Triamcinolone Acetonide versus Fluticasone Propionate in the Treatment of Perennial Allergic Rhinitis: A Randomized, Parallel-Group Trial

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Keywords

Fluticasone propionate · Nasal corticosteroid · Perennial allergic rhinitis · Reflective total nasal symptom score · Triamcinolone acetonide

Abstract

Background: Intranasal sprays are recommended as targeted therapy for allergic rhinitis (AR). Triamcinolone acetonide is a nasal corticosteroid preparation indicated for the treatment of seasonal and perennial AR (PAR) in different countries worldwide. **Objectives:** In order to determine the efficacy of triamcinolone acetonide in the treatment of PAR, the non-inferiority of triamcinolone acetonide to fluticasone propionate was assessed in Russian adults. **Methods:** In this randomized, double-blind, parallel-group, multicenter, prospective, non-inferiority, phase III clinical trial, a total of 260 patients with persistent PAR were randomized to receive either triamcinolone acetonide or fluticasone propionate nasal sprays for 4 weeks. The efficacy in symptom control was evaluated using the reflective total nasal symptom score

(rTNSS) from baseline (day 0) to day 28. Safety was assessed through the reporting of adverse events. **Results:** The rTNSS mean values decreased from baseline to the end of study treatment (day 28) in both groups: -8.2 ± 3.0 in the triamcinolone acetonide arm versus -8.0 ± 2.8 in the fluticasone propionate arm. The mean difference between the groups (triamcinolone acetonide – fluticasone propionate) for rTNSS change from baseline was -0.2 (95% confidence interval -0.89 to 0.54), with an upper confidence limit of 0.54 , which is lower than the non-inferiority margin of 0.8 . Triamcinolone acetonide was well tolerated, with no difference in adverse event occurrence compared with fluticasone propionate. **Conclusions:** Triamcinolone acetonide proved to be non-inferior to fluticasone propionate in adult patients with PAR; both treatments decreased rTNSS values and showed a good safety profile.

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Introduction

Allergic rhinitis (AR), the most common form of rhinitis, is a global health problem that affects 10–30% of the population worldwide [1]. In the last decades, the burden of AR has witnessed a steep increase alongside industrialization, climate change, and air pollution. The increased prevalence is largely attributed to both early and increased exposure to allergens, irritants, and pollutants, as well as changes in lifestyle [2, 3].

AR is a multifactorial disease, including genetic predisposition, immunological response, and environmental pollutants as causal factors [4]. The former classification of AR comprised seasonal AR (SAR), which was mainly linked to pollen allergy, and perennial AR (PAR), which was mainly linked to house dust mites. However, many shortcomings of this classification have become apparent over the years. For example, the SAR/PAR classification does not cover the severity or duration of the disease, which makes it difficult to decide upon the best treatment option [5]. Thus, currently, AR is classified according to the duration (intermittent or persistent) and severity (mild or moderate-to-severe) of symptoms [5]. However, the previous classification of AR as PAR and SAR is still widely used.

The hallmark of AR is an immunoglobulin E-mediated type 1 hypersensitivity reaction to an inciting inhaled seasonal or perennial allergen, triggering a cascade of immunological and biochemical events leading to clinical expression of the disease [6]. Thus, patients with AR exhibit signs of rhinorrhea, congestion, nasal itching, and obstruction. Consequently, affected subjects present systemic effects such as fatigue, sleepiness, and malaise, all contributing to an impaired quality of life (QoL) [7].

Nasal congestion is the most prominent symptom of AR (manifesting as nasal blockage [94.23%], followed by rhinorrhea [90.38%]) [3, 8]. Since these symptoms interfere with a patient's ability to eat, sleep, and function, and significantly impact QoL, especially in patients with persistent AR, it is important to treat nasal inflammation and restore normal breathing.

