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Original Research Article

# Efficacy and safety of the topical use of intranasal cinnamon bark extract in seasonal allergic rhinitis patients: A double-blind placebo-controlled pilot study

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ABSTRACT

The present study was aimed at the evaluation of the efficacy and safety of an intranasal spray of a type-A proanthocynidine polyphenol based standardized hydroalcoholic extract of *Cinnamonum zylanicum* bark (TAPP-CZ) in seasonal allergic rhinitis (AR) patients using a double-blind placebo-controlled parallel design. TAPP-CZ (nasal spray, 100 μg/100 μL in each nostril, twice a day) with matching placebo were administered for 4-weeks to 40 randomized patients (20 each in TAPP-CZ and placebo groups) who suffered from severe AR. The efficacy outcome measure scores were obtained from Juniper rhinoconjunctivitis quality of life questionnaire (RQLQ) instrument, nasal symptom scores (NSS), total NSS (TNSS), Work Productivity and Activities Impairment–Allergy Specific (WPAI–AS) instrument at baseline, end of 4-week treatment, and after 4-weeks of follow-up period. The safety outcome measures included pulmonary function tests (spirometry), vital signs, hematology, biochemistry, urinalysis parameters and adverse event (AE) monitoring at baseline and end of 4-week treatment. At the end of 4-week treatment of TAPP-CZ nasal spray showed statistically and clinically significant improvement for overall RQLQ and four of its individual domain scores (namely activities, emotional, nasal symptoms, and eye symptoms), TNSS and NSS. Work productivity was significantly improved on 4-weeks of treatment by TAPP-CZ nasal spray as compared with placebo. TAPP-CZ was found to have excellent safety and tolerability profile with no serious AEs. In conclusion, TAPP-CZ nasal spray was found to be a useful treatment in management of acute seasonal AR patients.



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## 1. Introduction

Allergic rhinitis (AR) is a common IgE-mediated inflammatory immune disease of the nasal mucosal membrane, affecting 500 million individuals worldwide. Allergic rhinitis (AR) is a highly prevalent allergic disease and also counts among the 10 most frequent reasons for a medical consultation (de la Hoz Caballer et al., 2012; Meltzer, 2007). AR is an inflammation of the nasal passages, usually with three cardinal symptoms namely, sneezing, nasal obstruction and mucous discharge with nasal itching. AR is hypersensitivity of nasal mucosa after allergen exposure due to an IgE-mediated inflammation of the membranes lining the nose (Lee et al., 2007). The prevalence of allergic rhinitis may vary in different countries due to the presence of different allergens; however, it has increased in the last two decades. AR can be classified as seasonal (intermittent) or persistent (perennial) based on frequency of attacks. AR is also classified as moderate or severe based on symptoms and quality of life (Bousquet et al., 2008). Allergic rhinitis has a significant negative impact on quality of life, mood, work performance and exacerbation of other medical conditions such as asthma and sinusitis (Gaga et al., 2000; Nathan, 2007).

Pharmacotherapy of AR is multifactorial as many interactive pathways are involved in its pathophysiology. Therefore, multi-directional treatment regimens such as allergen avoidance, symptomatic treatment and allergen immunotherapy have been used to control allergic responses (Nasser et al., 2008; Nouri-Aria, 2008). To target different symptoms, the class of drugs such as antihistamines, corticosteroids, mast cell stabilizers, decongestants, anti-leukotrienes and anticholinergics have been used (Al Suleimani and Walker, 2007; Leung and Hon, 2008). Although combination formulas containing antihistamines, decongestants and/or analgesics are sold over-the-counter (OTC) in large quantities for the common cold, the evidence of effectiveness is limited. Moreover, they are associated with adverse effects which limit their use. Therefore a search for novel agents in the treatment of AR is always ongoing. Medicinal plants and their bioactive compounds may provide a possible breakthrough in the treatment of AR.

Dietary polyphenols are reported to offer benefits in the management of many allergic disorders (Akazome, 2004; Bravo, 1998; Enomoto et al., 2006; Kojima et al., 2000). Cinnamon (*Cinnamomum zeylanicum* Syn *C. verum*, family: Lauraceae) bark polyphenol extract (CPE) has shown potential in the management of immune inflammation such as AR. Cinnamon bark widely used as a spice and flavorings agent, is native to Sri Lanka, Mayanmar (Burma) and the southern coastal strip of India. Being readily available as a food constituent, it also has a long history of traditional medicinal use in India, Sri Lanka, China, Egypt and European countries for many conditions including autoimmune (Kirtikar et al., 1975; Warrier et al., 1993) and inflammatory disorders (Khory and Katrak, 1903; Kirtikar et al., 1975; Warrier et al., 1993). Moreover, cinnamon bark is a certified GRAS (generally recognized as safe) ingredient in the USA.

Type-A proanthocynidins (TAPP) from cinnamon bark have been well-characterized components of CPE and thought to be responsible for many biological activities (Anderson et al., 2004). Proanthocyanidins are a combination of biologically active polyphenolic flavonoids including oligomeric proanthocyanidins that consist of a series of trimers and tetramer of flavan-3-ols, each with an A-type linkage (Anderson et al., 2004). Previous reports of immunomodulatory (Ravindran et al., 2004), anti-inflammatory (Cao et al., 2008; Cao and Anderson, 2011; Warrier et al., 1993), anti-arthritic (Joshi et al., 2001) and anti-viral (Shan et al., 2007) activities of TAPP from cinnamon bark further supports medicinal potential of TAPP in the management of immune inflammatory disorders such as AR.

