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ORIGINAL RESEARCH ARTICLE

A Real-World Observational Study to Evaluate the Safety and Effectiveness of Fluticasone Furoate–Oxymetazoline Fixed Dose Combination Nasal Spray in Patients with Allergic Rhinitis

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Abstract

Background Allergic rhinitis (AR) has shown an increasing prevalence leading to a considerable medical and social burden. Nasal congestion is the cardinal symptom of AR, and the upper respiratory tract is most affected by this long-lasting ailment. Intranasal corticosteroids alleviate nasal congestion, along with other symptoms of AR, but their effect is not evident immediately. Oxymetazoline has a rapid onset of action, but its use should be limited to 3–5 days.

Objective The study aimed to evaluate the safety and effectiveness of the fixed-dose combination nasal spray containing fluticasone furoate and oxymetazoline hydrochloride (FF + OXY) 27.5/50 mcg once daily in patients with AR in a real-world clinical setting.

Methods The study was a prospective, open-label, single-arm, multicenter, real-world observational study conducted in patients with AR for a period of 28 days. Patients ($n = 388$) with a diagnosis of AR were treated with a combination of FF + OXY nasal spray. Total nasal symptom score (TNSS), total ocular symptom score (TOSS) and total symptom score (TSS) were documented at baseline and at the end of study period. The overall effectiveness of treatment with FF + OXY was rated by the investigators as verygood/good/satisfactory/poor (4-point Likert scale) for each patient.

Results Treatment with FF + OXY resulted in significant reduction in the TNSS, TOSS and TSS, from 7.18 ± 3.38 at baseline to 0.20 ± 0.84 ($p < 0.001$), from 2.34 ± 2.29 at baseline to 0.09 ± 0.53 ($p < 0.001$), from 9.51 ± 4.94 at baseline to 0.29 ± 1.32 ($p < 0.001$) at 28 days respectively. With respect to effectiveness, the investigators reported very good effectiveness in 52.12% of patients. No serious adverse events were reported.

Conclusion The fixed-dose combination of once-daily fluticasone furoate and oxymetazoline hydrochloride nasal spray 27.5/50 mcg was effective in relieving the nasal congestion and reduction of TNSS, TOSS and TSS in patients suffering from AR. The combination was safe and well tolerated with no rebound congestion throughout the treatment period.

Key Points

Post-marketing safety and effectiveness studies are required for new drugs, including fluticasone furoate-oxymetazoline fixed dose combination nasal spray.
Using real-world data from a large group of patients with allergic rhinitis in India, we confirmed that FF+OXY nasal spray results in significant reduction in nasal as well as ocular symptoms, and was well-tolerated.

1 Introduction

Allergic rhinitis (AR) has a considerable medical and social burden, primarily because of its increasing prevalence, relationship with asthma and the impact on quality of life [1]. Although available data are limited to estimate the prevalence of AR in India, it is believed that AR accounts for about 55% of all allergies in the country [2]. A study conducted by Ghoshal et al. [2] demonstrated that AR is the second most common reason for adults to seek care for respiratory diseases in India.

The clinical and epidemiologic profiles of AR are classified as "sneezers and runners" and "blockers." The former is characterized by sneezing and a runny nose as the primary

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symptoms, while nasal congestion predominates in the latter [3, 4]. Clinical profile of AR with blockers shows more persistent disease [3].

Nasal congestion is the cardinal symptom of AR and the upper respiratory tract is most affected by this long-lasting ailment [5]. The symptoms of AR are extremely troublesome, known to affect daily activities of life such as working ability, examination performance, quality of life (QoL) and psychosocial comfort [5]. Nasal congestion is often the most bothersome symptom leading to feelings of discomfort, frustration, fatigue, irritability, and stress [6]. Of all symptoms of AR, nasal congestion is the most difficult to treat [7].