AR therapy is primarily based on allergen avoidance, symptomatic pharmacotherapy, and immunotherapy [3]. Based on the pathophysiology of the disease, corticosteroids are one of the main treatment options that prevent or suppress inflammation and immune responses to the inciting specific allergen in patients with PAR. The updated Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines (2016) recommend the use of intranasal corticosteroids alone over the combination with oral

H₁ antihistamines in PAR treatment [9]. In an international cross-sectional survey study conducted among otolaryngologists from Asia, Africa, Europe, and the Americas, 52 responses were obtained for the question “Which types of symptomatic drugs do you prescribe in allergic patients?” to which multiple answers were possible. Overall, 45/52 (86.54%) rhinology experts prescribed intranasal corticosteroids and 43/52 (82.69%) prescribed oral H₁ antihistamines to patients with AR. Moreover, it was reported that the combination of intranasal antihistamines and intranasal corticosteroids was prescribed by 18/52 (34.62%) rhinology experts [3]. Intranasal sprays are recommended as targeted therapy for AR by providing direct delivery of the medication to the nasal mucosa, reducing the potential for systemic adverse effects, decreasing the burden of disease, and improving QoL [10]. Triamcinolone acetonide, a synthetic fluorinated corticosteroid, is indicated for treatment of SAR and PAR symptoms in adults and pediatric patients (children 2 years of age and older) [11]. Currently, there are nine different Food and Drug Administration-approved nasal corticosteroid preparations indicated for SAR and PAR [12], while in Russia fluticasone propionate is the only intranasal corticosteroid available over the counter. However, when comparing the available intranasal corticosteroids, the overall clinical response does not appear to vary significantly between products, irrespective of the differences in topical potency, lipid solubility, and binding affinity [13]. In this regard, we have conducted the first trial in Russia (NASANIF) to demonstrate the non-inferiority of triamcinolone acetonide to fluticasone propionate in adults suffering from persistent PAR with respect to both efficacy and safety.

Materials and Methods

Study Design

The NASANIF study was a randomized (1:1), double-blind, parallel-group, multicenter, prospective, non-inferiority, phase III clinical trial (NCT03317015) conducted between November 30, 2016 and July 10, 2017 in 12 study centers located in Russia. This study was performed in compliance with good clinical practices and Russian regulations. Informed consent was obtained from all participants prior to their enrollment.

Patient Population

Patients aged between 18 and 50 years with previously diagnosed persistent PAR were included. Eligible patients had to have a positive skin prick test response to an appropriate allergen (house dust mites, molds, etc.), defined as a wheal of ≥ 3 mm in diameter, compared with a diluent control, with the test performed not more than 12 months prior to the screening visit. Moreover, eligible patients pre-

Fig. 1. NASANIF study CONSORT diagram [17]. In the triamcinolone group, 1 patient was excluded due to the “investigator’s or patient’s decision not to re-expose the patient to the investigational medicinal product at any time.” After the occurrence of an adverse reaction, the patient did not adhere to the visit schedule; for this reason, the investigator made a decision to exclude this patient. In the

fluticasone group, 2 patients discontinued the intervention, 1 of them due to the “patient’s decision to withdraw from the study.” After the occurrence of an adverse reaction, the patient made a decision to interrupt participation in the study. Another patient was excluded due to an SAE. Another patient was excluded from the analysis due to usage of a medicine prohibited for the period of study.

sented symptoms that lasted for more than 4 days a week and for more than 4 consecutive weeks. In addition, patients were considered eligible if they had a reflective total nasal symptom score (rTNSS) ≥ 8 within the past 24 h before the screening visit, with two or more symptoms rated as moderate or severe. Patients were excluded if they had SAR, intermittent AR, non-AR caused by viral or bacterial infection, rhinitis medicamentosa, bronchial asthma, or chronic sinusitis. Patients presenting with upper respiratory tract or sinus infections that required antibiotic therapy without at least a 14-day washout prior to the screening visit, or presenting with viral upper respiratory infections within 2 weeks prior to the screening visit, as well as patients who received specific immunotherapy that ended within the 6 months prior to the screening visit were also excluded. In addition, patients who had taken the following drugs, within a specific period (relative to each drug’s washout period) prior to screening were excluded, namely: corticosteroids, cromones, short-acting and long-acting antihistamines, as well as intranasal antihistamines, anticholinergics (intranasal, oral, or inhaled), oral antileukotrienes, and immunosuppressive medications.

