*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

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| **Sponsor / Company:** Sanofi<br>**Drug substance(s):** fexofenadine HCl | **Study Identifiers:** NCT01244217<br>**Study code:** SFY10717 |

**Title of the study:**

An open-label, uncontrolled 4-week study to assess the safety, efficacy and pharmacokinetics of Allegra® (dry syrup formulation) 15 mg or 30 mg twice daily in pediatric patients with perennial allergic rhinitis.

**Study center(s):** 15 study centers in Japan

**Study period:**

Date first patient enrolled: 27/Oct/2010

Date last subject/patient completed: 13/Aug/2011

**Phase of development:** III

**Objectives:**

The primary objective of this study is to evaluate the safety of fexofenadine HCl (dry syrup formulation) when administered for 4 weeks at doses of 15 mg or 30 mg twice daily to pediatric patients 6 months through 11 years of age with perennial allergic rhinitis (PAR).

The key secondary objectives of this study are:
- To evaluate the long-term safety of fexofenadine HCl (dry syrup formulation) when administered for 12 weeks at doses of 15 mg or 30 mg twice daily to pediatric patients with PAR.
- To evaluate the efficacy of fexofenadine HCl (dry syrup formulation) when administered for 4 weeks at doses of 15 mg or 30 mg twice daily to pediatric patients with PAR.
- To characterize population pharmacokinetics of fexofenadine in Japanese pediatric (6 months through 11 years of age) patients, including covariate effects, to facilitate subsequent modeling and simulation activities in support of the use of fexofenadine in Japanese patients with perennial allergic rhinitis (PAR) or with atopic dermatitis (AD).

**Methodology:**

This is an open-label, uncontrolled 4-weeks study. This study comprises 4 phases: an up-to 9-days screening phase, a main 4-weeks treatment phase, an 8-weeks extension phase, and an up-to 5- days post-treatment phase.

Patients 6 months to less than 2 years of age or body weight below 10.5 kg take 15 mg fexofenadine HCl with water twice daily. Patients 2 through 11 years of age (unless the body weight below 10.5 kg) take 30 mg fexofenadine HCl with water twice daily.

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| **Number of** subject/patients**:** | Planned: 100 |
| | Randomized: 109 |
| | Treated: 109 |
| **Evaluated:** | Efficacy: 109 |
| | Safety: 109 |
| | Pharmacokinetics: 108 |

**Diagnosis and criteria for inclusion:**

Pediatric patients 6 months through 11 years of age with perennial allergic rhinitis (PAR).

**Study treatments**

**Investigational medicinal product(s):**

Formulation: Fexofenadine hydrochloride (HCl) dry syrup formulation;
- One sachet containing 15 mg fexofenadine HCl
- One sachet containing 30 mg fexofenadine HCl

Route(s) of administration: Oral

Dose regimen: Patients 6 months to less than 2 years of age or body weight below 10.5 kg take 15 mg fexofenadine HCl with water twice daily. Patients 2 through 11 years of age (unless the body weight below 10.5 kg) take 30 mg fexofenadine HCl with water twice daily.

**Noninvestigational medicinal product(s):** NA

**Duration of treatment:** 12 weeks

**Duration of observation:** 14 weeks

**Criteria for evaluation:**

Efficacy: Efficacy over 4 weeks of treatment:

・ Changes from baseline (Day -1) in total and individual nasal symptom scores on patient diary over full observation period (Day 2 to Day 28) in patients 2 through 11 years of age

・ Changes from baseline (Day -1) in total and individual nasal symptom scores on patient diary by each week in patients 2 through 11 years of age

・ Time-course changes in total and individual nasal symptom scores on patient diary in patients 2 through 11 years of age

・ Changes from baseline (Day 1) in total and individual nasal symptom severity scores assessed by investigator or sub-investigator at week 2 and week 4 (or discontinuation) in patients 2 through 11 years of age

・ Nasal findings at Day 1, week 2, and week 4 (or discontinuation)

・ Patient's or guardian's impression at week 2 and week 4 (or discontinuation)

Safety: Primary endpoint is the safety over 4 weeks of treatment on the adverse events and laboratory findings. Secondary endpoint is the overall safety over 12 weeks of treatment on the adverse events and laboratory findings.

Pharmacokinetics: The population PK analysis with the data from SFY10717 and SFY10718 studies.

**Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:**

Two PK sampling have been performed for each patient: one at week 4 (peak) and one at week 12 (trough).

**Statistical methods:**

The primary population is safety population defined as all treated patients. The secondary population is modified Intention-to-treat (mITT) population defined as all registered patients whose total scores of 3 nasal symptoms for patients aged 2 years and older or nasal findings for patients aged <2 years both baseline and post treatment are available.

Using safety population, treatment emergent adverse events (TEAE) occurring up to 4 weeks after registration will be summarized overall, by age strata (<2 years, 2 to <7 years, and >=7 years) and dose. Clinically significant abnormalities for laboratory findings will be summarized overall, by age strata (<2 years, 2 to <7 years, and >=7 years) and dose.

The secondary endpoints will be summarized in the same manner as primary analysis using safety population for safety endpoints, and mITT population for efficacy endpoints respectively.

The PopPK analysis was performed with the NONMEM computer program (version 7.1.2) running on a LINUX cluster of multi-processor computers. All runs were performed using the Stochastic Approximation Expectation-Maximization method. Data from SFY10717 study (108 patients, 206 concentration-time points) and from SFY10718 study (102 patients, 175 concentration-time points) were included in the current PopPK analysis. Data from POH0199 study (305 patients, 699 concentrations-time points), a previous PopPK analysis, were added to these 210 patients (381 PK samples).