Intranasal corticosteroids (INCS) and intranasal decongestants are the two most effective drug classes providing relief from nasal congestion [8]. Intranasal corticosteroids alleviate nasal congestion, along with other symptoms of AR; however, their effectiveness may not be immediately apparent, with relief typically seen 12 h after administration [9]. Relief of nasal congestion within a few minutes with oxymetazoline hydrochloride (OXY) helps to shorten the time to relief [9]. Oxymetazoline has a rapid onset of action, taking effect within 5–10 min of administration with a duration of action between 5 and 6 h [9]. However, it is recommended that use of intranasal decongestants alone should be limited to 3–5 days due to the risk of rebound congestion associated with prolonged use [9]. However, when an INCS is administered with oxymetazoline, the combination can be given for a longer period of time without causing rebound congestion [10–12].

Considering the limited efficacy of INCS in patients with AR having nasal obstruction and the beneficial effects of oxymetazoline in the management of nasal obstruction, a fixed-dose combination of the INCS fluticasone furoate and oxymetazoline hydrochloride nasal spray has been developed and marketed in India by M/s Zydus Healthcare Limited, India (Fluticone OX™). The efficacy and safety of the fixed-dose combination nasal spray has been evaluated in a prospective, randomized, double-blind, active-controlled, Phase III clinical trial, where the combination was administered for 28 days without causing rebound congestion [10]. This study aimed to evaluate the safety and effectiveness of the fixed-dose combination nasal spray containing FF + OXY in patients with AR in a real-world clinical setting.

2 Patients and Methods

2.1 Study Design

This was a prospective, open-label, single-arm, multicenter, real-world observational study conducted in patients with AR.

2.2 Patient Selection

Patients with the clinical diagnosis of AR and where the treating physician deemed the patient suitable to receive treatment with the fixed-dose combination nasal spray of INCS and nasal decongestant, were included in the study. No further inclusion or exclusion criteria were defined beyond the information given in the package insert.

2.3 Methodology

Data including demographic details, i.e., age, sex, duration of symptoms, medical history, previous medications for AR, concomitant diseases with its medications and rebound congestion were collected from patients enrolled in the study. Depending upon the type of AR, patients were classified as: persistent or intermittent; and runners (predominant runny nose/itchy eyes symptoms) or blockers (predominant nasal blockage symptoms) or combined.

Total nasal symptom score (TNSS) [13], total ocular symptom score (TOSS) [13] and total symptom score (TSS) [13] were documented at baseline. The nasal symptoms evaluated were congestion, itching, rhinorrhea and sneezing and the ocular symptoms evaluated were itching/burning, tearing/watering and redness. Each of the 7 symptoms were rated on a 4-point scale ranging from 0–3, where 0 indicated none/no symptoms, 1 indicated mild symptoms, but not affecting any activities during the day/sleep at night; 2 indicated moderate symptoms affecting at least 1 activity or disturbing sleep and 3 indicated severe symptoms affecting > 2 daily activities/disturbing sleep all night/most of the night. The TNSS score was calculated by adding the score of 4 nasal symptoms that ranged from 0–12. The TOSS score was calculated by adding the scores of 3 ocular symptoms that ranged from 0–9. The TSS was calculated by adding the scores of all 7 symptoms including nasal as well as ocular, i.e., TNSS + TOSS that ranged from 0–21.

The duration of treatment with fluticasone furoate and oxymetazoline hydrochloride (FF + OXY) was as per the discretion of the treating physician, for a maximum of 28 days. The recommended dose was two spray actuations (27.5 mcg of FF and 50 mcg of OXY per spray actuation) in each nostril once daily at bedtime (total daily dose, 110 mcg of FF and 200 mcg of OXY). Concomitant medications for the management of AR were allowed at the discretion of the treating physician. All concomitant medications taken during the study were recorded. Compliance was verbally confirmed by the investigators during the follow-up visits and recorded in case record forms (CRF) as "compliance to therapy". Adverse events (AEs)

were recorded in the CRF and graded as mild, moderate or severe based on the Common Terminology Criteria for Adverse Events (CTCAE) criteria.