Clinical, epidemiological and pathophysiological studies suggest a strong functional and immunological relationship between asthma and AR (Cruz et al., 2007; Feng et al., 2012; Palma-Carlos et al., 2001; Pawankar et al., 2012). Both AR and asthma have similar cellular responses, the inflammatory cascade and eosinophil infiltration of the nasal and bronchial epithelium exhibit different symptoms based on the differences in the physical structures involved (Kim et al., 2008). Furthermore, AR is implicated as one of the multiple risk factors for asthma development (Cruz et al., 2007). Recently, we have demonstrated ameliorative effects of TAPP based standardized extract of cinnamon bark (TAPP-CZ) in well-validated animal models of AR (Kandhare et al., 2013a) and asthma (Kandhare et al., 2013b). The present study was undertaken with the object of evaluating the efficacy and safety of TAPP-CZ in patients with seasonal allergic rhinitis.

Both topical (e.g. nasal) and systemic (e.g. oral) agents are found to be equally efficacious formulations against AR. However, topical formulations are preferred over systemic administration. Nasal formulations have been found to be better in terms of efficacy, tolerability, and patient preference and adherence and so considered for first-line treatment for AR. For example, nasal spray formulation of corticosteroids is more strongly recommended than systemic formulation due to lesser side effects (Karaki et al., 2012). Therefore, the present study was designed to evaluate efficacy and safety of TAPP-CZ nasal spray in patients with seasonal AR.

Although not a life threatening disease, AR is known to deleteriously affect quality of life by causing fatigue, headache, cognitive impairment and other associated symptoms (Wallace et al., 2008). The Juniper rhinitis quality of life questionnaire (RQLQ) is a validated tool for assessing quality of life in allergic rhinitis (Juniper and Guyatt, 1991; Juniper, 1997). In previous studies this outcome has shown strong evidence for reproducible therapeutic effects and there are established data on which to base power calculations and clinically significant changes for definitions of equivalence or non-inferiority limits. It is based on the impact of symptoms for individuals and thus meets the criteria for efficacy assessment of AR.

Therefore, the present study was conducted as a double blind, placebo controlled proof-of-concept study to evaluate the efficacy and safety of TAPP-CZ as a nasal spray in seasonal AR patients with special reference to quality of life measurement (RQLQ) and nasal symptoms (obstructions, drainage, itch and sneezing).

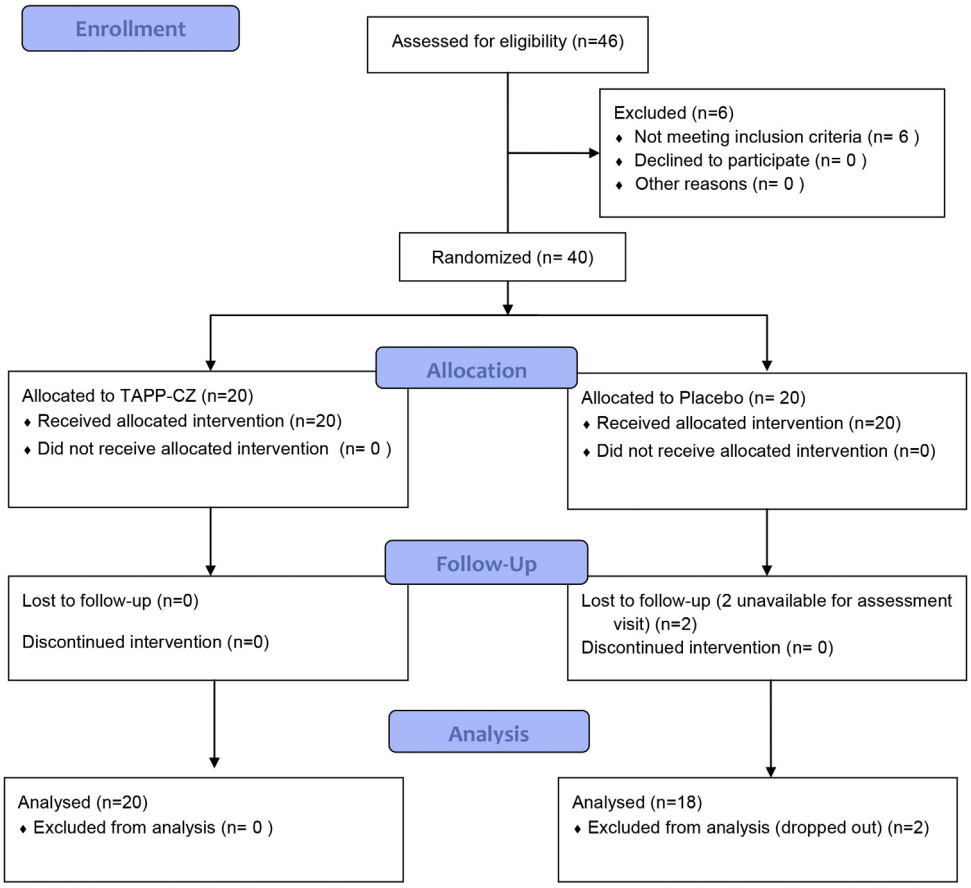


**Fig. 1 – Study flowchart (CONSORT format).**

## 2. Materials and methods

### 2.1. *Recruitment*

To achieve 32 evaluatable patients, 40 patients were recruited from the existing patient databases at the study center, Ethika Clinical Research Centre, Prakruti Hospital, Siddheswar Arcade, Kalwa West, Thane 400605, Maharashtra, India. The study was performed according to the principles of the ICH-GCP guidelines and the ethical principles according to the Declaration of Helsinki. The flow-chart of design and conduct of the study is presented as Fig. 1. The trial protocol was approved by the Independent Ethics Committee for human ethics requirement (protocol number – TAPP-CZ-AR) and is registered with Clinical Trial Registry of India (CTRI), New Delhi, India (Registration No. CTRI/2012/05/002664).

