SYNOPSIS

Name of Sponsor/Company	Johnson & Johnson Consumer Inc.
Name of Investigational Product	RHINOCORT® (budesonide)

Status: Approved
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Prepared by: Janssen Research & Development, LLC

Protocol No.: 5034003ALY4002/CCSURA001265

Title of Study: A Phase 4, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Intranasal Budesonide Aqueous Spray for Treatment of Rhinitis During Periods of High Airborne Pollution

NCT No.: NCT04132570

Clinical Registry No.: CCSURA001265

Coordinating Investigator(s): Luo Zhang, MD - Beijing Tongren Hospital, Beijing, China

Study Center(s): China (6 sites)

Publication (Reference): None

Study Period: 22 October 2019 (Date first subject signed informed consent) to 22 January 2020 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 4

Objectives:

The primary objective was to assess the effectiveness of intranasal budesonide aqueous spray 256 mcg/day for treatment of rhinitis symptoms during times of high airborne pollution.

Methodology:

This was a parallel-group, randomized, double-blind, placebo-controlled, multi-center study conducted at multiple sites in northern China during the cool season (approximately October through February) that evaluated budesonide in subjects with rhinitis during times of high airborne pollution. The planned total sample size was approximately 230 subjects aged 18 to 80 years old. Subject's participation consisted of a Screening Phase (up to 2 days prior to Day 1), a Double-blind Treatment Phase (from Day 1 to Day 10 [+/-3 days]), and a Post-treatment Phase. After screening, eligible subjects were randomized in a 1:1 ratio to receive either budesonide 256 mcg/day (two 64 mcg/sprays in each nostril once daily) or placebo (2 sprays in each nostril once daily), with the first dose administered on the morning following the baseline visit and continuing until the morning of the Final Efficacy Assessment. An interim statistical analysis was conducted after a protocol amendment was done and approved due to the enrollment interruption by COVID-19. It was determined that the interim results were sufficiently powered to demonstrate efficacy; the study was stopped to avoid unnecessarily exposing additional subjects to clinical research during the COVID-19 pandemic.

Number of Subjects (planned and analyzed):

Planned: Approximately 230 subjects were planned to be enrolled in the study (115 per treatment arm). Analyzed: 206 subjects randomized and treated (Full Analysis Set/Safety Analysis Set: 103 in budesonide

arm; 103 in placebo arm, respectively). Per-Protocol Set: 96 subjects in budesonide and 92 subjects in placebo arm, respectively.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were required to have moderate to severe rhinitis symptoms (defined by a 24-hour reflective total nasal symptom score [rTNSS] of at least 5 [maximum 9]) triggered or worsened by airborne pollution, regularly have outdoor exposure during a normal week in the winter season, including ≥1 hour on most days, and reside in the same city as the study site that they visited. Full criteria for inclusion and exclusion refer to the study protocol.

Test Product, Dose and Mode of Administration, Batch No.:

Budesonide nasal spray 64 mcg/spray (RHINOCORT®): 2 sprays in each nostril once daily.

Batch number: MBDD1906028 (Jun-2021).

Reference Therapy, Dose and Mode of Administration, Batch No.:

Placebo nasal spray: 2 sprays in each nostril once daily.

Batch number: C19061701 (16-Jun-2021)

Duration of Treatment:

10+/-3 days

Criteria for Evaluation:

Evaluations of treatment efficacy were conducted using questionnaires. Subjects reflectively assessed individual nasal symptoms daily over the previous 24 hours on a four-point scale (from 0=none to 3=severe). Individual non-nasal symptoms were assessed using a questionnaire similar to that used for the nasal symptoms. Subjects and Investigators rated Global Impression of Change on a 5-point scale from 0 (symptoms were aggravated) to 4 (total control over symptoms). The impact of treatment on health-related quality of life indices was evaluated at Baseline Visit and at Final Efficacy Assessment (FEA) Visit with the standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) that includes 28 questions in 7 domains measured on a 7-point scale from 0 (not troubled or none of the time) to 6 (extremely troubled or all of the time). Factors related to user experience and perception of treatment benefits was rated on a 7-point scale (form 1=strongly disagree to 7=strongly agree) at FEA Visit. Safety was evaluated based on spontaneously reported adverse events (AEs), urine pregnancy test, vital sign measurements, physical examinations, and nasal examinations.