2.4 Assessment of Safety and Effectiveness

The safety of FF + OXY was enquired and assessed by recording the AEs (local or systemic) that occurred during the treatment and was reported by the investigator during each follow-up (two follow-up visits before 28 days) for all the patients enrolled in the study. All abnormalities observed during the clinical evaluation (physical examination [including vitals] and laboratory investigations) were also considered as AEs. The incidence of rebound congestion was recorded as "Yes" or "No" while compliance to therapy was recorded as: Good (> 80%) or Poor (< 80%)]. The overall safety and tolerability to FF + OXY was rated by the investigators as very good/good/satisfactory/poor. To evaluate effectiveness, TNSS, TOSS and TSS were recorded at baseline and follow-up visits (two follow-up visits on or before 28 days). The overall effectiveness of treatment with FF + OXY was rated by the investigators as very good/good/satisfactory/poor (4-point Likert scale) for each patient.

2.5 Statistical Analysis

Categorical variables were summarized by frequency and percentage. Continuous parameters were summarized by mean and standard deviation (SD). TNSS, TOSS and TSS scores were compared across follow-up periods against baseline. The mean scores with SD were reported at different time points. Repeated measure ANOVA was applied for statistical validity of the reduction across time points-concomitant medications during the study period and after completion of the study period. A p-value of < 0.05 was considered to be of statistical significance. Statistical software R version 4.2.3 (R Core Team, 2023, Vienna, Austria) was used for statistical analysis.

3 Results

A total of 423 patients were enrolled, and 388 completed the study with 2 visits. The mean duration of first follow-up was 10.24 ± 6 days while that of second follow-up was 23.37 ± 5 days (Fig.1).

Most patients were suffering from intermittent AR (n = 221; 56.96%) while the remaining had persistent AR (n = 167; 43.04%). In the total cohort, 46.10% (n = 142) patients were blockers, 18.83% (n = 58) were runners, 35.06% (n = 108) were combined. Fifty-nine (15.21%) patients had a history of concomitant asthma. The baseline

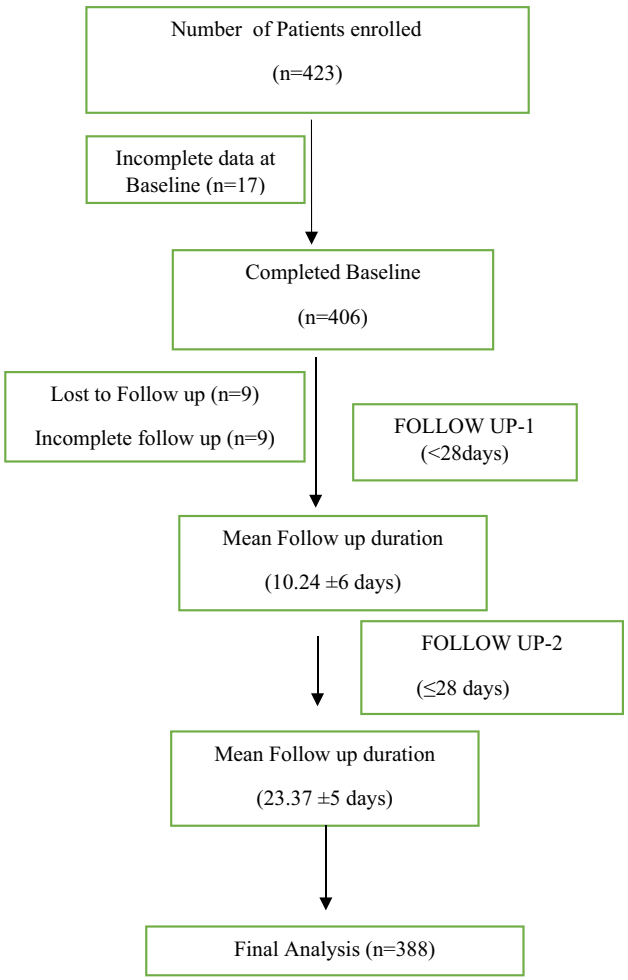

Fig. 1 Flow chart

characteristics of patients enrolled in the study are summarized in Table 1.