The inclusion criteria consisted of male or female patients with a diagnosis of severe seasonal AR (RQLQ score of >3.5 and ≤5 at baseline), aged between 20 and 55 years inclusive, willing to give written informed consent and willing to use effective contraceptive measures such as oral contraceptive or intra-uterine device (in case of female with childbearing potential).

The exclusion criteria were as follows: patients with any clinically significant medical condition or abnormality (chronic diseases like hypertension, ischemic heart disease, diabetes, psychiatric, any cancer and CNS disorders, bacterial sinusitis or asthma), alcoholics, drug addicts, smokers, people with allergies to ethyl alcohol or cinnamon, having steroid therapy within 6 weeks prior to study, having discomfort with nasal spray containing ethyl alcohol (ethanol), or using or had used inhaled or oral corticosteroids in the last 3 months, females who were pregnant, lactating or planning to become pregnant were excluded from study, i.e. as per ICH-CPG guidelines since the test extract had not been evaluated in pregnant women they were excluded as a precautionary measure.

### 2.2. *Screening and randomization*

With sufficient statistical power, even the most trivial differences between the treatment groups can reach statistical significance (Juniper et al., 1997). To interpret RQLQ data that reaches statistical significance, it is important to know what magnitude of change or difference can be considered, i.e. clinically important difference (CID). The minimal clinically important difference (MCID) is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and would mandate, in the absence of troublesome side effects or excessive cost, a change in the patient's management" (Juniper et al., 1994). MCID for the RQLQ is reported to be a difference of 0.5 (Juniper et al., 1996). Therefore, the sample size for our study was determined on the basis

of the MCID of 0.5 between placebo and active groups with error rates of $\alpha = 0.05$ (two-sided) and $\beta = 0.1$.

A strong placebo effect has been observed in allergic diseases, where the evaluating parameters tend to be physical or subjective (del Cuvillo et al., 2011) and therefore we designed the present study as double blind and placebo controlled. Potential participants were screened and requested to attend an information session. They were informed of the trial process and asked to provide their consent for trial participation. During the screening visit, the medical history and demography of consenting subjects were taken and physical examination, laboratory investigations and clinical examination were performed and recorded in case report forms (CRFs). The medication was dispensed and baseline values of outcome measures were also recorded. Participants were randomized to receive either Active treatment or Placebo in line with a computer-generated randomization list. Randomization was based on a total of 40 subjects, randomly allocated into two arms of equal numbers of subjects ($n = 20$ for each group). Patient drop-outs were not replaced. Patients were recruited at one site and allocated a unique randomization number at the randomization visit. Outcome measures were recorded at baseline, and at the end of 2-weeks, 4-weeks (end of treatment) and 8-weeks (follow up).

### 2.3. *The treatments*

The active treatment product is a nasal spray containing 15 ml of TAPP-CZ (Type-A proanthocynidins based standardized hydroalcoholic extract of *Cinnamonum zylanicum* bark) at concentration of 1 μg/μL). TAPP-CZ was prepared as per reported procedure (Kandhare et al., 2013b) and supplied by Indus Biotech Private Limited, Pune. Matching placebo was prepared by solution of ethyl alcohol and water. Both TAPP-CZ and placebo were analyzed and complied with quality requirements related to microbial content, heavy metals in raw material of active ingredient, isotonicity and sterility.

The solutions of TAPP-CZ and the placebo solutions (conc. 1 μg/μL) were supplied in 15 ml plastic bottles with a screw-on pump with a cap and diptube length 58 mm (Valois/Aptar Pharma, USA). The TAPP-CZ and placebo nasal spray containers were identical in function and appearance and individually coded. This system is air filtered and preservative free and can deliver a dose of 100 μL solution (containing 100 μg of TAPP-CZ or placebo) with each shot. The patients were instructed to take one shot per nostril in the morning and evening twice daily with actuation of spray if needed, i.e. activation of the spray once outside of the nostril before use to ensure a proper dose of treatment solution.

### 2.4. *Outcome measures*

The primary outcome measure of the study was a change in the individual or total score obtained from Juniper rhinoconjunctivitis quality of life questionnaire (RQLQ) instrument. RQLQ has excellent reliability, responsiveness and construct validity and has been used successfully in a number of clinical trials (Juniper and Guyatt, 1991). The RQLQ was developed to measure the functional problems (physical, emotional, social and occupational) that are most debilitating to adults (17–70 years) with either seasonal or perennial rhinoconjunctivitis of either allergic or non-allergic origin. Patients need to identify the functional problems they may experience in their daily lives, and were most troublesome. The problems considered of highest importance to patients are scored in the RQLQ. There are 3 'patient-specific' questions in the activity domain which allow patients to select 3 activities in which they are most limited by their rhinoconjunctivitis. Patients recall how affected they have been by their rhinoconjunctivitis during the previous week and to respond to each question on a 7-point scale (0 = not impaired at all to 6 = severely impaired). The RQLQ has 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function). The overall RQLQ score is the Average (mean) of all 28 responses and the individual domain scores are the means of the items in those domains.

The secondary findings were changes in the individual nasal symptom scores (NSS) and total NSS that was scored by each patient (every morning and night in supplied diary) and by investigators (at visits). The nasal symptoms of obstruction/blockage/congestion, drainage [anterior/posterior], nasal itch, and sneezing were scored on a scale from 0 (none) to 6 (very severe).

