Sponsor / Company: Sanofi	**Study Identifiers:** NCT02175485, UTN U1111-1152-0373
Drug substance(s): fexofenadine/pseudoephedrine	**Study code:** FEXHYL06934

Title of the study: Evaluation of Efficacy of Dellegra® combination tablet (fexofenadine hydrochloride 30mg /pseudoephedrine hydrochloride 60mg) in Allergic Rhinitis after Japanese Cedar Antigen Exposure in Japanese Population. Open label study

Study center(s): 1 study center in Japan

Study period:

Date first patient enrolled: 02/Jun/2014

Date last patient completed: 17/Jun/2014

Phase of development: Phase 4

Study rationale

In Japan, Japanese cedar pollen is dominant antigen causing allergic rhinitis. Although Dellegra which include fexofenadine and pseudoephedrine has so far been investigated and proved its efficacy in randomized controlled study focusing on Japanese population, no clinical data including change in Total Nasal Symptom Score (TNSS) under high density pure Japanese cedar pollen exposure in Japanese population are provided.

Based on these backgrounds, we aimed to demonstrate changes in TNSS after administration of Dellegra by oral route under high density Japanese cedar pollen exposure in Japanese population.

Objectives:

Primary Objective

To analyze and evaluate changes in TNSS in Japanese Seasonal Allergic Rhinitis (SAR) patients treated with oral Dellegra during high-density exposure to pure Japanese cedar pollen.

Secondary Objective(s)

To analyze and evaluate changes in Total Symptom Score (TSS), symptom scores, amount of nasal discharge, number of sneeze and patient's impression in patients with Allergic Rhinitis, and to evaluate the safety of Dellegra administered by oral route in patients receiving high-density exposure to pure Japanese cedar pollen.
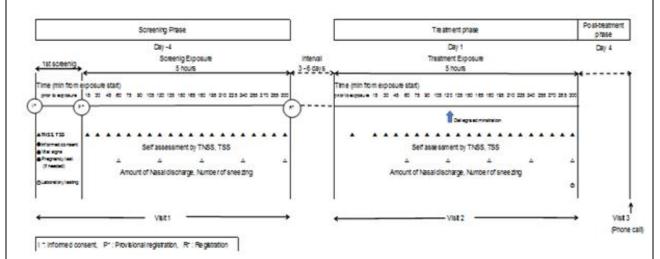
Methodology: To evaluate the efficacy and safety of Dellegra through Phase IV, single-center, nonblinded, noncontrolled, single-group study in Japanese SAR patients exposed to quantitative high-density Japanese cedar pollen.

Visit 1 (Screening Phase): Patients were exposed to 8,000 grains/m^3 of Japanese cedar pollen for 5 hours in Environmental Exposure Unit.

Visit 2 (Treatment Phase): Three days after Visit 1, patients were exposed to 8,000 grains/m^3 of Japanese cedar pollen for 5 hours. The patients received 2 tablets of Dellegra at 2 hours after the start of the pollen exposure.

Each symptom score (Sneezing, Rhinorrhea, Nasal congestion, Itchy nose, Itchy eyes, Watery eyes), nasal discharge amount, number of sneeze, and patient's impression were assessed by the patient and safety was also evaluated.

Ethical Considerations

Independent Ethics Committee or Institutional Review Board:

The protocol was submitted to Institutional Review Board (IRB) for review and written approval. Ethical Conduct of the Study:

The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol also complied with the laws and regulations such as the Good Clinical Practices (GCP) and the Good Post-marketing Study Practices (GPSP), as well as any applicable guidelines, of the country where the study was conducted.

Patient Information and Consent:

Informed consent was obtained prior to the conduct of any study-related procedures.

Number of patients:	Planned: 24
	Included: 24
	Treated: 24
	Evaluated: 24
Evaluated:	
	Efficacy: 24
	Safety: 24

Diagnosis and criteria for inclusion:

Inclusion criteria

1.   Japanese patients with SAR.

•   Patients with a history of symptoms of Japanese cedar pollinosis for at least 2 years.

•   A positive IgE (for Japanese cedar pollen antigen): Determined by Fluorescence-Enzyme Immunoassay (FEIA) or Chemiluminescent Enzyme Immunoassay (CLEIA) within 1.5 years prior to the day of the screening exposure test.