3.1 Effectiveness Assessment

3.1.1 Total Nasal Symptom Score (TNSS)

Treatment with FF + OXY resulted in a significant reduction in the TNSS score from 7.18 ± 3.38 at baseline to 1.79 ± 2.00 ($p < 0.001$) at the first follow-up visit and 0.20 ± 0.84 ($p < 0.001$) at the second follow-up visit (Fig. 2). The treatment with FF + OXY showed significant reduction in nasal congestion from 2.22 ± 0.97 at baseline to 0.59 ± 0.66 ($p < 0.001$) at the first follow-up visit and 0.05 ± 0.25 ($p < 0.001$) at the second follow-up visit (Fig. 2). Reduction in TNSS from baseline to end of the study period was 97.21% (Fig. 2).

Table 1 Summary of patient demographics at baseline, $N = 388$

Variable	Value, *n* (%)
Age (years, mean ± SD)	39.91 ± 14.90
Weight (kg, mean ± SD)[a]	62.85 ± 13.03
Sex	
Female	171 (44.07)
Male	217 (55.9)
Allergic rhinitis type	
Intermittent	221 (56.96)
Persistent	167 (43.04)
Predominant nasal symptom[b]	
Blocker	142 (46.10)
Runner	58 (18.83)
Combined	108 (35.06)
Concomitant asthma and allergic rhinitis	
No	329 (84.79)
Yes	59 (15.21)
History of using nasal decongestants	
No	337 (86.86)
Yes	51 (13.14)

[a]For remaining 121 patients, weight was not captured in the case record forms

[b]For remaining 80 patients, the predominant nasal symptom was not defined by the investigators

3.1.2 Total Ocular Symptoms Score (TOSS)

A significant reduction in the TOSS from 2.34 ± 2.29 at baseline to 0.41 ± 0.95 ($p < 0.001$) at the first follow-up visit and 0.09 ± 0.53 ($p < 0.001$) at the second follow-up visit was observed with treatment of FF + OXY. The reduction in the individual symptoms of ocular itching/burning, tearing/watering and ocular redness from baseline at follow-up visits is depicted in Fig. 3. Reduction in TOSS from baseline to end of the study period was 96.15% (Fig. 3).

3.1.3 Total Symptom Score (TSS)

A significant reduction in the TSS score from 9.51 ± 4.94 at baseline to 2.20 ± 2.67 ($p < 0.001$) at the first follow-up visit and 0.29 ± 1.32 ($p < 0.001$) at the second follow-up visit. Reduction in TSS at the end of study period was 96.97% (Fig. 4).

With respect to effectiveness reported by the investigators in 330 patients; 52.12% ($n = 172$) of the study participants showed very good effectiveness, 41.52% ($n = 137$) showed good effectiveness, and 4.85% ($n = 16$) had satisfactory effectiveness. Only 5 (1.52%) patients had poor effectiveness with the FF + OXY combination therapy.

3.2 Safety and Tolerability

The overall incidence of AEs reported during the study period was in 1.28% patients ($n = 5$; Table 2). No AEs required termination of the treatment. No serious adverse events were reported. The assessment of overall safety and tolerability in the study participants ($n = 315$) was reported by investigators as very good or good for 94% of patients ($n = 296$), and satisfactory or poor for around 6% of patients