Statistical Methods:

A sample size of 100 subjects per arm (200 for two groups) was estimated to provide 90% power to detect an effect size (difference in means divided by standard deviation; based on primary endpoint of rTNSS) of 0.47 at the 0.05 significance level, two-sided. This sample size also provided 82% power should the effect size be 0.41. If a 15% attrition was anticipated, randomizing approximately 230 subjects was recommended. Effect size of 0.47 was estimated from previous studies. However, enrollment interruption occurred due to the COVID-19 pandemic at the point where 206 subjects were enrolled and randomized, thus, an interim analysis was approved and conducted to determine if the study could be stopped. The interim analysis results were sufficiently powered to demonstrate efficacy, and the study was stopped to avoid unnecessarily exposing additional subjects to clinical research during the pandemic. The alpha level was adjusted from 0.025 to 0.0125 for the interim analysis. To control the alpha level at 0.0125, one-sided for the primary and secondary efficacy endpoints, the following sequential testing procedure were used:

- The comparison of Test to placebo for rTNSS was tested at α =0.0125, one-sided in the first step. In the case of demonstrated statistical significance, for rTNSS, testing proceeded to the second test of SGIC. Otherwise, all tests for the following secondary endpoints would be considered exploratory.
- The comparison of Test to placebo for SGIC was tested at α =0.0125, one-sided. In the case of demonstrated statistical significance for SGIC, testing proceeded to the individual nasal symptoms scores (nasal obstruction, secretion/runny nose, and itching/sneezing). Otherwise, all tests for the following secondary endpoints would be considered exploratory.
- Individual nasal symptom scores were statistically evaluated using multiway averages. For statistical significance to apply to any individual nasal symptoms score, its p-value would need to be below 0.0125, one-sided, and so would the p-values for its pairwise averages with the other two nasal symptoms scores. If all individual scores and its pairwise averages all had p-values <0.0125, one-sided, then testing would proceed. Otherwise, all tests for the following secondary endpoints would be considered exploratory.
- Hochberg approach was applied for non-nasal symptoms. Statistical significance would apply to both non-nasal symptoms (cough and postnasal drip) if both non-nasal symptoms had a p value of <0.0125, one-sided. If p ≥0.0125, one-sided for one of non-nasal symptoms, then statistical significance would apply to the other endpoint if p<0.00625, one-sided. Otherwise, no statistical significance would apply to either endpoint.

The efficacy assessment was based on the Full Analysis Set which included all randomized subjects who had baseline and at least one post treatment diary data. The primary efficacy analysis for the change from baseline in 24-hour rTNSS over the first 10 days treatment period was based on repeated measure mixed model (MMRM) including terms for treatment, day, center, and baseline rTNSS as covariate. The treatment difference and the 97.5% confidence interval (CI) for the treatment difference were estimated from the model. The same approach was used for analyzing individual nasal/non-nasal symptoms scores. However, if there was a convergence issue for the MMRM model, an analysis of covariance (ANCOVA) model including terms for treatment, center, and baseline as covariate would be used for the mean change from baseline average over the 10 days. For the primary efficacy analysis of rTNSS, sensitivity analyses were planned, and an analysis based on Per-Protocol Set which include all randomized subjects having baseline and at least one post treatment diary data and without major protocol deviations (PDs), was added. An analysis of variance (ANOVA) model including terms for treatment and center was used for Global Impression of Change. RQLQ was analyzed by ANOVA including terms for treatment, center, and baseline as covariate.

RESULTS:

STUDY POPULATION:

A total of 206 subjects were enrolled and randomized to receive either budesonide or placebo treatment (103 subjects each). Demographic and baseline characteristics were generally balanced between the treatment arms. Fifty-one percent (105/206) of subjects were male. The median age was 34.5 (range: 20 to 70) years. At screening, the median 24-hour rTNSS score was 7.0. The median value of individual nasal symptoms for nasal obstruction, secretion/runny nose, and itching/sneezing was 3.0, 2.0, and 3.0, respectively.