**Summary:**


Population characteristics:

All 109 registered patients completed 4 weeks main treatment period. 102 patients (93.6 %) agreed to enter the additional 8 weeks extension treatment phase. For the rest of 7 patients, the reason not entered the extension phase were, patient's refusal of further blood sampling (n=3), not effective (n=2), due to Adverse Drug Reaction (ADR) (n=1), or couldn't make next study visit scheduling (n=1).

1 patient prematurely discontinued the study during the extension treatment phase. The reason of discontinuation in detail was because of the parent's burden to continue writing the diary.

Number of patients in age strata <2 years was 7 (6.4 %) as smallest and was 51 (46.8 %) for both in 2 to <7 years and in >=7 years. The patients mean age was 6.2 years and the median was 6.0 years. There was no major bias between each age strata in the nasal symptom scores and nasal findings at baseline. There were 5 patients with the body weight >10.5 kg in age strata <2 years, and no patient with the body weight <=10.5 kg in the age strata 2 to <7 years.

Efficacy results:

Overall, the 4 weeks treatment of fexofenadine dry syrup made a decrease of the total nasal symptoms score from the baseline. The mean decrease in the total symptoms score was -1.78. The mean decrease in the each symptom score of sneezing, rhinorrhea and nasal congestion was -0.45, -0.89 and -0.44, respectively. The similar treatment effect on nasal symptoms score was observed in each age strata. The weekly changes of the nasal symptoms score indicated that the major decrease was observed in week 1 and continued the same score level or less during the following weeks. The degree of nasal symptoms score decrease and the trend in weekly changes were as similar as past controlled Japanese pediatric O3101 study in age 7 to 15 years.

The proportion of the impression after 4 weeks fexofenadine dry syrup treatment was "Slightly better" (36.7%), "Better" (35.8%), "Much better" (14.7%), "Unchanged" (11.9%) and "Worse" (0.9%). The impression trends were mostly similar in the each age strata.

Safety results:

Primary safety over 4 weeks of treatment:

2 (28.6 %) in patients <2 years, 39 (76.5 %) in patients 2 to <7 years and 28 (54.9%) in patients >=7 years were reported TEAEs. Among those, one “Somnolence” in patients 2 to <7 years was an ADR. There was no treatment emergent serious AE and TEAE leading to permanent treatment discontinuation.
One TEAE “Somnolence” in patient 2 to <7 years was considered related to Investigational Product (IP) by the investigator. 4-year-old male patient (392010015) received IP. The patient developed “Somnolence” on day 1, but the IP was continued by the end of the main treatment phase. The patient refused to enter the extension phase. After completion of the 4 weeks (32 days) main treatment phase, the patient recovered from the event on day 33.
Most frequently reported TEAE over 4 weeks of treatment was “Nasopharyngitis” and the incidence was 31.4% in patients 2 to <7 years and 25.5% in patients >=7 years, respectively. There was no TEAE more than 1 event in patients <2 years over 4 weeks of treatment.

2 patients met Potentially Clinically Significant Abnormalities (PCSA) for hemoglobin and 14 patients met PCSA for hematocrit. The values of hemoglobin and hematocrit in all cases were within normal range or became within normal range during the treatment and the changes of value in all cases were limited.
1 patient met PCSA, but the value was within normal range.
The percentage of patients with 30% or more change of creatinine level from baseline over 4 weeks of treatment was 1.8 % (2 of 109 patients). The clinical meaning of this result is limited to see that the all values which met PCSA were below the normal range.

Secondary safety over 12 weeks of treatment:

6 (85.7 %) in patients <2 years, 46 (90.2 %) in patients 2 to <7 years and 38 (74.5%) in patients >=7 years were reported TEAEs. Among those, one “Somnolence” in patients 2 to <7 years was an ADR, the same event mentioned above. There was no SAE and TEAE leading to permanent treatment discontinuation.
Most frequently reported TEAE over 12 weeks of treatment was “Nasopharyngitis” and the incidence were 57.1% in patients <2 years, 51.0% in patients 2 to <7 years and 43.1% in patients >=7 years, respectively.
One ADR “Somnolence” in patient 2 to <7 years was the same event mentioned above. No further ADR was reported.

2 patients met PCSA for hemoglobin and 25 patients met PCSA for hematocrit. The values of hemoglobin and hematocrit in all cases were within normal range or became within normal range during the treatment and the changes of value in all cases were limited.
2 patients met PCSA. The value was within normal range in one patient (the same event mentioned above) and another one was considered to be caused by influenza by the investigator.
The percentage of patients with 30% or more change of creatinine level from baseline over 12 weeks of treatment was 2.8 % (3 of 109 patients). The clinical meaning of this result is limited to see that the all values which met PCSA were below the normal range.

Pharmacokinetic results :

A two-compartment population PK model was developed and validated with data from patients treated with fexofenadine included in SFY10717 and SFY10718 studies. This model showed good agreement between predicted and observed plasma concentrations of fexofenadine.

Inter-patient variability in elimination clearance, central volume, intercompartmental clearance and peripheral volume in patients were about 28, 112, 41 and 59%, respectively. The residual (intraindividual) variability was about 37%.

Exposure variables observed in infants and in 2 to 7 year-old children were similar to those observed in adolescents and in adults, but $C_{maxSS}$, $C_{troughSS}$ and $AUC_{0\text{-}24SS}$ were approximately 35% lower in 7 to 12 year-old children.

**Issue date:** 24 January 2013