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Sponsor / Company: Sanofi **Drug substance(s):** fexofenadine HCl	**Study Identifiers:** NCT01244230 **Study code:** SFY10718

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 atopic dermatitis.

Study center(s): 13 study centers in Japan

Study period:

Date first patient enrolled: 09/Nov/2010

Date last patient completed: 08/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 atopic dermatitis (AD).

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 AD.
- 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 AD
- 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.

Number of subjects/patients	Planned: 100
	Randomized: 103
	Treated: 103
Evaluated:	Efficacy: 103
	Safety: 103
	Pharmacokinetics: 102

Diagnosis and criteria for inclusion:

Pediatric patients 6 months through 11 years of age with atopic dermatitis (AD).

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):

Formulation: 0.1% hydrocortisone butyrate ointment;

Route(s) of administration: Topical application to the skin

Dose regimen: Mandatory background therapy as a standard topical treatment, 0.1% hydrocortisone butyrate ointment is applied to the tested sites (except for the face and scalp) by simple application method in screening phase and main treatment phase (not specified in extension phase).

Duration of treatment: 12 weeks

Duration of observation: 14 weeks

Criteria for evaluation:

Efficacy: Efficacy over 4 weeks of treatment (the tested sites except for the face and scalp):

・ Changes from baseline in main itching scores on patient diary over full observation period (Day 2 to Day 28) (baseline = mean score of main itching scores for the last consecutive three days before the day of registration)

・ Changes from baseline in main itching scores on patient diary by each week

・ Time-course changes in main itching scores on patient diary

・ Changes from baseline (Day 1) in pruritus intensity scores assessed by investigator or sub-investigator at week 2 and week 4 (or discontinuation)

・ Conditions of rashes 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 the safety population defined as all treated patients. The secondary population is modified Intention-to-treat (mITT) population defined as all registered patients whose main itching scores 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 103 registered patients completed 4 weeks main treatment period. 78 patients (75.7 %) agreed to enter the additional 8 weeks extension treatment phase. For the rest of 25 patients, the reason not entered the extension phase were, no need because relieved from itching (n=11), not effective than expected (n=4), intend to prioritize the treatment for concomitant disease or Serious Adverse Events (SAE) (n=3), patient's refusal of further study procedure such as blood sampling (n=3), due to parent's burden to administer the drug (n=2), or parent's move etc. (n=2).

1 patient prematurely discontinued the study during the extension treatment phase. The reason of discontinuation in detail was because the patient and mother moved far from the hospital after the major earthquake.

Number of patients in age criteria <2 years was 49 (47.6 %) as largest and was followed by 31 patients (30.1 %) in 2 to <7 years and 23 patients (22.3 %) in >=7 years. The patients mean age was 3.4 years and the median was 2.0 years. There was no major bias between each age criteria in the main itching score, pruritus intensity score and condition of rashes at baseline. There were 9 patients with the body weight >10.5 kg in age criteria <2 years, and 1 patient with the body weight <=10.5 kg in the age criteria 2 to <7 years.

Efficacy results:

Overall, the 4 weeks treatment of fexofenadine dry syrup made a decrease of the patients' itching score from the baseline. The mean decrease in the itching score was -0.46. The similar treatment effect on main itching score was observed in each age criteria. The weekly changes of the main itching score indicated that the mean value was gradually decreased from week 1 to week 3, and the same score level was continued in week 4 as in week 3. This trend was as same as past controlled Japanese pediatric O3102 study in age 7 to 15 years.

The pruritus intensity score and the condition of rashes were assessed by the investigator. The mean change in pruritus intensity score from the baseline was -0.8, much more decrease than the main itching score which indicating the medical observation such as scratch mark supported the treatment effect additionally to the patient's score decrease. The pruritus intensity score gradually decreased by each 2 weeks, and showed a same efficacy trend within each age criteria. The condition of rashes was evaluated with the severity of the rash in atopic dermatitis. The fexofenadine treatment made a decrease of severity score of rashes from the baseline. The mean decrease in the severity score was -0.4. The severity was decreased gradually by each 2 weeks, and showed a same trend of the change within each age criteria.

The major proportion of the impression after 4 weeks fexofenadine dry syrup treatment was "Better" and "Slightly better" with the percentage of 32.0% for both, followed by "Much better" with the percentage of 25.2%. The impression trends were mostly similar in the each age criteria.