Study Treatments

Eligible patients were randomized to receive for 4 weeks either intranasal triamcinolone acetonide (Nasacort®, Sanofi-Aventis), 55 μg per dose, 2 sprays in each nostril (220 μg in total), once daily (OD) in the morning, or intranasal fluticasone propionate (Flixonase®, GlaxoSmithKline), 50 μg per dose, 2 sprays in each nostril (200 μg in total), OD in the morning. Adhering to the double-blind, double dummy design of the study, both medicinal products were masked by placing them in pre-prepared bottles of the same shape and size with a similar movable upper part.

Study Endpoints

The primary efficacy variable was the change in the 24-h rTNSS from baseline (day 0 of treatment) to the end of treatment (day 28). The rTNSS is a validated symptom scoring system that consists of the sum of four individual participant-assessed symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing. Each symptom was evaluated over the preceding 24 h, according to the 5-point scale: 0 = none (no sign/symptom pres-

Table 1. Demographics and baseline characteristics of the ITT population ($n = 260$)

	Triamcinolone ($n = 129$)	Fluticasone ($n = 131$)
Male/female	46/83	54/77
Age, years	33.3±8.5	31.8±8.47
PAR duration, months	52.0±68.9	47.2±66.0
Prick test response		
House dust mites	116 (89.92)	118 (90.08)
<i>D. pteronyssinus</i>	90 (69.77)	96 (73.28)
Currently active concurrent disease	26 (20.16)	25 (19.08)
Concomitant medications	16 (12.40)	14 (10.69)

Data are presented as the mean ± SD or n (%), with % calculated as n/N . PAR, perennial allergic rhinitis.

Table 2. Change in the rTNSS from baseline in the per-protocol population ($n = 256$)

rTNSS	Triamcinolone ($n = 128$)	Fluticasone ($n = 128$)
Baseline	10.3±2.08	10.1±1.87
Day 28	2.1±2.13	2.1±2.09
Change from baseline (95% CI)	-8.2±3.00 (-8.72 to -7.67)	-8.0±2.80 (-8.51 to -7.53)
Difference in rTNSS change between groups (95% CI)	-0.17 (-0.89 to 0.54)	

Values are the mean ± SD, unless otherwise indicated. rTNSS, reflective total nasal symptom score.

ent), 1 = mild (symptom present but not annoying or troublesome; easily tolerated), 2 = moderate (symptom frequently troublesome but not interfering with normal daily activities or sleep; tolerable), 3 = severe (symptom sufficiently troublesome to interfere with normal daily activities or sleep; hard to tolerate), or 4 = very severe (symptom severe enough to warrant an immediate visit to the physician) [14].

Secondary efficacy variables were QoL measured by the mini Rhinoconjunctivitis Quality of Life Questionnaire (miniRQLQ) [15] from baseline to the last day of treatment, and patient and physician satisfaction with therapy (measured by a 5-point scale questionnaire) after 28 days of treatment. Safety variables included the incidence of adverse events (AEs) and rate of premature withdrawals.

Statistical Considerations

Data were appropriately summarized and analyzed per treatment group by descriptive statistics using tabulation and graphs regarding demographics and baseline characteristics, efficacy, and safety observations and measurements. Standard descriptive summary statistics were performed for continuous variables (i.e., arithmetic mean, standard deviation [SD], minimum/maximum value, lower/median/upper quartile, and number of non-missing values). Categorical data are displayed in frequency tables using counts and percentages.

The safety analyses were run on the safety population which included all randomized patients treated with at least one dose of the investigational treatments. Efficacy analyses were conducted on the intention-to-treat (ITT) population, which encompassed all patients randomized and treated and the per-protocol (PP) population (primary analysis set), which included patients from the ITT population who completed the study with no significant deviations from the protocol.