The presence of ocular and nasal symptoms among patients with AR may often result in reduced work productivity (Szeinbach et al., 2007; Virchow et al., 2011). Therefore, we also measured the Work Productivity of recruited patients using the Work Productivity and Activities Impairment–Allergy Specific (WPAI–AS) questionnaire score. WPAI–AS questionnaire contained 9 questions related to how allergies affected the patient's ability to work, attend classes, and carry out daily activities. These questions were answered in writing by each patient at baseline and after 4-weeks of treatment during visits to the study center. Each question was scored on a likert scale of 0 (no effect) to 10 (prevention of activity). Question No. 9 of the WPAI–AS, "During the past seven days, how much did your allergies affect your ability to do your regular daily activities, other than work at a job or attend classes?", was answered by all patients and hence considered for efficacy assessment as a secondary endpoint.

### 2.5. *Safety evaluation*

Spirometry (meaning the measuring of breath) is a pulmonary function test (PFT) which is helpful in assessing measurement of lung function (amount/volume and/or speed/flow) of air that can be inhaled and exhaled. In the past, a strong functional and immunological relationship between asthma and AR was suggested by clinical, epidemiological and pathophysiological studies of AR (Cruz et al., 2007; Feng et al., 2012; Palma-Carlos et al., 2001; Pawankar et al., 2012). Therefore, we recorded a pneumograph of each patient at baseline and final visit and calculated important spirometry parameters namely Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), FEV1/FVC ratio (FEV1%), Forced Expiratory Flow 25–75%, and Peak Expiratory Flow (PEF). The pneumograph output consist of both raw data (liters, liters per second) and predicted percentage, i.e. the test result as a percentage of the "predicted values" for patients of similar characteristics

**Table 1 – Demographic and clinical characteristics of patients.**

| Variable | Mean ± SD | | P-value |
|---|---|---|---|
| | TAPP-CZ ($n = 20$) | Placebo ($n = 20$) | |
| Gender | | | |
| Male | 7 | 9 | ns |
| Female | 13 | 11 | ns |
| Age (years) | 32.10 ± 8.93 | 39.85 ± 10.81 | $P < 0.05$ |
| Weight (kg) | 56.10 ± 15.48 | 59.85 ± 11.20 | ns |
| Systolic blood pressure (mmHg) | 119.00 ± 12.52 | 119.50 ± 11.46 | ns |
| Diastolic blood pressure (mmHg) | 78.00 ± 11.52 | 79.20 ± 7.96 | ns |
| Pulse rate (bpm) | 78.80 ± 5.37 | 81.00 ± 9.75 | ns |
| Body temperature (°F) | 98.08 ± 0.73 | 97.97 ± 1.24 | ns |
| Overall RQLQ score | 3.84 ± 0.28 | 3.9 ± 0.29 | ns |

The data is represented as mean ± standard deviation and analyzed by unpaired paired 't' test. ns – not significant; RQLQ – rhinoconjunctivitis quality of life questionnaire; bpm – beats per min.

(height, age, sex, and sometimes race and weight). As the present study was conducted in an Indian population, the percentage of the "predicted values" based on average values in an Indian population were taken for data analysis.

The vital signs, namely blood pressure (systolic and diastolic), pulse rate, heart rate and body temperature were measured at the initial screening visit, baseline after 2-weeks, 4-week and at a follow up visit (4-weeks after the treatment was finished). A 12-lead ECG was recorded at the screening visit and after 4-weeks of treatment. The ECG recoding parameters included RR interval (milliseconds), PQ interval (milliseconds), QRS duration (milliseconds), QTC (corrected QT interval, milliseconds), ST (segment deviation), QTcB (QT interval corrected for heart rate – Bazett correction), QTcBD (QT interval corrected for heart rate – dynamic beat rate) and Sokolow (Sokolow-Lyon index – diagnostic sign for hypertrophy of heart muscles). The safety measurements included adverse event monitoring and laboratory assessments. The laboratory assessment (hematology, biochemistry and urinalysis) was performed at baseline and at the end of the treatment period. All patients were monitored for compliance with the protocol by telephone or face-to-face communication. Patients were asked to return all used and unused bottles of nasal spray. The average weight of the empty bottle, weight of the bottle at the randomization visit and at the patient's last visit was recorded. The percent compliance was calculated by percent weight loss from each bottle for the specific patient.

### 2.6. Data analysis

The differences between the treatment groups was analyzed by unpaired "t' test. The $P$ values less than 0.05 (two-sided) were considered significant. The data of efficacy outcome measures were analyzed per protocol (PP, number of patients who completed the protocol) population ($n = 20$ in active and $n = 18$ in placebo group). For the safety outcome measures, all the available data of safety outcome measures from all the randomized patients ($n = 20$ in each group) was considered as "full analysis set" and used for analysis. The "full analysis set" means all available data is in agreement with definition of intention-to-treat (ITT) population as defined in Topic E9 (Statistical Principles for Clinical Trials) of International Conference of Harmonization (ICH). For hypothesis testing, decision on choice of the parametric test or its non-parametric alternative is taken on the normality of the data. Mean difference between values of TAPP-CZ and Placebo at end of the treatment period (4-weeks) was calculated as MCID.

## 3. Results

### 3.1. Demographics and baseline characteristics

Forty patients were enrolled and randomized between active group ($n = 20$) and placebo group ($n = 20$). As shown in Table 1, the patient population was found uniform in respect of demographic and baseline parameters such as gender, weight, blood pressure (systolic and diastolic), pulse rate, body temperature, but not the age. Mean age of patient on placebo group (39.85) is significantly more ($P < 0.05$) than that of active group (32.10). Out of 40 patients, 38 patients (20 in active group and 18 from placebo group) completed the study and were included for analysis for the efficacy measure per-protocol (PP) population. None of the patients dropped out from the active group. However, two patients from the placebo group were lost to follow-up (these patients had consulted other physicians and started nasal anti-histamines, withdrawn their consent by telephone and not reported for any site visits) and hence considered as 'drop-outs' from the study.