2. Patients with TNSS of 8 or more and nasal congestion score of 2 (moderate) or more at least one assessment point of 90 to 150 minutes after the start of the screening exposure. (TNSS and nasal congestion scores may be at any other assessment points if it meets the criteria)

3. Age ≥20 and ≤65 years (no gender preferences).

4. Patients with signed informed consent.

Exclusion criteria

1.   Patient with symptoms of Perennial allergic rhinitis.

2.   Patients with severe asthma, bronchiectasis, severe hepatic, renal, or cardiac dysfunction, hematological, endocrine disease, and other serious complications.

3.   Patients with nasal diseases (hypertrophic rhinitis, paranasal sinusitis, nasal polyps, deviation of the nasal septum, etc.) or eye diseases that could interfere with judgment of the efficacy of Dellegra Combination Tablets.

4.   Patients with evidence of upper and/or lower respiratory tract inflammation (acute rhinitis, chronic rhinitis, congestive rhinitis, atrophic rhinitis, purulent nasal discharge, sinusitis in the presence of cold-like, etc.) on the day of treatment exposure.

5.   Patients who have taken any of the following medications that may affect the evaluation of Dellegra Combination Tablets (except for the use of topical preparation in which Investigator/sub-investigator judged them not to affect the efficacy evaluation; the treated site is different, etc.):

Within 2 weeks prior to the day of the screening exposure test:

•   Antiallergic drugs, antihistamines (H1 and H2 blockers: oral administration, nose drops, eye drops, injection, and topical use), anticholinergic agents, vasoconstrictor nose drops, antihistamine-containing cold remedies, agents that can be expected to have an anti-allergic/antihistaminic effect (including Chinese medicines and glycyrrhizin), and other agents that are indicated for allergic symptoms (sneezing, rhinorrhea, nasal congestion, and eye itching etc.).

•   Steroids (oral, inhaled, nose drops, eye drops, or topical use), immunosuppressants (oral, topical use, or injected), azole fungicides, and histamine containing gamma-globulin preparations.

•   Azole fungicides, macrolide antibiotics, and preparations containing aluminum hydroxide/magnesium hydroxide.

Within 4 weeks prior to the day of the screening exposure test: Depot steroid preparations.

•   Depot steroid preparations.

Within 6 months prior to the day of the screening exposure test:

•   Steroid injections.

Within 1 year prior to the day of the screening exposure test:

•   Patients receiving maintenance therapy for specific hyposensitization or receiving nonspecific alternative therapy.

6. Patients who are participating in another study or who have previously participated in another study within the previous 6 months prior to the informed consent.

7. Patients who are considered by the Investigator/sub-investigator to be unsuitable for enrollment in the study for any other criterion.

8. Patient with a history of hypersensitivity to antihistamines or antihistaminic agent (fexofenadine HCl is included), and the pseudoephedrine hydrochloride.

9. Patients who are participating in another study or who have previously participated in another study within the previous 6 months prior to the day of the screening exposure test.

10. Patients with severe hypertension or severe coronary artery disease, narrow angle glaucoma, urinary retention, or those who have shown sensitivity to adrenergic agents (manifestations include insomnia dizziness, weakness, tremor, or arrhythmias).

11. Patients receiving monoamine oxidase (MAO) inhibitor therapy or within 2 weeks prior to the day of the screening exposure test.

12. Women who are pregnant, may be pregnant, or currently breast-feeding.

13. Patient with a possibility of revealing drug-induced hepatitis.

- Patients with underlying hepatobiliary disease.

- ALT (alanine aminotransferase) >3 upper limit of normal (ULN).

Study treatments

Investigational medicinal product(s): Dellegra Combination Tablet (Fexofenadine Hydrochloride 30 mg/Pseudoephedrine Hydrochloride 60 mg)

Formulation: Tablet

Route(s) of administration: Oral

Dose regimen: Two Dellegra Combination Tablets (Fexofenadine Hydrochloride 60 mg/Pseudoephedrine Hydrochloride 120 mg) were orally administered once with water.

Duration of treatment: 1 day

Duration of observation: 2 days (Visit 1: one day for screening exposure, Visit 2: 1 day for treatment period exposure) Follow-up assessment for safety (phone call) took place after 3-9 days from the test drug administration (Visit 3).

Visit 1: Patients were exposed to 8,000 grains/m^3 of Japanese cedar pollen for 5 hours in Environmental Exposure Unit.

Visit 2: Three days after Visit 1, patients were exposed to 8,000 grains/m^3 of Japanese cedar pollen for 5 hours. And the patients received 2 tablets of Dellegra 2 hours after the start of the pollen exposure.

