SAFETY OF A SUBLINGUAL TABLET OF HOUSE DUST MITE ALLERGEN EXTRACTS IN AN ENVIRONMENTAL EXPOSURE CHAMBER STUDY

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ABSTRACT

Rationale: The efficacy of house dust mite (HDM) sublingual tablets was demonstrated in an environmental exposure chamber (EEC) study of patients with allergic rhinitis upon exposure to HDM allergens. Here we report the safety results.

Methods: Adults (18-55 years) with medically confirmed HDM-associated allergic rhinitis were randomized in this DBPC study to receive 500IR, 300IR or 100IR HDM tablet or placebo daily for 6 months. Patients with intermittent asthma were eligible. Participants were exposed to five 4-hour allergen challenges in the EEC (baseline, treatment months 1, 2, 4, 6). Adverse events (AE) were monitored throughout the study and analyzed descriptively. All patients receiving at least one dose of the investigational product were included in the safety set.

Results: 355 patients (safety set: 500IR=93, 300IR=86, 100IR=89 and Placebo=87) were randomized. 94% (500IR), 91% (300IR), 97% (100IR) and 83% (Placebo) reported at least one AE on treatment. Application site reactions were the most commonly reported AEs (500IR=74%, 300IR=70%, 100IR=69%, and Placebo=37%). The incidence of asthma and related symptoms was higher during the peri-EEC challenge periods (i.e., the day of and the day after challenge; range: 37%-45%) than outside these periods (16%-21%) but was similar across treatment groups. No anaphylaxis or serious drug-related AEs were reported. 20 patients withdrew due to a TEAE, mostly due to application site reactions.

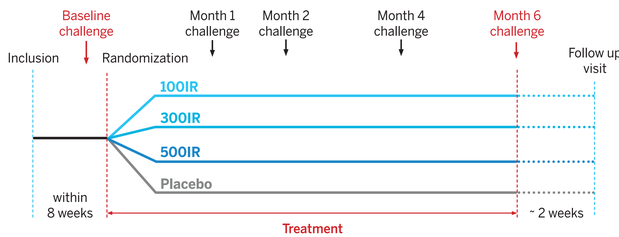
Conclusions: Treatment with HDM sublingual tablets was generally well tolerated regardless of dose. While asthma and related symptoms were more common during the peri-EEC challenge periods, rates did not differ between active and placebo treatment.

METHODS

Randomized, double-blind, placebo-controlled study in an environmental exposure chamber (EEC) in Canada

Design

- Patients received either 100IR, 300IR, 500IR, house dust mite (HDM) or placebo tablets (1:1:1:1) once daily for 6 months



Allergen challenge

- 4-hour duration
- Allergen particles obtained by milling whole bodies of *D. pteronyssinus*
- Turbulent airflow delivered a constant flux of allergen
- Patients scored their symptoms every 15 to 30 minutes, 13 times over the 4 hours

Population

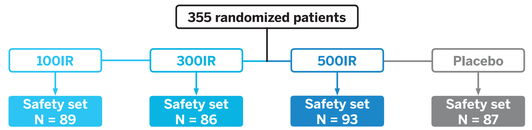
- Adults (18-55 years) with HDM-associated allergic rhinitis for at least one year
- Positive skin prick test for *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*
- *D. pteronyssinus*- and/or *D. farinae*-specific serum IgE ≥0.7 kU/L
- Rhinitis Total Symptom Score (RTSS, scale 0-12) ≥6 for at least 2 timepoints during the 4-hour baseline challenge. RTSS is based on patients' evaluation of rhinorrhea, sneezing, nasal pruritus and nasal congestion, scale 0 to 3 for each.
- Patients with intermittent asthma were eligible.