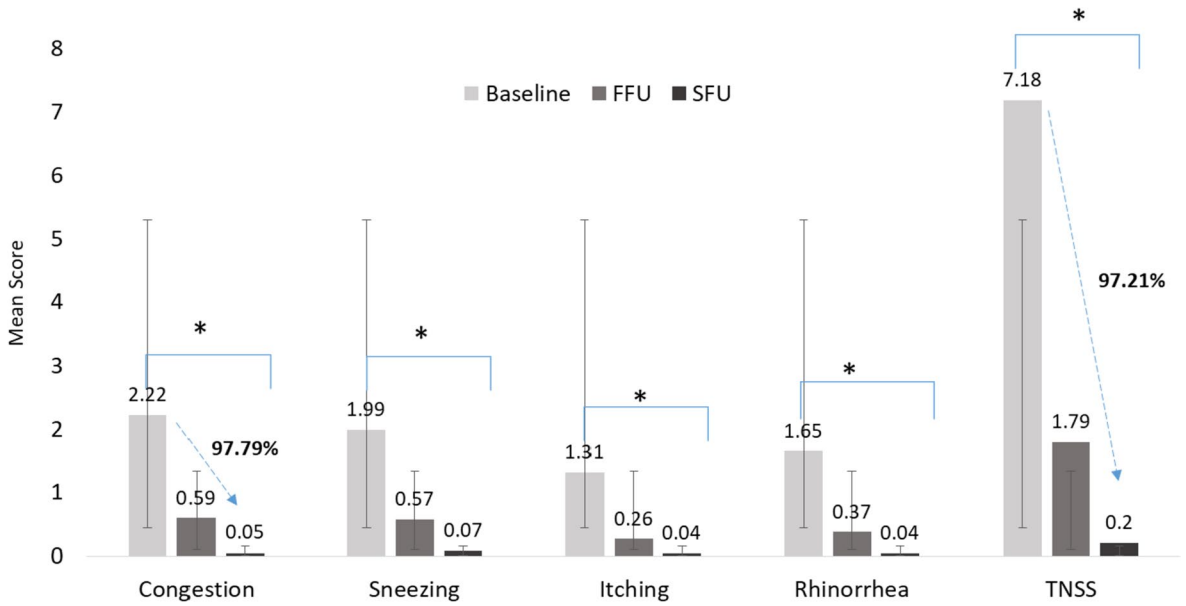

Fig. 2 Reduction in total nasal symptom score (TNSS). Values are mean (95% CI). *CI* confidence interval, *FFU* first follow-up, *SFU* second follow-up. *The declining trend from baseline to respective follow-up is statistically significant with $p < 0.001$