Criteria for evaluation:

Efficacy:

- Primary efficacy endpoint: Change in TNSS from 2 hours after antigen exposure (baseline) to 3 hours after intake of Dellegra.

TNSS: Total score of Sneezing, Rhinorrhea, Nasal congestion and Itchy nose

Each symptom was assessed by the patients in the following 5 categories;

1=none (no symptoms); 2=mild (symptoms present but easily tolerated); 3=moderate (awareness of symptoms; bothersome, but tolerable); 4=severe (definite awareness of symptoms; difficult to tolerate, but does not interfere with the activities of daily living), and 5=very severe (difficult to tolerate and interferes with the activities of daily living).

- Secondary efficacy endpoints: Change in TSS, changes in each symptom score, nasal discharge amount, number of sneeze, and patient's impression.

    TSS: Total score of sneezing, rhinorrhea, nasal congestion, itchy nose, itchy eyes, and watery eyes

    Nasal discharge amount: The weight of tissue papers after blowing patient's nose was measured every 1 hour. A difference from the weight before blowing the nose was calculated as nasal discharge amount.

    Number of sneezing: Patients recorded number of sneezing by themselves every 1 hour.

Safety:

Adverse events, clinical laboratory tests (white blood cell count, red blood cell count, hemoglobin, hematocrit and platelet count in blood, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase test (ALP), gamma-glutamyl transpeptodase (GTP), lactate dehydrogenase (LDH), total cholesterol, total bilirubin, total proteins, blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), chloride (Cl), calcium (Ca) and Magnesium (Mg) in serum, protein, glucose, urobilinogen occult blood in urine, and pregnancy test in urine (only for woman), vital signs (body temperature, systolic and diastolic blood pressure, and pulse).

The time frame for TNSS, TSS and each symptom score evaluation was set up prior to exposure; 15, 30, 45, 60, 75, 90, 105, 165, 180, 195, 210, 225, 240, 255, 270, 285, 300 minutes after the exposure start.

The time frame for nasal discharge amount and number of sneezing evaluation was set up for every 1 hour after the exposure start.

Safety was continuously evaluated from written informed consent signature to 3-9 days after the test drug treatment.

Statistical methods:

Sample size determination:

- The sample size was calculated based on the preceding study of Dellegra (Berkowitz et al 2006) and the exposure study using cedar pollen in Japan (Hashiguchi et al 2009, Enomoto et al 2009), the mean change in TNSS score from 2 hours after antigen exposure (baseline) to 3 hours after intake of Dellegra under the cedar pollen exposure condition in Japan and the standard deviation were conservatively set at -2.0 and 3.0, respectively. The target number of subjects was calculated to be N=21 in the case where paired t-test would be performed with the type 1 error at α=0.05 (one-sided) and statistical power of 0.9. For the actual study, the target number of subjects will be set at N=24 additionally including 3 spare subjects in consideration of the drop-out rate of 10% so that the study can include enough subjects to ensure reproducibility of the nasal congestion score.

Berkowitz RB, McCafferty F, Lutz C, et al. Onset of Action of Fexofenadine Hydrochloride 60 mg/Pseudoephedrine Hydrochloride 120 mg in Subjects Aged_>12 Years with Moderate to Severe Seasonal Allergic Rhinitis: A Pooled Analysis of Two Single-Dose, Randomized, Double- Blind, Placebo-Controlled Allergen Exposure Unit Studies. Clinical Therapeutics 2006; 26: 1658-1669.

Hashiguchi K, Tang H, Fujita T, et al. Validation Study of the OHIO Chamber in Patients with Japanese Cedar Pollinosis. Int. Arch Allergy Immunol 2009; 149:141-149.

Enomoto T, Lu H-Q, Yin M, et al. Evaluation of the Efficacy and Safety of Olopatadine and Fexofenadine Compared with Placebo in Japanese Cedar Pollinosis Using an Environmental Exposure Unit. J Investig Allergol Clin Immunol 2009; 19(4): 299-305.

Analysis Population:

- Efficacy analysis population: The primary population was the modified intention-to-treat (mITT) population, which was defined as the subset of all patients referred to the ITT population, who took the Dellegra Combination Tablet, and a change in the TNSS from the baseline can be evaluated.

- Safety analysis population: The safety population was defined as all the patients within the ITT population exposed to the drug.