Data analysis

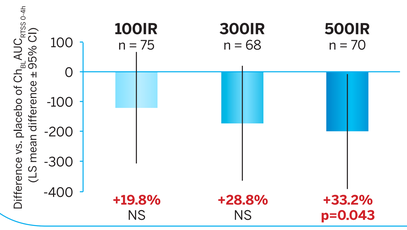
- Primary efficacy endpoint: Change from baseline of the Area Under the Curve (AUC) of the RTSS during the 4 hours of the allergen challenge in the EEC ($Ch_{BL}AUC_{RTSS\ 0\text{-}4h}$) assessed after 6 months of treatment in the Full Analysis Set (FAS) - Analysis of covariance
- Safety set identical to the FAS: All patients who received at least one dose of the investigational product
- Descriptive analysis of Treatment-Emergent Adverse Events (TEAEs)

RESULTS

Patient disposition



Primary Endpoint: Rhinitis Total Symptom Score during the 4 hours of the allergen challenge after 6 months of treatment



n = Number of patients with available data in the FAS

- Dose response of HDM sublingual tablets observed on the $Ch_{BL}AUC_{RTSS\ 0\text{-}4h}$ after 6 months of treatment

LS = Least Squares; NS = Not significant

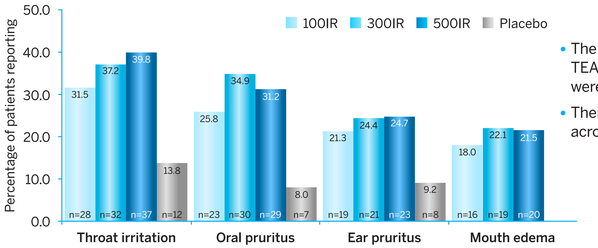
Overview of Treatment-Emergent Adverse Events

Patients with at least one:	100IR (N = 89) n (%)	300IR (N = 86) n (%)	500IR (N = 93) n (%)	Placebo (N = 87) n (%)
TEAE	86 (96.6)	78 (90.7)	87 (93.5)	72 (82.8)
Drug-related TEAE	60 (67.4)	59 (68.6)	66 (71.0)	38 (43.7)
Serious TEAE	1 (1.1)	1 (1.2)	2 (2.2)	0
Serious drug-related TEAE	0	0	0	0
TEAE leading to withdrawal	4 (4.5)	5 (5.8)	11 (11.8)	0

- The incidences of drug-related TEAEs were similar between the three active groups
- There were no deaths, no intensive care admissions, no serious drug-related AEs, no reports of anaphylaxis and no use of epinephrine

Application site reactions

	100IR (N = 89)	300IR (N = 86)	500IR (N = 93)	Placebo (N = 87)
Patients with at least one application site reaction TEAE, n (%)	61 (68.5)	60 (69.8)	69 (74.2)	32 (36.8)



- The most commonly reported TEAEs in the active groups were application site reactions
- Their incidences were similar across the active groups

Bronchospasm, asthma and asthma-related symptoms

Patients with at least one report of bronchospasm, asthma or an asthma-related symptom:	100IR (N = 89) n (%)	300IR (N = 86) n (%)	500IR (N = 93) n (%)	Placebo (N = 87) n (%)
During the peri-EEC periods*	40 (44.9)	38 (44.2)	34 (36.6)	39 (44.8)
Outside the peri-EEC periods	19 (21.3)	14 (16.3)	15 (16.1)	14 (16.1)

*Peri-EEC period = the day of and the day after an allergen challenge

- The incidence of bronchospasm, asthma and related symptoms was higher during the peri-EEC challenge periods (37%-45%) than outside of these periods (16%-21%) but was similar across treatment groups

Discontinuations due to Treatment-Emergent Adverse Events

- Among 20 patients withdrawn due to a TEAE, 12 discontinued for adverse reactions, mostly application site reactions (e.g., mouth edema): 2/3 pts in the 100IR group, 2/3 in the 300IR group and 4/6 in the 500IR group
- 7 patients (3 in the 100IR group, one in the 300IR group and 3 in the 500IR group) withdrew due to bronchospasm, asthma or associated symptoms during and immediately after an allergen challenge
- 6 patients in the placebo group withdrew because they did not tolerate the EEC challenge

Conclusions

Treatment with house dust mite sublingual tablets was generally well tolerated regardless of dose. While asthma and related symptoms were more common during the peri-EEC challenge periods, rates did not differ between active and placebo treatment.

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