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Sponsor / Company: Sanofi **Drug substance(s):** fexofenadine HCl - pseudoephedrine HCl combination	**Study Identifiers:** NCT01306721 **Study code:** EFC11243
Title of the study: A randomized, double blind, parallel group study for assessing the efficacy and safety of a twice-daily fexofenadine HCl 60 mg - pseudoephedrine HCl 60 mg combination or fexofenadine HCl 60 mg - pseudoephedrine HCl 120 mg combination versus Allegra® 60 mg in patients with seasonal allergic rhinitis.	
Study center(s): 3 study sites in Japan	
Study period: Date first patient enrolled: 03/Mar/2011 Date last patient completed: 14/Apr/2011	
Phase of development: III	

Objectives:

The primary objective of this study is to evaluate the efficacy on the nasal congestion of a twice-daily fexofenadine HCl 60 mg - pseudoephedrine HCl 60 mg combination (FEX60/PSE60) and fexofenadine HCl 60 mg - pseudoephedrine HCl 120 mg combination (FEX60/PSE120) versus fexofenadine HCl 60 mg (FEX60) in patients with seasonal allergic rhinitis (SAR).

The key secondary objectives of this study are:
・ To evaluate the efficacy of a twice-daily FEX60/PSE60 and FEX60/PSE120 versus FEX60 on nasal symptoms (sneezing, rhinorrhea, and nasal congestion), eye symptom, and daily activity impairment;
・ To assess the safety of a twice-daily FEX60/PSE60 and FEX60/PSE120 versus FEX60.

Methodology:

This is a multicenter, randomized, double-blind, parallel group, fexofenadine HCl 60 mg controlled study.

After a screening phase, subjects were centrally randomized (utilizing permuted block randomization schedule) via IVRS in a 1:1:1 ratio to one of the 3 treatment groups and treated each active and placebo tablets by double-blind manner for approximately 2 weeks. Treatment groups are composed of:
・ FEX60 group
・ FEX60/PSE60 group
・ FEX60/PSE120 group.

Number of patient**:**	Planned: 520
	Randomized: 520
	Treated: 520
Evaluated:	Efficacy: 520
	Safety: 520
	Pharmacokinetics: NA

Diagnosis and criteria for inclusion:

Patients with seasonal allergic rhinitis (SAR).

Study treatments

Investigational medicinal product(s):

Formulation:
FEX60 group; fexofenadine HCl 60 mg mono tablet,
FEX60/PSE60 group; fexofenadine HCl 60 mg - pseudoephedrine HCl 60 mg combination tablet,
FEX60/PSE120 group; fexofenadine HCl 60 mg - pseudoephedrine HCl 120 mg combination tablet

Route(s) of administration: Oral

Dose regimen: Twice-daily

Noninvestigational medicinal product(s): NA

Duration of treatment: 14 days

Duration of observation: 17 days

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint is the change from baseline (the last 3 days during the placebo lead-in period) to treatment period (Day 2 to Day 14) in average nasal congestion scores.

The secondary efficacy endpoints are:

- Change in the nasal congestion score.
- Changes in the total score of 4 symptoms and it's change from baseline.
- Changes in the each symptom (sneezing, rhinorrhea and eye symptom) score and the daily activity impairment score and it's change from baseline.
- Nasal findings (Swelling of the inferior turbinate mucosa, color of the inferior turbinate mucosa, amount of watery mucus, properties of the nasal mucus).
- Patient's impression.

Safety:

- Adverse events, laboratory findings, vital signs.

Pharmacokinetics: NA

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: NA

Statistical methods:

Primary population is mITT (modified intention-to-treat) population which is defined as a subset of all randomized patients referred as ITT population, who take at least one investigational product, and have available change from baseline in nasal congestion score. Safety population is defined as all exposed patients within ITT population.

The primary efficacy endpoint, change from baseline to treatment period in average nasal congestion score ([treatment period] − [baseline]) was analyzed by analysis of covariance (ANCOVA) model including treatment group as independent variable, and average nasal congestion score at baseline and region (Tokyo, Osaka) as covariates. In the model, the mean change from baseline in average nasal congestion score was compared between FEX60/PSE60 group and FEX60 group, FEX60/PSE120 group and FEX60 group by using Dunnett's method with significance level of two sided 5% for adjusting multiplicity due to two comparisons. Two sided 95% confidence intervals (CIs) for each treatment difference (FEX60/PSE60 − FEX60, FEX60/PSE120 − FEX60) corresponding to Dunnett's method was provided. In the analysis, no imputation was made for patients whose endpoint is missing.

Using this ANCOVA model, the followings were provided:

- Point estimate and standard error of least square mean (LS mean) by treatment group;
- Two sided 95% CI of LS mean by treatment group;
- Point estimate and standard error of least square mean (LS mean) for each treatment difference (FEX60/PSE60 − FEX60, FEX60/PSE120 − FEX60);

Average nasal congestion scores at baseline, treatment period, and its change from baseline to treatment period were summarized by treatment group using descriptive statistics (the number of observations, mean, SD, median, minimum, and maximum).

For each of sneezing, rhinorrhea, eye symptom, total score of 4 symptoms, and daily activity impairment score, change from baseline to treatment period in average score were analyzed in the same manner as primary endpoint. Change in the each symptom and in total score of 4 symptoms was presented in time profile plots over placebo lead-in period (D-3 to D-1) and treatment period (D2 to D14) by treatment group.