### 3.2. RQLQ – overall and individual domain scores

The data of RQLQ or any of its individual domain scores is presented in Tables 1 and 2. Four week treatment of TAPP-CZ nasal spray caused a significant ($P < 0.05$) decrease in overall RQLQ and 5 individual domain scores (activities, non-hay fever symptoms, nasal symptoms, eye symptom and emotional) as compared to placebo group. However, no significant change was observed for domain related to "sleep" and "practical problems".

At the end of the 4 week treatment period a decrease of 31.77% in overall RQLQ score was observed in patients treated with TAPP-CZ compared to a 18.21% decrease in the placebo group. The difference of overall RQLQ scores between TAPP-CZ and placebo groups was statistically significant ($P < 0.05$).

**Table 2 – Effect of rhinoconjunctivitis quality of life questionnaire (RQLQ) of patients with allergic rhinitis (efficacy outcome measure).**

| Parameter | Treatment | RQLQ domain score, mean ± SD | | | |
|---|---|---|---|---|---|
| | | Baseline | 4-weeks | CID (Week-4) | Follow-up |
| Overall RQLQ (average RQLQ) | TAPP-CZ | 3.84 ± 0.28[ns] | 2.62 ± 0.50[a] | 0.52[b] | 2.32 ± 0.66[ns] |
| | Placebo | 3.9 ± 0.29 | 3.14 ± 0.79 | | 2.66 ± 0.78 |
| RQLQ-activities | Active | 3.97 ± 0.53[ns] | 2.8 ± 0.69[a] | 0.55[b] | 2.37 ± 0.82[ns] |
| | Placebo | 4.09 ± 0.58 | 3.35 ± 0.98 | | 2.89 ± 0.98 |
| RQLQ-sleep | TAPP-CZ | 3.7 ± 0.96[ns] | 2.47 ± 0.88[ns] | 0.38 | 2.2 ± 1.02[ns] |
| | Placebo | 3.48 ± 0.88 | 2.85 ± 1.02 | | 2.46 ± 0.96 |
| RQLQ-non-hay fever symptoms | TAPP-CZ | 4.01 ± 0.51[ns] | 2.94 ± 0.55[a] | 0.46 | 2.57 ± 0.76[ns] |
| | Placebo | 4.1 ± 0.36 | 3.4 ± 0.84 | | 2.91 ± 0.84 |
| RQLQ-practical problems | TAPP-CZ | 3.6 ± 0.45[ns] | 2.4 ± 0.61[ns] | 0.36 | 2.17 ± 0.83[ns] |
| | Placebo | 3.78 ± 0.65 | 2.76 ± 0.87 | | 2.35 ± 0.84 |
| RQLQ-nasal symptoms | TAPP-CZ | 4.03 ± 0.39[ns] | 2.41 ± 0.67[a] | 0.73[b] | 2.3 ± 0.85[ns] |
| | Placebo | 4.11 ± 0.40 | 3.14 ± 1.05 | | 2.54 ± 0.95 |
| RQLQ-eye symptoms | TAPP-CZ | 3.44 ± 0.74[ns] | 2.29 ± 0.57[a] | 0.57[b] | 2.04 ± 0.61[ns] |
| | Placebo | 3.5 ± 0.73 | 2.86 ± 0.96 | | 2.35 ± 0.94 |
| RQLQ-emotional | TAPP-CZ | 3.95 ± 0.60[ns] | 2.78 ± 0.71[a] | 0.5[b] | 2.33 ± 0.71[ns] |
| | Placebo | 3.97 ± 0.50 | 3.28 ± 0.85 | | 2.86 ± 0.90 |

The data is represented as mean ± standard deviation and analyzed by unpaired 't' test, ns – not significant.

[a] $P < 0.05$ as compared with scores of placebo group of respective domain. CID – clinically important difference (difference of mean scores between active and placebo at respective time and domain).

[b] Clinical significance (MCID ≥ 0.5) is achieved.

At the end of the 4 week treatment period a decrease of 29.47%, 33.24%, 26.68%, 33.33%, 40.20%, 33.43% and 29.62% was found in patients treated with TAPP-CZ compared to baseline values in individual domains of RQLQ namely activities, sleep, non hay fever symptoms, practical problems, nasal symptoms, eye symptoms, and emotional problems respectively. In the same 4-week period, the placebo group showed a decrease of 18.09%, 29.60%, 17.07%, 26.98%, 23.60%, 18.29%, and 17.18% in corresponding domains. The differences between TAPP-CZ and placebo groups were statistically significant ($P < 0.05$) for all domains of RQLQ except sleep and practical problems.

After 4 weeks of treatment clinical significance (CID > 0.5) was achieved between TAPP-CZ and placebo group in terms of overall RQLQ and individual domain scores (activities, nasal symptoms, eye symptoms and emotional).

The overall RQLQ or its individual domains scores of the TAPP-CZ group at a follow-up visit (4-weeks after the treatment was finished) were not significantly different from the corresponding values of placebo group.