Considering an attrition rate of 5.5% for the sample size calculation of this non-inferiority trial, a total sample size of 260 patients (130 in each group) was appropriate to describe the above statistical criteria. Two-sided 95% confidence intervals (CIs) were calculated for the primary efficacy endpoint (change in rTNSS from baseline to study end) and for other comparisons as well. For confirmation of non-inferiority, the upper limit of one-sided 97.5% CI for the difference in rTNSS change from baseline between the two treatment groups (triamcinolone acetonide – fluticasone propionate) had to be less than +0.8 (+10%), which is equal to the upper limit of two-sided 95% CI [16]. Secondary efficacy variables were evaluated using descriptive statistics primarily and the Wilcoxon two-sample test. Individual nasal symptom scores (sneezing, nasal itching, rhinorrhea, nasal obstruction) were summarized using descriptive statistics and one-sided 97.5% CIs for the difference in treatment arm means.

Fig. 2. Individual nasal symptom scores after 28 days of treatment in the PP population ($n = 256$). Descriptive statistics and one-sided 97.5% CIs were used for the difference in treatment arm mean values.

Statistical testing was done using a two-sided 5% alpha level. The randomization plan was generated with the PLAN software procedure of SAS[®] 9.3, and the statistical analyses were performed using the statistical software SAS[®] version 9.3.

Results

Participant Characteristics

Overall, 260 patients with a diagnosis of persistent PAR were randomized and treated with the study drugs (129 patients in the triamcinolone acetone group and 131 patients in the fluticasone propionate group) constituting the ITT population and safety population. While 3 patients discontinued the study prematurely (1 in the triamcinolone acetone group and 2 in the fluticasone propionate group) and 1 patient was excluded by deviation, a total of 256 patients completed the study (128 in each treatment group), constituting the PP population (Fig. 1).

Demographics and baseline characteristics in the ITT population were balanced between the two treatment groups (Table 1). The overall (mean $\pm$ SD) age was 32.5 ± 8.47 years, and 160 patients (61.5%) were women. The mean $\pm$ SD PAR duration was 49.5 ± 67.4 months. A total of 244 patients had received previous treatments at least once prior to study entry, with decongestants and other nasal preparations for topical use (mainly corticosteroids) being the most frequently used prior medications in 78.29% of patients in the triamcinolone acetone group versus 81.68% in the fluticasone propionate group. The prick test was positive in all patients; house dust mite allergens were the most common allergic responses, affecting 90% of the ITT population, and *Dermatophagoides pteronyssinus* was the most frequently detected house dust mite allergen (71.5%). At baseline, the recorded primary comorbidities included allergic conjunctivitis and allergic dermatitis (in 28.7% of patients in the triamcinolone acetone group vs. 34.4% in the fluticasone propionate group).

nate group, $p = 0.352$, and in 8.5 vs. 9.2%, $p > 0.999$, respectively).

Efficacy

In the PP population ($n = 256$), the rTNSS (mean $\pm$ SD) values decreased from baseline to the end of study treatment (day 28) in both groups; the associated change from baseline (mean $\pm$ SD) was -8.2 ± 3.00 in the triamcinolone acetate group versus -8.0 ± 2.80 in the fluticasone propionate group (Table 2). The mean difference between the treatment groups (triamcinolone acetate – fluticasone propionate) for rTNSS changes from baseline to day 28 was -0.17 (95% CI -0.89 to 0.54). The upper confidence limit of the two-sided 95% CI at 0.54 lies below the non-inferiority margin of 0.8, indicating non-inferiority between the two treatments with respect to rTNSS change.

Overall, a considerable improvement in the individual nasal symptom score was observed in both groups, with the majority of patients having no nasal symptoms after treatment (over 64% for sneezing and itchy nose, over 52% for rhinorrhea, and over 41% for nasal congestion; Fig. 2). Similar results were obtained in the ITT population set analysis.

Substantial improvement of QoL was observed in both treatment groups. Change of the total score of miniRQLQ (over 24 h) from baseline to the last day of treatment was -2.2 ± 1.04 (range -5.2 to 0.1) for the triamcinolone acetate group, and -2.2 ± 1.08 (range -5.9 to -0.1) for the fluticasone propionate group, with no significant difference between study groups ($p = 0.909$).