Efficacy (primary endpoint) Analysis:

In order to evaluate the effect of the Dellegra Combination Tablet on the SAR symptoms, the mean change of the TNSS, the standard deviation, median, minimum, maximum, the two-sided 95% and 90% confidence intervals at 3 hours after treatment of the Dellegra Combination Tablet were calculated, and a paired t-test with the significance level (one-sided) set at 0.05 was performed between baseline (just before treatment of the Dellegra) and 3 hours after treatment with Dellegra.

Efficacy (secondary endpoints) Analysis:

In order to evaluate the severity of the TNSS, the TSS, each symptom scores, amount of nasal discharge and number of sneeze, the mean, the standard deviation, median, minimum, and maximum were calculated at each point.

In order to evaluate the effect of the Dellegra Combination Tablet on the SAR symptoms, the mean changes of the TNSS, the TSS, each symptom scores, amount of nasal discharge and number of sneeze, the two-sided 95% and 90% confidence intervals at each point after treatment of the Dellegra were calculated, and a paired t-test with the significance level (one-sided) set at 0.05 was performed between baseline (just before treatment of the Dellegra) and each point after treatment of the Dellegra.

In order to evaluate the patient's impression, the frequencies and rates of patient's impression classified into the following categories, the mean, the standard deviation, median, minimum and maximum were calculated.

- Greatly improved

- Improved

- Slightly improved

- Not changed

- Slightly worsened

- Worsened

- Greatly worsened

Safety analysis

In order to evaluate the safety of Dellegra Combination Tablets, the frequencies and rates of adverse events (AE) classified into the following categories were calculated in the safety population. And the summary statistics of clinical laboratory tests and vital signs were also calculated.

- Adverse event (AE)

- Adverse drug reaction (only in the treatment period)

- Death or Serious adverse event (SAE)

- Death or Serious adverse drug reaction (only in the treatment period)

- Adverse event with special interest (AESI) : ALT >3 ULN, Pregnancy and Over dose

Summary:

Population characteristics:

24 patients out of 39 screened in this study were included. All of the patients were administered with the test drug and completed the treatment period. The mITT group for efficacy analysis and the safety evaluation group were determined as analysis subject and no cases were excluded.

Demography characteristics of mITT group: the mean age ± SD of the registered 24 patients was 41.7 ± 9.7 years old, and 18 out of the 24 (75.0%) were women.

Disease characteristics: The mean values of TNSS and TSS at the baseline (2 hours after antigen exposure) were 9.1 ± 2.8 and 12.3 ± 3.4; the median values were 8.5 and 12.0, respectively.

Efficacy results:

Primary endpoint: The TNSS at 3 hours after test drug administration significantly decreased from baseline (just before test drug administration) ($p < 0.0001$).

Secondary endpoints: Regarding the mean values of TNSS, TSS, symptom scores, nasal discharge amount, and number of sneeze at each point, TNSS and TSS showed a significant decrease at 30 minutes after test drug administration (150 minutes after the start of exposure [$p < 0.0001$]). Symptom scores except sneezing, which constructs the 2 scores also showed similar changes, and the mean value of nasal obstruction showed a decrease at 15 minutes after test drug administration (135 minutes after the start of exposure). Three hours after test drug administration (5 hours after the start of exposure), the mean values of symptom scores were in the range of 0.2-1.3, and the mean values of nasal discharge amount and sneezing numbers were 2.63 g and 1.2 times each. The symptoms generally improved.

The mean values of change in regards to each point of TNSS, TSS, symptom scores, nasal discharge amount, and sneeze numbers between the baseline (2 hours after the start of exposure) and 3 hours after test drug administration (5 hours after the start of exposure) also showed a decrease from 30 minutes after test drug administration (150 minutes after the start of exposure). These effects were continued up to the end of observation (3 hours after test drug administration, 5 hours after the start of exposure) and statistically significant at almost all points ($p < 0.05$).

Patient's perception: After completion of treatment period, most of the patients out of 24 showed positive response. "1. Greatly improved" 8 patients (33.3%); "2. Improved" 8 patients (33.3%); "3. Slightly improved" 7 patients (29.2%).

Safety results:

Neither SAE nor AESI was observed in this study.

During the treatment period, 2 patients out of 24 (8.3%) reported sleepiness. It was reported by the study Investigator/physician as related to the study drug, though the symptom improved without treatment within the onset day. Therefore, the severity of this AE was determined as mild by the Investigator.

Clinical laboratory tests and Vital signs: No clinically concerned change was recognized both before exposure during screening period and after exposure during treatment period.

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