### 3.3. *NSS and TNSS*

The data for TNSS and individual NSS such as obstruction, drainage, nasal itch and sneezing is presented in Table 3. The TAPP-CZ nasal spray treatment group had improved TNSS by 37.59% as compared to the baseline values whereas the placebo group showed only 21.97% improvement. The difference between TAPP-CZ and placebo was significant clinically (CID = 3.13) and statistically ($P < 0.01$). The TAPP-CZ nasal spray group showed a 40.48% decrease in nasal obstruction compared to a 22.88% decrease for placebo. The difference between the two groups however was neither clinically or statistically significant. TAPP-CZ nasal spray group improved the scores for nasal drainage by 42.25% compared to 24.64% for placebo. The difference between the two treatment groups was significant clinically (CID = 1.13) and statistically ($P < 0.05$). Nasal itch scores were decreased by 22.79% for the treatment group compared to 24.80% for placebo. The difference between the two groups, however, was not significant clinically or statistically. Sneezing scores were decreased by 37.68% for the treatment group compared to 15.40% for placebo. The difference between the two groups was significant clinically (CID = 1.09) and statistically ($P < 0.01$). The mean NSS or TNSS scores were not significantly different from corresponding values of placebo group at follow-up visit (4-weeks after the treatment was finished).

### 3.4. *WPAI–AS score*

As shown in Table 3, Question 9 of WPAI–AS was answered by all patients and considered as a basis of work productive evaluation. At baseline, there was no significant difference between WPAI–AS score for Q.9 (WPAI–AS-Q9) between active and placebo group. At week-4, TAPP-CZ nasal spray treatment group showed significant improvement (23.3% decreases in score, $P < 0.05$) whereas placebo showed 15.7% improvement (not significant). However, WPAI–AS-Q9 score was not significantly different from the corresponding value of placebo group at follow-up visit (4-weeks after the treatment was finished). The answers to the questions Q.1 to Q.8 in WPAI–AS were not applicable to all patients. For example, Q.3 and Q.4 are only for those who are working people and Q.6, Q.7 and Q.8 are only related to students. Due to small sample size, subgroup analysis (for Q.1 to Q. 8) was not performed.

**Table 3 – Effect on total nasal symptom scores (TNSS), nasal symptom scores (NSS) and Work Productivity and Impairment–Allergy Specific (WPAI–AS) questionnaire of patients with allergic rhinitis (efficacy outcome measure).**

| Parameter | Treatment | Mean ± SD | | | |
|---|---|---|---|---|---|
| | | Baseline | 4-weeks | CID (Week-4) | Follow-up |
| Total Nasal Symptoms Score (TNSS) | TAPP-CZ | 14.50 ± 1.64[ns] | 9.05 ± 2.42[b] | 3.13[c] | 8.65 ± 3.18[ns] |
| | Placebo | 15.61 ± 2.17 | 12.18 ± 4.10 | | 10.17 ± 4.37 |
| NSS-Obstruction | TAPP-CZ | 4.20 ± 0.62[ns] | 2.50 ± 1.00[ns] | 0.5 | 2.40 ± 1.05[ns] |
| | Placebo | 3.89 ± 0.76 | 3.00 ± 1.28 | | 2.33 ± 1.28 |
| NSS-Drainage | TAPP-CZ | 3.55 ± 0.89[*] | 2.05 ± 0.89[a] | 1.13[c] | 1.95 ± 0.95[ns] |
| | Placebo | 4.22 ± 0.81 | 3.18 ± 1.29 | | 2.67 ± 1.41 |
| NSS-Nasal Itch | TAPP-CZ | 3.30 ± 0.73[ns] | 2.35 ± 0.75[ns] | 0.41 | 2.15 ± 0.93[ns] |
| | Placebo | 3.67 ± 1.03 | 2.76 ± 1.15 | | 2.44 ± 1.10 |
| NSS-Sneezing | TAPP-CZ | 3.45 ± 0.76[ns] | 2.15 ± 0.81[b] | 1.09[c] | 2.15 ± 1.04[ns] |
| | Placebo | 3.83 ± 0.71 | 3.24 ± 0.09 | | 2.72 ± 1.07 |
| WPAI–AS-Q9 | TAPP-CZ | 6.65 ± 0.75[ns] | 5.10 ± 0.79[b] | – | 4.60 ± 1.95[ns] |
| | Placebo | 7.00 ± 0.92 | 5.90 ± 1.17 | | 4.94 ± 1.21 |

The data is represented as mean ± standard deviation and analyzed by unpaired paired 't' test, ns – not significant.
[a] $P < 0.05$, [b] $P < 0.01$ as compared with scores of placebo group of respective domain. CID – clinically important difference (difference of mean scores between active and placebo at respective time and domain).
[c] Clinical significance (MCID ≥ 0.55) is achieved. WPAI–AS – Work Productivity and Activities Impairment–Allergy Specific. Q9 of WPAI–AS was "During the past seven days, how much did your allergies affect your ability to do your regular daily activities, other than work at a job or attend classes?"

### 3.5. *Safety evaluation*

There were no deaths or serious adverse events (SAE) during the study which confirms the excellent safety profile of TAPP-CZ. Total 15 patients (7 from active group and 8 from placebo groups) showed 25 AEs. Nine AEs (mild severity) were observed in active (TAPP-CZ) group whereas 14 AEs (12 mild and 2 moderate severities) were observed in placebo groups. However, they were neither severe nor suspected or related to active treatment (TAPP-CZ). The AEs that were observed in TAPP-CZ group were cough, fever, headache, body aches, and throat irritation. These are known symptoms of disease condition of patients (AR) and found common in both TAPP-CZ and placebo groups. The AEs such as cold, ear ache, fatigue, itching in eyes, throat irritation and watery eyes were found in the placebo group only. No sedation was found in any of the patients either in the active or placebo group.