With regard to patient satisfaction, a substantial improvement was marked by 85.5% of patients (83.6 vs. 87.5%), little improvement by 13.7% (14.8 vs. 12.5%), and no change by 0.8% (1.6 vs. 0.0%) in the triamcinolone acetate and fluticasone propionate groups, respectively. There was no significant difference in patient satisfaction by study group ($p = 0.352$). Similarly, substantial improvement was marked by 87.9% of physicians (84.4 vs. 91.4%), little improvement by 11.7% (14.8 vs. 8.6%), and no change by 0.4% (0.8 vs. 0.0%) in the triamcinolone acetate and fluticasone propionate groups, respectively. There was no significant difference in physician satisfaction by study group ($p = 0.082$).

Safety

Nearly all treated patients received the study medications according to the study design for at least 28 days, yielding good compliance to the planned treatment regimen. A total of 65 individual AEs were documented in 47 of the 260 treated patients (18.1%), with no difference in AE occurrence between the groups (31 in the triamcino-

Table 3. Most common TEAEs (>2%) by preferred term in the safety population ($n = 260$)

	Triamcinolone ($n = 129$)		Fluticasone ($n = 131$)	
	n (%)	AEs, n	n (%)	AEs, n
Patients with any TEAE	25 (19.38)	31	22 (16.79)	34
Headache	12 (9.30)	13	6 (4.58)	8
Nasal dryness	3 (2.33)	3	4 (3.05)	4
Nasal discomfort	1 (0.78)	1	3 (2.29)	3
Application site pain	3 (2.33)	3	0 (0.00)	0
Abdominal pain upper	0 (0.00)	0	3 (2.29)	3

% is calculated as n/N . AEs, adverse events; TEAE, treatment-emergent adverse event.

lone acetate group vs. 34 in the fluticasone propionate group). In terms of severity, the AEs were rated as mild for 21/129 patients (16.3%) in the triamcinolone acetate group versus 20/131 (15.3%) in the fluticasone propionate group, and moderate for 3 patients (2.3%) in each treatment group. Only 1 patient in the fluticasone propionate group exhibited a severe AE; it was a case of acute tracheobronchitis in a 33-year-old woman, who required hospitalization. This severe AE was considered unrelated to the treatment. All AEs were resolved at study end, and no deaths occurred during the study.

Treatment-emergent AEs (TEAEs) were recorded in 25/129 patients (19.4%) in the triamcinolone acetate group compared to 22/131 patients (16.8%) in the fluticasone propionate group. Of these, 13/129 patients (10.1%) in the triamcinolone acetate group and 12/131 (9.2%) in the fluticasone propionate group experienced AEs that were related to treatment. The most frequently reported TEAE (>2%) was headache in 9.3% of patients in the triamcinolone acetate group versus 4.6% in the fluticasone propionate group (Table 3). None of the TEAEs required a dose change, while premature discontinuation of the study due to a TEAE occurred with 3/260 patients (1.2%).

Discussion

To the best of our knowledge, the number of trials evaluating the direct comparative efficacy of triamcinolone acetate relative to other nasal corticosteroids in the PAR indication are limited [18], highlighting the importance and added value our trial has provided. This

study is the first head-to-head comparison of triamcinolone acetonide and fluticasone propionate in PAR management. Efficacy results revealed that treatment with intranasal spray triamcinolone acetonide is non-inferior to fluticasone propionate in terms of PAR symptom control. In addition, no difference was observed between the two drugs regarding safety and tolerability. Considering that the most common complaint of patients with AR is nasal congestion, rated as “extremely bothersome” [8, 19], a validated efficacy assessment for such drugs is the rTNSS outcome as evaluated in this trial [6]. Both sprays decreased rTNSS values from baseline to the end of study treatment with a mean difference of 0.2 (95% CI –0.89 to 0.54) between the two treatment groups, with the upper CI limit being less than the stated non-inferiority margin of 0.8, confirming that triamcinolone acetonide is non-inferior to fluticasone propionate with respect to symptom control. Additionally, these PP findings were confirmed by the supportive analysis of the ITT population.