For safety endpoints, the followings were performed using safety population:
- Treatment emergent adverse events (TEAEs) were summarized by treatment.
- Individual clinical laboratory data, vital signs were summarized, listed and flagged for potentially clinically significant abnormalities (PCSAs) and for lower and upper clinical laboratory limits.

Summary:

Population characteristics:

Out of the 734 patients screened, 520 (70.8%) patients were randomized to one of the three treatment groups (173 in the FEX60 group, 173 in the FEX60/PSE60 group, 174 in the FEX60/PSE120 group) in 3 centers in Japan. All 520 randomized patients were exposed to double-blind treatment. No patient was excluded from mITT population for efficacy analysis or from safety population.

Out of the 520 randomized and treated patients, 509 patients were completed 2 weeks double-blind treatment. Totally 11 patients were prematurely discontinued from study treatment, 2 (1.2%) in the FEX60 group, 3 (1.7%) in the FEX60/PSE60 group, and 6 (3.4%) in the FEX60/PSE120 group. The most common reason for treatment discontinuation was “other reason”. The breakdown of the other reason were, 2 patients in the FEX60/PSE120 group could not continue the study because they had escaped far from the sites in Tokyo after the major earthquake, each 1 patient in all the 3 groups could not keep the scheduled visit by their business reason, and 1 patient in the FEX60/PSE60 group used prohibited concomitant medication. 2 patients (1.1%) in the FEX60/PSE120 group and 1 (0.6%) patient in the FEX60/PSE60 group discontinued the treatment with the reason of adverse event. 1 patient (0.6%) in the FEX60 group and 1 (0.6%) patient in the FEX60/PSE120 group discontinued the treatment with the reason of lack of efficacy.

The distributions of demographic and baseline information were generally similar between three treatment groups. The number of pediatric patients aged lower than 16 years old were totally 55 (10.6%). The mean nasal congestion score at baseline was 2.43 in overall.

Efficacy results:

Based on the primary analysis, the FEX60/PSE120 group demonstrated statistically significant reduction of nasal congestion score from baseline to treatment period compared to the FEX60 group (LS mean difference = −0.14; adjusted p-value = 0.0201). On the other hand, the FEX60/PSE60 group showed a reduction of nasal congestion score, however not statistically significant compared to the FEX60 group (LS mean difference = −0.08; adjusted p-value = 0.2993).

The mean total score changes from baseline in FEX60/PSE60 group (−1.21) and FEX60/PSE120 group (−1.27) are both greater than that in FEX60 group (−0.86), indicating the numerical improvement of total score changes. However those reductions were not significant compared to FEX60 group (p-value = 0.3094 and 0.1843, respectively).

On each symptom score of sneezing, rhinorrhea and eye symptom, and on daily activity impairment score, the mean score changes from baseline in FEX60 group were as the similar level as those in FEX60/PSE60 group and FEX60/PSE120 group. There were no statistically significant differences in the changes of these secondary endpoints compared to FEX60 group.

Safety results:

10 (5.8 %) patients in FEX60/PSE60 group and 8 (4.6 %) patients in FEX60/PSE120 group reported TEAEs, while 4 (2.3 %) patients reported TEAEs in FEX60 group. Among those, 1 (0.6 %) in FEX60/PSE60 group, 4 (2.3 %) in FEX60/PSE120 group, and 1 (0.6 %) in FEX60 group were the adverse drug reactions (ADR). The most frequently reported TEAE was nasopharyngitis, 4 (2.3 %) in FEX60/PSE60 group, 2 (1.1 %) in FEX60/PSE120 group and 1 (0.6 %) in FEX60 group. The second most frequently reported TEAE was headache, 2 (1.1 %) in FEX60/PSE120 group and 2 (1.2 %) in FEX60 group.

1 (0.6 %) patient in FEX60/PSE60 group and 2 (1.1 %) patients in FEX60/PSE120 group reported TEAEs leading to permanent treatment discontinuation. Among those, 1 (0.6 %) in FEX60/PSE120 group was the ADR. Nasopharyngitis (1 in FEX60/PSE60 group, 1 in FEX60/PSE120 group) and rash generalized (1 in FEX60/PSE120 group) were the TEAEs of the reason lead treatment discontinuation. Rash generalized (1 in FEX60/PSE120 group) was the ADR of the reason lead treatment discontinuation. The rash was occurred in 1 week after the IP treatment initiation and the event continued for 10 days. The patient stopped IP administration on the third day of the event.

There were totally 6 patients reported ADRs. 4 patients were in FEX60/PSE120 group. The most frequently reported ADR was headache, 2 (1.1 %) in FEX60/PSE120 group and 1 (0.6 %) in FEX60 group. Although each incidence was small, there was each one ADR of rash generated (0.6%), fatigue (0.6%), thirst (0.6%) occurred only in FEX60/PSE120 group which made the reported numbers and incidence of ADRs in FEX60/PSE120 group higher than the other groups. The rash (0.6%) was also the one ADR occurred only in FEX60/PSE60 group.

There were no SAE, and no TEAE leading to death.

Laboratory tests and vital signs were evaluated with PCSA criteria. 2 patients in FEX60/PSE60 group, 2 patient in FEX60/PSE120 group met hemoglobin criteria and 2 patients in FEX60/PSE60 group, 4 patient in FEX60/PSE120 group met hematocrit criteria. The clinical meaning of these results are very limited to see the change from baseline.

Pharmacokinetic results: NA

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