All the spirometry parameters of patients were found to be within a normal range during our study. As compared to placebo, no significant change was observed in values of FVC, FEV1, FEF 25–75 or PEF values in patients with TAPP-CZ treatment. However, on 4-weeks of treatment, mild but significant difference was found in FEV1% ($P < 0.05$) of patients on TAPP-CZ treatment as compared with placebo (Table 4). Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature) of patients were also found within normal range (Table 5). No clinically significant change was observed in ECG parameters of patients of either TAPP-CZ group or placebo group.

All the patients were evaluated for safety outcome measures (hematology, biochemistry, liver function test and kidney function test) at baseline and end of the study. The differences between values at baseline and at end of the study were found to be non-significant.

## 4. Discussion

Due to the classic symptoms of AR (sneezing, pruritus, rhinorrhea and nasal obstruction), it may have a significantly negative impact on quality of life (Camelo-Nunes and Sole, 2010). In addition, the pathophysiology of allergic rhinitis often disrupts sleep, leading to fatigue, irritability, memory deficits, daytime sleepiness and depression (Camelo-Nunes and Sole, 2010). AR can also impact on work productivity and can lead to other immune inflammatory respiratory conditions such as asthma (Nathan, 2007).

Health-related quality of life focuses on patients' perceptions of their disease and measures impairments that have a significant impact on the patient. (Ozdoganoglu et al., 2012). Because so many factors are involved in health-related quality of life, there are multiple ways available in which it can be measured. Therefore, numerous validated questionnaires are available and many studies have been performed evaluating health related quality of life (HRQoL) in people affected by AR (Baiardini et al., 2008; Kremer, 2004).

The Juniper's rhinoconjunctivitis quality of life questionnaire (RQLQ) is one of the most validated tools for assessing quality of life in allergic rhinitis (Thompson et al., 2000). Due to high reproducibility, responsiveness and validity, RQLQ has been proved useful as an efficacy measurement of HRQoL in clinical trials in both rhinoconjunctivitis and rhinitis (Juniper and Guyatt, 1991). Therefore, RQLQ was classed as a primary outcome measure in the present study. Statistical significance was achieved between the TAPP-CZ and placebo group for overall RQLQ and 4 individual domain scores namely activities, non-hay fever symptoms, nasal symptoms and eye symptoms and emotional. These results suggested therapeutic improvement in quality of life with respect to important nasal symptoms which were confirmed by statistically

**Table 4 – Pulmonary function test (safety outcome measure).**

| Parameter | Treatment | Mean ± SD | |
|---|---|---|---|
| | | Baseline | 4-weeks |
| Forced Vital Capacity (FVC) | TAPP-CZ | 77.94 ± 15.72[ns] | 77.83 ± 18.66[ns] |
| | Placebo | 82.67 ± 17.30 | 79.47 ± 20.06 |
| Forced Expiratory Volume in 1 second (FEV1) | TAPP-CZ | 75.44 ± 13.20[ns] | 76.02 ± 15.27[ns] |
| | Placebo | 74.37 ± 15.77 | 73.08 ± 20.15 |
| FEV1/FVC ratio (FEV1%) | TAPP-CZ | 82.46 ± 1.94[ns] | 82.46 ± 1.94[a] |
| | Placebo | 81.15 ± 2.63 | 80.89 ± 2.15 |
| Forced Expiratory Flow 25–75% (FEF 25–75) | TAPP-CZ | 60.19 ± 19.82[ns] | 55.34 ± 26.21[ns] |
| | Placebo | 62.76 ± 18.71 | 54.20 ± 24.69 |
| Peak Expiratory Flow (PEF) | TAPP-CZ | 72.57 ± 17.48[ns] | 72.55 ± 17.69[ns] |
| | Placebo | 67.68 ± 17.07 | 68.98 ± 23.86 |

The data is represented as mean ± standard deviation and analyzed by unpaired paired 't' test, ns – not significant.
[a] $P < 0.05$ as compared with scores of placebo group of respective domain.

**Table 5 – Effects on vital signs (safety outcome measure).**

| Parameter | Treatment | Mean ± SD | | |
|---|---|---|---|---|
| | | Baseline | 4-weeks | Follow-up |
| Systolic blood pressure (mmHg) | TAPP-CZ | 122.00 ± 6.96[ns] | 121.00 ± 6.41[ns] | 119.00 ± 8.52[ns] |
| | Placebo | 119.00 ± 7.88 | 119.41 ± 6.59 | 122.78 ± 6.69 |
| Diastolic blood pressure (mmHg) | TAPP-CZ | 79.50 ± 8.26[ns] | 77.50 ± 10.70[ns] | 78.00 ± 7.68[ns] |
| | Placebo | 78.50 ± 10.40 | 78.24 ± 10.15 | 81.11 ± 5.83 |
| Pulse rate (bpm) | TAPP-CZ | 77.80 ± 4.49[ns] | 77.35 ± 4.11[ns] | 75.50 ± 2.97[ns] |
| | Placebo | 79.55 ± 5.67 | 75.65 ± 4.32 | 76.00 ± 2.47 |
| Body temperature (°F) | TAPP-CZ | 97.83 ± 0.62[ns] | 97.97 ± 0.80[ns] | 97.74 ± 0.82[ns] |
| | Placebo | 97.50 ± 1.03 | 97.59 ± 0.70 | 97.69 ± 0.85 |

Unpaired *t* test. ns – not significant as compared to Placebo of respective parameter at respective time period.

significant differences found in TNSS and NSS (drainage and sneezing).