The findings of this non-inferiority trial support the results of previous randomized, parallel-group studies, indicating that triamcinolone acetonide and fluticasone propionate are equally effective for the relief of nasal symptoms in patients with AR [20–23]. In a study by Berger et al. [22] in 295 patients with symptomatic SAR, the mean $\pm$ SD change in the total nasal symptom score was equivalent between the study medications: -3.15 ± 0.19 with triamcinolone acetonide and -3.17 ± 0.18 with fluticasone propionate after 21 days of treatment. Similarly, Kaiser et al. [21] found a mean change in the total symptom score of -4.84 with triamcinolone acetonide and -4.81 with fluticasone propionate in 150 patients with severe SAR who were treated for 3 weeks. Each of these prior studies administered intranasal triamcinolone acetonide at a daily dose of 220 μ g and intranasal fluticasone propionate at a daily dose of 200 μ g, which is in accordance with the dosages given in our study [20–23].

The clinical equivalence of single daily doses of 220 μ g of triamcinolone acetonide and 200 μ g of fluticasone propionate that was documented in this study and in prior studies shows that the higher molecular potency of fluticasone propionate compared to triamcinolone acetonide does not translate into superior clinical efficacy [24, 25]. This lack of clinical differentiation may be explained by the inhibition of the inflammatory processes in AR by recommended doses of glucocorticoids of various potencies that may far exceed the minimally effective doses [24]. Hence, it is important to extrapolate with caution any molecular potency claims into clinical efficacy [22].

Although AR is traditionally subdivided into SAR and PAR, the ARIA classification system, in which the duration of AR is split into intermittent and persistent patterns, was introduced in 2001 [26]. The relevance of the traditional classification of AR has been revised to adjust to SAR and PAR definitions in real life, as 80% of AR cases were reported to have a mixed form [27]. A British, multicenter, non-interventional study by Scadding et al. [28] conducted in 192 patients revealed that the majority of patients had AR of mixed form (SAR in combination with PAR) or of unknown cause, and only 10.4% had SAR alone. Therefore, AR is now classified according to symptom duration (intermittent or persistent) and severity [26]. Since a 2003 French, cross-sectional study found that nearly half of so-called SAR patients had persistent AR, and nearly half of PAR patients had intermittent AR [29], we only included patients with persistent PAR in our study to avoid potential therapeutic effects due to patient selection. Thus, in our study, the enrolled patients can be considered as homogenous, taking into account the strict non-inclusion criteria, ruling out any association of PAR with SAR or non-AR. Moreover, the diagnostic tools (allergen sensitization [skin prick test]) and medical history assessment (comorbidities and allergy duration) are considered valid examinations to identify and enroll patients with persistent PAR alone [30, 31].

Allergens derived from house dust mites have been recognized as an important cause of immunoglobulin E antibody responses for more than 30 years [32]. It has been estimated that house dust mites are responsible for the sensitization of more than 50% of allergic patients, and most house dust mite allergies are caused by sensitization to the pyroglyphid mite species *D. pteronyssinus* [33]. This is consistent with the findings of our study, in which house dust mite allergens were the most common allergic responses and *D. pteronyssinus* was responsible for the sensitization of more than 70% of patients. During allergen sensitization and provocation in allergen-induced inflammation, mite allergens break the anatomical barrier of the mucosal membrane and are processed by professional antigen-presenting cells, such as dendritic cells or macrophages. These cells mature and present processed allergen peptides to resting naïve T cells in the draining lymph nodes, which result in the production of cytokines such as interleukins-3, 4, 5, and 13, which recruit, mature, and activate eosinophils [32].

Conclusively, the design and methods adopted in this study guaranteed a reliable investigation of non-inferior effects of triamcinolone acetonide compared to fluticasone propionate. Indeed, selecting parallel groups of

medications combined with a randomization plan performed by an independent third party provided reliable evaluation. The conservative choice of defining a 10% non-inferiority margin is more than two times greater than the benefit of topical corticosteroids demonstrated in placebo-controlled studies [16, 34], and the pre-set treatment duration of 4 weeks is adequate for treatment comparison in the PAR setting, as longer study periods do not seem to add to the assessment of drug efficacy [35].