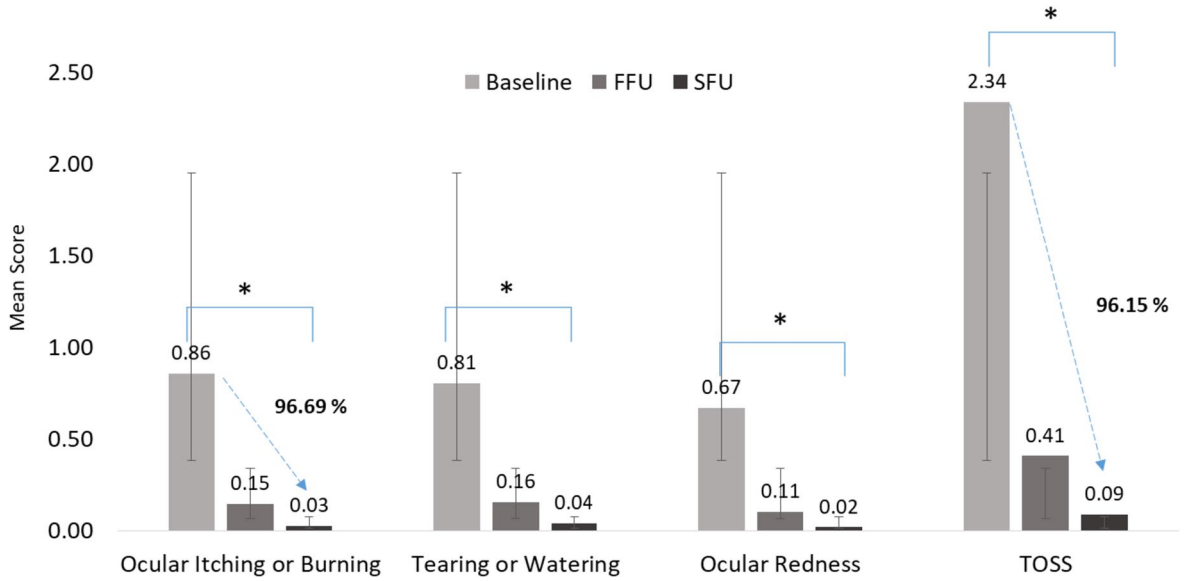

Fig. 3 Reduction in total ocular symptom score (TOSS). Values are mean (95% CI). *CI* confidence interval, *FFU* first follow-up, *SFU* second follow-up. *The declining trend from baseline to respective follow-up is statistically significant with $p < 0.001$

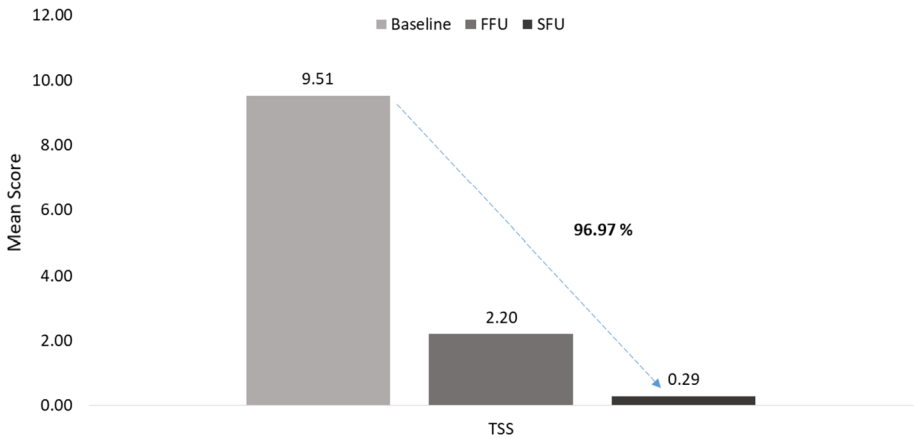

Fig. 4 Reduction in total symptom score (TSS). Values are mean (95% CI). *CI* confidence interval, *FFU* first follow-up, *SFU* second follow-up. The declining trend from baseline to respective follow-up is statistically significant with $p < 0.001$

Table 2 Safety assessment, $N = 388$

Variable	Value, *n* (%)
Rebound congestion after using FF + OXY	
No	379 (97.68)
Yes	9 (2.32)
Adverse events	
Bitter taste	2 (0.5)
Dry mouth	1 (0.2)
Dryness in nose	2 (0.5)

FF + OXY fluticasone furoate and oxymetazoline hydrochloride

($n = 19$). Rebound congestion was seen in only 2.32% of patients ($n = 9$). Further, it was seen that 94.85% ($n = 258$) patients showed good compliance at the first follow-up visit and 93.33% ($n = 140$) patients showed good compliance at the second follow-up visit.

4 Discussion

This real-world observational study demonstrated the effectiveness and safety of a novel fixed-dose combination of FF + OXY nasal spray 27.5/50 mcg in Indian patients with AR. The study demonstrated that FF + OXY nasal spray was effective in improving the TNSS, TOSS and TSS without causing significant AEs including rebound congestion or rhinitis medicamentosa. This metered-dose nasal spray is available for the management of AR in India and the

recommended regimen is two nasal sprays administered in each nostril once daily at night.

The results of the current study support the evidence from previous publications involving the evaluation of this combination as nasal spray. Kumar et al. assessed the efficacy of FF+OXY compared to fluticasone monotherapy in a double-blind randomized controlled trial in patients with allergic rhinitis with moderate-to-severe nasal congestion. It was shown that the combination resulted in a significant decrease in the TNSS scores as early as 3 days after treatment began and was maintained until the end of the 28-day treatment period without leading to development of rebound congestion or rhinitis medicamentosa after withdrawal of the treatment [10]. They also demonstrated significantly greater relief in nasal congestion throughout the day compared to monotherapy that sustained until the end of the treatment period with FF + OXY [10]. Additionally, the reduction in TOSS and TSS scores were significantly higher across all time points in the FF+OXY group versus FF only group [10].

