therefore, 98% of patients achieved  $\geq 1$  grade reduction in the ocular itching score (Figure 2).

### 3.2.3 Conjunctival redness



(Fig.3: Changes in grades of conjunctival redness score from visit 1 to End of study visit)

The mean conjunctival redness score dropped from  $2.18 \pm 0.39$  at baseline to  $1.34 \pm 0.63$  at first follow-up visit ( $p < 0.001$ ) and to  $0.0 \pm 0.0$  by EOS visit ( $p < 0.001$ ). By the first follow-up visit, 12%, 82%, and 6% of patients achieved zero, one, and two grades' reduction in the conjunctival redness score, respectively. Therefore, 88% of patients achieved  $\geq 1$  grade reduction in conjunctival redness score. By the EOS visit, 36%, 52%, and 12% of patients achieved one, two, and three grades' reduction in the conjunctival redness score, respectively. Therefore, 100% of patients achieved  $\geq 1$  grade reduction in conjunctival redness score (Figure 3).

### 3.2.4 Overall therapeutic response

From the investigator's point of view, the overall therapeutic response at the EOS visit was "Much Improved" for 100% of subjects.



### 3.2.5 Total signs and symptoms score

Table 2: Score change in total symptoms and signs of bacterial conjunctivitis

TSSS	Visit 2	First follow-up visit	MD (Visit 2 – First follow-up visit)	P value	End of study visit	Mean Difference (Visit 2- EOS visit)	P value
Symptoms of bacterial conjunctivitis	1.49 ± 0.69	1.28 ± 0.59	0.67 ± 0.46	< 0.001	0.00 ± 0.00	1.94 ± 0.69	< 0.001
Signs of bacterial conjunctivitis	1.12 ± 0.60	0.40 ± 0.43	0.72 ± 0.46	< 0.001	0.00 ± 0.00	1.12 ± 0.60	< 0.001

(Data are means ± standard deviations. EOS: End of Study, MD: Mean Difference)

We recorded a significant reduction in the TSSS score at first follow-up and EOS visits ( $p < 0.001$ ), compared to baseline scores; Table 2.

### 3.3 Safety Outcomes

One subject (2%) experienced a severe headache. The adverse event was non-serious and related to Study Drug. The subject took paracetamol 1 gm and fully recovered. Otherwise, no adverse events were recorded.

## 4.0 Discussion

This study confirmed the value of concomitant administration of corticosteroids as anti-inflammatory agents and sympathomimetics as vasoconstrictor agents, along with antibiotics in treating bacterial conjunctivitis. Our results indicate that co-administration of ofloxacin, prednisolone, and tetrahydrozoline was effective in achieving the primary endpoint of our study (disappearance of conjunctival discharge), as well as other secondary endpoints (as itching and redness). From the investigator's point of view, the overall therapeutic response at the EOS visit was "Much Improved" for 100% of subjects. Collectively, this indicates the high efficacy of Loxtra<sup>TM</sup> combination eye drops in treating bacterial conjunctivitis.

We followed some precautions before prescribing this product to our patients. First, we excluded pregnant women from participation in our study as ofloxacin is classified as a class C drug by the FDA (meaning that risk cannot be ruled out). Moreover, patients must have instructed and fully agreed not to use contact lenses during the study period. This is because Loxtra<sup>TM</sup> solution contains benzalkonium chloride as a preservative, which may be deposited in soft contact lenses. Further, due to corticosteroid content, all patients with viral conjunctivitis and corneal infections were excluded from the study.

Regarding safety, we recorded no adverse events in this study, except for one patient who experienced severe headache. This side effect is listed as a possible side effect in the product's pharmaceutical brochure and could have been caused by any of the three active



components. Moreover, it was not serious and resolved after receiving 1 gram of paracetamol. These results indicate the high safety of the product; however, further confirmation would be needed in future larger studies.

#### ***4.1 Limitations and future research recommendations***

In this study, we aimed to evaluate the safety and efficacy of Loxtra™ eye drops at a single center; therefore, we assessed various endpoints at two distinct follow-up periods. However, the main limitation of this study is that the maximum follow-up period was somewhat short. Future studies should use larger sample sizes involving multiple centers and perform longer follow-up to establish the safety of the drug on a longer term. Moreover, researchers are encouraged to compare the currently available combinations of antibiotic, anti-inflammatory, and decongestant drugs to elucidate the optimal pharmaceutical combination with the highest safety and efficacy in the treatment of bacterial conjunctivitis patients.

## **5.0 Conclusion and recommendation**

Loxtra™ eye drops demonstrated high safety and efficacy in treating patients with bacterial conjunctivitis and ameliorating their symptoms. Therefore, we recommend this product for clinical use in patients with bacterial conjunctivitis.

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**Ethical Approval:** This study complied with the recommendations of the 18th World Health Congress (Helsinki, 1964) and all the applicable amendments, as well as the laws and regulations and any applicable guidelines of the kingdom of Saudi Arabia where the study was conducted.

## Declaration

Authors declare that there are no conflicts of interests.

## Authors contribution

Author 1: Alwadani S. was the Principal Investigator of the trial. He was in charge of the communication with IRB/IEC, he ensured that all study related duties were carried out in compliance with the study protocol, and supervised the delegated study tasks conducted at the trial site. He also recruited eligible patients, obtained the consent of the trial subjects and informed them about the study details. He was responsible for all trial-related medical decisions, and ensured that adequate medical care was provided to a subject for any adverse events. He ensured the integrity of the study tasks performed and any data generated as well as the accuracy, completeness, legibility, and timeliness of the reported data. He was also in charge of writing and reviewing the manuscript.

Author 2: Alkharashi M. was the Sub-Investigator of the trial. He contributed to finding potential patients, referring them to the PI for recruitment in the study and followed up with the patients to comply with the schedule of assessment visits.

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