No placebo arm was used in this trial because triamcinolone acetonide and fluticasone propionate are already well-established treatments of PAR. In 1995, in a randomized, double-blind, placebo-controlled study of 178 patients with symptomatic PAR, triamcinolone acetonide aqueous nasal spray given at a daily dose of 220 µg provided clinically and statistically ($p \leq 0.05$) greater improvements in nasal stuffiness, sneezing, nasal index, and nasal itching over a 4-week treatment period compared to placebo [36]. Similarly, nasal stuffiness, nasal discharge, sneezing, nasal itching, and the nasal index were all significantly reduced in patients who received triamcinolone acetonide nasal spray at daily doses of 220 and 440 µg ($p < 0.05$) compared to placebo in a 12-week, randomized, double-blind, placebo-controlled study conducted in 305 adult and older pediatric patients with PAR [37].

Both triamcinolone acetonide and fluticasone propionate were safe and well-tolerated in the present clinical trial. Indeed, this study did not reveal any potentially new or unexpected AEs allocated to the study drugs. Observations like headache and nasal symptoms, such as nasal dryness and discomfort, are typical AEs for this therapeutic class. Moreover, headache, which was the most frequently reported AE in this trial (9.3% in the triamcinolone acetonide group vs. 4.6% in the fluticasone propionate arm), has been listed as a common AE (>1% incidence) of triamcinolone acetonide [11]. This finding is in line with a previous placebo-controlled, parallel-group study including 28 patients with pediatric AR who received OD triamcinolone acetonide aqueous nasal spray (220 µg), in which headache was the most frequently reported AE, occurring in 18% of patients [38]. Similarly, headache was also the most frequently reported AE in the Berger et al. [22] study, which compared the safety and efficacy of triamcinolone acetonide and fluticasone propionate in 295 patients with spring SAR (6.8 and 4.1% in the triamcinolone acetonide and fluticasone propionate treatment groups, respectively). Even though headache was considered as a TEAE in this study, a strong connection between AR and the occurrence of migraine

appears to exist. According to Ku et al. [39], more than 34% of patients with AR experience migraine headaches, compared with only 4% of people without AR. Among mechanisms involved in the development of headaches in patients with AR is implication of the immune system with histamine release [40]. The favorable safety profile of intranasal triamcinolone acetonide can be explained by its little or no systemic accumulation, as was shown by Nayak et al. [38], who found a rapid decline of triamcinolone acetonide from plasma, with little to no accumulation of the drug administered at the highest dose level of 440 µg/day over a 6-week period.

The present study had some limitations inherent to its design. For instance, a cross-over design could have been more informative, whereby patients could serve as their own control. In addition, the study did not compare the efficacy of triamcinolone acetonide versus fluticasone propionate in subgroups of interest defined by age, gender, ethnicity, or concomitant diseases. Nevertheless, these limitations were balanced by a number of strengths. Firstly, potential bias has been ruled out by masking the study treatments which differ in volume and shape, in addition to the multicenter recruitment approach which eliminated potential investigator bias. Secondly, the set of study participants treated with the study medications was shown to be homogenous, and therefore as suitable for the specific investigations planned for this study. Moreover, the strict non-inclusion criteria of concomitant or previous study medications precludes any concomitant or carry-over effect on the study results. Finally, the selection of patients for this type of non-inferiority trial adds to the authenticity of its results; patients with a relatively long duration of PAR (median 24.5 months) and moderate to severe symptoms could not have remained in this 28-day study without the intervention of the investigated treatment, demonstrating its efficacy in symptoms control.

In conclusion, the NASANIF study demonstrated non-inferior efficacy, estimated by rTNSS changes, of triamcinolone acetonide compared to fluticasone propionate after 28 days of treatment in Russian adult patients suffering from persistent PAR. Triamcinolone acetonide was well tolerated with a good safety profile in patients with PAR, with no difference in AE occurrence compared with fluticasone propionate. Thus, the results of the NASANIF trial support the known efficacy and safety of triamcinolone acetonide and its role in the treatment of adult patients with PAR.

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Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and Russian regulations. Informed consent was obtained from all participants prior to their enrollment. The study protocol was approved by the research ethics committees at each study site.

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Disclosure Statement

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A.V.K., T.V., A.O., and N.N. supervised the design of the study and acted as clinical trial investigators in the study. All authors contributed to the preparation and review of the report. All authors read and approved the final version of the report.

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