Safety results:

Primary safety over 4 weeks of treatment:

30 (61.2 %) in patients <2 years, 22 (71.0 %) in patients 2 to <7 years and 6 (26.1%) in patients >=7 years were reported TEAEs. Among those, one "White blood cell decreased" in patients >=7 years was an Adverse Drug Reaction (ADR). There was one serious AE "Pneumonia" in patients <2 years, but no TEAE leading to permanent treatment discontinuation.
One TEAE "White blood cell decreased" (WBC) in patient >=7 years was considered related to Investigational Product (IP) by the investigator. 8-year-old male patient (392002003) received IP. The patient developed "Gastroenteritis", on day 23 and "White blood cell decreased" on day 31. Laboratory results showed decreased WBC at 2000/MCL (baseline value: 7900/MCL, normal range: 4100-13700/MCL) on the same day. IP was continued and the patient recovered from "White blood cell decreased" on day 57 when the laboratory result showed WBC at 9300/MCL.
One SAE "Pneumonia" in patient <2 years was reported. 1-year-old male patient (392008006) received IP. The patient developed "Pneumonia" on day 26. On day 31 the patient was hospitalized for treatment. On day 36, the patient recovered from the event. Relationship to IP of the event was denied by the investigator.
Most frequently reported TEAE over 4 weeks of treatment was "Nasopharyngitis" (24.5%) in patients <2 years, "Upper respiratory tract inflammation" (12.9%) and "Vomiting" (12.9%) in patients 2 to <7 years and "Nasopharyngitis" (17.4%) in patients >=7 years, respectively.

13 patients met Potentially Clinically Significant Abnormalities (PCSA) for hematocrit. The values of hematocrit in all cases were within normal range and the changes of value in all cases were limited.
2 patient met PCSA. One case with decrease of WBC was considered as an ADR but another case with increase of WBC was not considered as TEAE by the investigators.
The percentage of patients with 30% or more change of creatinine level from baseline over 4 weeks of treatment was 10.4 % (5 of 48 patients) in patients <2 years, 0% (0 of 31) in patient 2 to <7 years and 4.3 % (1 of 23 patients) in patient >=7 years. The clinical meaning of this result is limited to see that the values of creatinine in all cases including that of PCSA were below the normal range.
1 patient met PCSA for Alanine Amino Transferase (ALT) and aspartate aminotransferase (AST). Increase of ALT and AST were considered as a symptom of TEAE "Upper respiratory tract inflammation" by the investigator.

Secondary safety over 12 weeks of treatment:

38 (77.6 %) in patients <2 years, 28 (90.3 %) in patients 2 to <7 years and 10 (43.5%) in patients >=7 years were reported TEAEs. Among those, one "White blood cell decreased" in patients >=7 years was an ADR, the same event mentioned above. There was one SAE "Pneumonia" in patients <2 years, the same event also mentioned above. No further SAE was reported. There was no TEAE leading to permanent treatment discontinuation.
Most frequently reported TEAE over 12 weeks of treatment was "Nasopharyngitis" (36.7%) in patients <2 years, "Upper respiratory tract inflammation" (25.8%) in patients 2 to <7 years and "Nasopharyngitis" (17.4%) in patients >=7 years, respectively.
There was one ADR "White blood cell decreased" in patient >=7 years, the same event mentioned above. No further ADR was reported.

15 patients met PCSA for hematocrit, but the values of hematocrit of all cases were within normal range and the change of values in all cases were limited.
Regarding the number of patients with PCSA for White blood cells (WBC) over 12 weeks of treatment, 2 patients met PCSA, the same events mentioned above. No further PCSA was reported.
The percentage of patients with 30% or more change of creatinine level from baseline over 12 weeks of treatment was 18.4% (9 of 49 patients) in patients <2 years , 0% (0 of 31) in patient 2 to <7 years and 4.3% (1 of 23 patients) in patient >=7 years. The clinical meaning of this result is limited to see that the values of creatinine in all cases including that of PCSA were below the normal range.
1 patient met PCSA for ALT and AST, the same events mentioned above. No further PCSA was reported regarding liver function.

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 CmaxSS, CtroughSS and AUC0-24SS were approximately 35% lower in 7 to 12 year-old children.

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