Matreja et al. [11] demonstrated that the addition of OXY to FF adds to the efficacy in the treatment of AR. The combination was effective in improving the daytime nasal symptom score in patients with allergic rhinitis. The therapy of oxymetazoline with fluticasone furoate significantly improved these scores as compared to fluticasone furoate alone. A trial by Baroody et al. [9] proved a significant reduction in the TNSS and a faster onset of symptom relief. Therapy with FF-OXY for 4 weeks resulted in significant improvement in nasal congestion.

Both steroids and oxymetazoline assist each other; efficacy of steroids is enhanced by oxymetazoline while steroids enhance the long-term safety and tolerability of oxymetazoline [10]. There is a fear of developing rhinitis medicamentosa with oxymetazoline when used for more than 4–5 days [10]. Kumar et al. [10] demonstrated that using steroid along with oxymetazoline ameliorates the chances of developing rebound congestion and rhinitis medicamentosa even with long-term continuous use of the nasal decongestant.

A steroid added to oxymetazoline prevents rebound congestion and tachyphylaxis [12]. There are two postulated mechanisms for the prevention of rebound congestion: (i) acting directly through glucocorticoid response elements restores the G-protein–adrenoceptor coupling, increases the cell surface receptor numbers, and reverses the adrenoceptor down-regulation; and (ii) by indirectly increasing the duration of action of oxymetazoline, which requires once-daily dosing only [10]. When oxymetazoline is given with intranasal steroid, the duration of action of the former increases and shows good efficacy even in a once-daily dosing regimen; the effect remains throughout the day [10].

In this study, only five patients reported mild AEs such as dryness in the nose/mouth and bitter taste. No patients experienced watering of the eyes, sneezing, or a burning and stinging sensation, which had been reported in earlier studies [10, 11].

This study findings support the previous research findings indicating that in patients with AR, the combination of FF + OXY is safe and effective for the relief of symptoms of AR, thereby improving patients' overall QoL.

4.1 Strengths and Limitations of the Study

The strength of this study lies in a larger cohort size than previous studies in real-world settings. Since this is a real-world observational study, the patient population is representative of those encountered in actual clinical practice as opposed to the strictly selected population in randomized controlled trials. As a result, the findings of this study have wider generalizability and clinical implications for practicing physicians. The study also has certain limitations—it was a single-arm study and the duration of the study was small. A longer trial duration of the combination will be helpful in further evaluating the long-term safety and effectiveness.

5 Conclusion

This prospective, open-label, single-arm, multicenter, real-world observational study showed that the fixed-dose combination of once-daily fluticasone furoate and oxymetazoline hydrochloride nasal spray 27.5/50 mcg was effective in relieving the nasal congestion and reduction of TNSS, TOSS and TSS in patients suffering from AR. The beneficial effects of FF + OXY were seen before 28 days and continued until the end of the treatment period (28 days). The combination was safe and well-tolerated with no rebound congestion throughout the treatment period.

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Author Contributions All authors have contributed equally to this work. All authors have reviewed and approved the final manuscript.

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Data Availability Statement The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Insignia Communications Pvt. Ltd., India.

Code Availability Not applicable.

Declarations

Conflict of Interest Dr. Ravi Tejraj Mehta and Dr. Ashok Jaiswal are employees of Zydus Healthcare Limited, India. Other authors report no conflicts of interest with regard to this study.

Ethics Approval This study was approved by the Ethics Committee, dated: 01/03/2022. The study was registered on Clinical Trials Registry-India, Registration No: CTRI/2022/05/042785 [Registered on: 24/05/2022].

Consent to Participate Patients provided written informed consent to participate in the study.

Consent to Publish Not applicable.

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