Of the 206 treated subjects, 197 (95.6%) subjects completed the study, and 6 of the remaining 9 subjects also completed the study but showed violation of at least one inclusion criterium. Three subjects discontinued the study.

The median duration of treatment was 11.0 (range: 3.0 to 12.0) and 12.0 (range: 6.0 to 12.0) days for budesonide arm and placebo arm, respectively.

EFFICACY RESULTS:

- Due to the enrollment interruption by COVID-19 pandemic, an interim analysis was approved and conducted to determine if the study could be stopped. The interim results were sufficiently powered to demonstrate efficacy and the study was stopped.
- Budesonide had a significantly greater reduction in rTNSS over the first 10-days treatment period compared with placebo (LS Mean: 2.20 vs 1.72, for budesonide vs placebo, respectively; One-sided p-value =0.011 [<0.00125 one sided]; 97.5% CI: 0.01, 0.94). Consistent result was obtained by analysis based on Per-Protocol population (LS Mean: 2.30 vs 1.70, for budesonide vs placebo, respectively; p-value =0.003; 97.5% CI: 0.11, 1.09). Preplanned sensitivity analyses also yield similar results, although did not meet statistical significance.
- No significant difference in averaged SGIC between treatment arms was observed (LS Mean: 2.35 vs 2.20, for budesonide vs placebo, respectively; p-value =0.105; 97.5% CI: -0.12, 0.41). Similar result was also observed in Physician-assessed Global Impression of Change (PGIC) (LS Mean: 2.41 vs 2.20, for budesonide vs placebo, respectively; p-value =0.075; 97.5% CI: -0.02, 0.44). Because statistical significance was not demonstrated for SGIC, all tests for the following secondary endpoints was considered exploratory.
- Budesonide significantly improved itching/sneezing averaged over the first 10-days treatment period (LS Mean: 0.75 vs 0.51 for budesonide vs placebo, respectively; p-value =0.001; 97.5% CI: 0.07, 0.42), as well as the combined nasal symptom scores of nasal obstruction+itching/sneezing (LS Mean: 1.48 vs 1.11, for budesonide vs placebo, respectively, p-value =0.006, 97.5% CI: 0.04, 0.69) and secretion/runny nose+itching/sneezing (LS Mean: 1.47 vs 1.12, for budesonide vs placebo, respectively, p-value =0.006, 97.5% CI: 0.03, 0.67).
- Budesonide did not significantly improve non-nasal symptoms compared with placebo (cough: p-value =0.183 [97.5% CI: -0.10, 0.23]; postnasal drip: p-value =0.079 [97.5% CI: -0.06, 0.26].

SAFETY RESULTS:

- Thirteen subjects (budesonide: 5 [4.9%] subjects; placebo: 8 [7.8%] subjects) had at least one treatment-emergent AE (TEAE), with a total of 14 TEAEs reported. The most frequently reported TEAE was upper respiratory tract infection (6 [2.9%] subjects).
- Three subjects (budesonide: 2 [1.9%]; placebo: 1 [1.0%]) had treatment-related AE. The treatment-related AEs included epistaxis, nasal discomfort, and sneezing.
- No SAE or death was occurred during the study.
- No AEs leading to treatment discontinuation or study withdrawal were reported.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

This study demonstrated that the intranasal budesonide aqueous spray 256 mcg/day is effective in the treatment of rhinitis symptoms during times of high airborne pollution. Specifically, budesonide resulted in a significantly greater reduction in rTNSS over the first 10-days treatment period compared with placebo. This improvement was further supported by the analysis based on Per-Protocol Set.

Budesonide was well tolerated in subjects with rhinitis. The safety profile was comparable between both budesonide and placebo arms. Low proportion of subjects had TEAEs, and all TEAEs were mild and manageable. No TEAEs led to treatment discontinuation or withdrawal. No new safety concerns were identified.

This is the first Phase 4 multicenter, randomized, double-blind, placebo-controlled study performed to evaluate the efficacy of an intranasal steroid for the treatment of rhinitis during periods of airborne pollution. Phase 4 study results demonstrate that budesonide 256 mcg/day effectively relieves nasal symptom of rhinitis during periods of airborne pollution.