The concept of minimal clinically important difference (MCID) illustrates the smallest change in a given outcome that is meaningful to a patient. When presented with results from clinical measurements or research findings, clinicians must first make an interpretation of their importance, not only in statistical terms, but also the 'clinical importance' given the size of the change observed. To do this, they require an understanding of the relationship between their outcome measures, and the patient's perception of change. The minimal clinically important difference (MCID) illustrates this relationship by calculating the smallest change in a given outcome that is meaningful to a patient. Mean changes in score more than MCID can be considered of clinical importance and would justify a change in the patient's treatment in the absence of troublesome side effects or excessive cost (Barnes et al., 2010). In case of AR patients, MCID measurement is shown as >0.5 for overall RQLQ and domains (Juniper and Guyatt, 1991) and >0.55 for mean TNSS and NSS (Barnes et al., 2010). Any difference between two comparative groups in a clinical trial is considered clinically significant if MCID is achieved.

In the present study, MCID was achieved between TAPP-CZ and placebo group for overall RQLQ and 5 individual domain scores (activities, non-hay fever symptoms, nasal symptoms, eye symptoms, and emotional domains), TNSS and 2 NSS (drainage and sneezing).

Nasal congestion is the most common and bothersome symptom, and is often associated with sleep-disordered breathing, which is thought to be the reason for sleep impairment in individuals with AR (Craig et al., 2010; Sardana and Craig, 2011). Nasal congestion also demonstrates circadian rhythm and positional variability, worsening during night time hours and in the supine position (Gonzalez-Nunez et al., 2013). The degree of sleep disturbance is directly related to the severity of the disease (Colas et al., 2012; Gonzalez-Nunez et al., 2013). During our study, TAPP-CZ was shown to reduce nasal congestion clinically and statistically as compared with placebo and could have positive impact on night sleep.

Sleep impairment is very common in AR patients and has a significant impact on disease-specific measures of general health and quality of life. AR significantly contributes to sleep-disordered breathing through multiple mechanisms, with the greatest impact mediated through nasal obstruction (Gonzalez-Nunez et al., 2013).

Nighttime sleep disturbances in AR lead to fatigue and daytime somnolence, impaired performance, productivity and social functioning, and an increased risk of associated diseases (Gonzalez-Nunez et al., 2013). Furthermore,

daytime sleep disturbance, sedation and fatigue are common side effects associated with the response to topical nasal corticosteroids (Craig et al., 1998) and antihistaminic drugs (De Sutter et al., 2009). For most AR patients, practical medications are beneficial in reducing symptoms without producing the side effects of sedation (Hadley, 1999). The sleep domain score (measured for daytime activities) in RQLQ was not affected by TAPP-CZ treatment as compared with placebo. However, lack of effect on sleep by TAPP-CZ treatment suggested non-sedative nature of TAPP-CZ.

In addition to quality of life and sleep, nasal congestion affects AR patients with emotional functions, productivity and the ability to perform daily activities (de la Hoz Caballer et al., 2012; Shedden, 2005). AR is one of the major causes of absenteeism and loss of productivity in the workplace and the classroom (Reily et al., 1996). Work productivity is not only affected by AR symptoms but also affected by anti-histaminic medication (Szeinbach et al., 2007). The added presence of ocular symptoms in AR patients suffering with nasal symptoms may lead to further lost productivity and places a higher burden on resource utilization (Kakutani et al., 2005; Virchow et al., 2011). Therefore, MCID that is achieved by TAPP-CZ treatment on eye and nose symptoms domains of RQLQ in addition to TNSS as compared with placebo is an indicator of improved work productivity.

The multi-dimensional, HRQoL questionnaires such as RQLQ can assess the role of impairment (e.g., whether less was accomplished, whether time spent on activities was reduced). However, these instruments did not distinguish "work" related impairment from impairment in other activities such as housework or school, nor did they quantify the absolute amount of the impairment (Bush et al., 1982). WPAI–AR is a patient-reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to AR (Reilly et al., 1993, 1996). Therefore, we have included WPAI–AR scores as a measure of work related productivity as a secondary efficacy measure. TAPP-CZ treatment improved work productivity in WPAI–AR score as compared with placebo during our study.

Although used mainly for the diagnosis of asthma and COPD, lung function tests are used as a measure of severity of airway obstruction. Lung function tests were measured by spirometry. Spirometry (the volume of air that the patient can expel from the lungs after a maximal inspiration) is a common non-invasive method used for lung function measurement. It can also be used to assess the response to therapy that is improving the air passage through bronchi, such as bronchodilators and monitoring disease progression. The FEV1% is the ratio of FEV1 to FVC (expressed as a fraction or percentage) that is the most useful spirometry parameter which is a marker of airway obstruction (Celli and Halbert, 2010; Cerveri et al., 2008; Juusela et al., 2013; Khan et al., 2010). Values of FEV1 and FVC are measured in liters and are also expressed as a percentage of the predicted values for that individual. The FEV1% is normally between 0.7 and 0.8. During our study, all spirometry parameters were found to be normal with small reduction FEV1% in placebo group. The efficacy shown by TAPP-CZ in maintenance in FEV1% along with nasal obstruction score in a RQLQ measurement is indicating ability of TAPP-CZ in removing airway obstruction.

The TAPP-CZ treatment was well tolerated during the period of the study. All safety parameters were found to be within normal range during the study period. There were no deaths or serious adverse events (SAE) during the study which confirms the excellent safety profile of TAPP-CZ.

## 5. Conclusions

In conclusion, the use of TAPP-CZ nasal spray as instructed showed significant improvement in quality of life, nasal symptoms and work productivity in severe seasonal AR patients. The TAPP-CZ was well tolerated and safe in AR patients.

## Conflict of interest

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