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Sponsor: Sanofi **Drug substance(s):** M016455	**Study Identifiers:** NCT02401191 **Study code:** FEXHYL07477
Title of the study: M016455 PO Open-label Clinical Study	
Study center(s): 3 sites in Japan	
Study period: Date first subject enrolled: 06/Mar/2015 Date last subject completed: 02/Jul/2015	
Phase of development: Phase 3	
Objectives: Primary objective: To assess the safety of twice-daily fexofenadine 60 mg/phenylephrine 10 mg (FEX60/PE10) combination tablet with allergic rhinitis. Secondary objective: To evaluate the effectiveness of a twice daily FEX60/PE10 combination tablet on nasal symptoms (sneezing, rhinorrhea, and nasal congestion) and daily activity impairment.	
Methodology: This study evaluated the safety and the effectiveness on nasal symptoms (sneezing, rhinorrhea, and nasal congestion) and daily activity impairment of a twice-daily FEX60/PE10 tablet.	
Number of subjects:	Planned: Approximately 105 subjects Treated: 105 subjects Completed: 104 subjects
Evaluated:	Efficacy: Modified Intent-to-Treat (mITT) population: 105 subjects Safety: Safety analysis set: 105 subjects

Diagnosis and criteria for inclusion:

Inclusion criteria

1. Patients with seasonal or perennial allergic rhinitis:
   - Patients with a history of seasonal or perennial allergic rhinitis for at least 1 year.
   - Patients confirmed by positive skin prick test to out or indoor allergens (wheal ≥3mm compared to control [diluent]) or positive specific IgE Antibody test* (ie, radioallergosorbent [RAST],etc.) on the day of provisional inclusion in the trial.

   *Data of tests performed within 12 months prior to the day of inclusion in the trial, is available. Over Class 2 in RAST is needed for inclusion.

   - Patients who meet the criteria of symptom score:
     - Nasal congestion score for last 3 days of the screening period is continuously 2 or more and not 4.
     - Score of sneezing or rhinorrhea is continuously 2 or more and not 4 throughout the last 3 days of the screening period.

2. Patients aged 15 years or older, with no restriction on gender.
3. Patients with written informed consent (The legal representative of subjects aged less than 20 years old also had to give written consent).
4. Girls with childbearing potential must have a negative pregnancy test performed within seven days prior to the start of study drug and adequate contraception during the study.
5. Outpatients.

Exclusion criteria

1. Patients with nasal diseases (hypertrophic rhinitis, paranasal sinusitis, nasal polyps, acute rhinitis, deviation of the nasal septum, etc.) that could interfere with judgment of the efficacy of the investigational product (IP) and patients developing cold-like symptoms during screening period.
2. Patients with severe asthma, bronchiectasis, severe hepatic, renal, or cardiac dysfunction, hematological, endocrine disease, and other serious complications.
3. Patients with unstable medical conditions like diabetes mellitus, heart failure, hepatic and renal impairment.
4. Patients with a history of epilepsy or with organic brain disease, which may cause epilepsy.
5. Patients who have taken any of the following medications that may affect the evaluation of the IP, Patients using intranasal or systemic decongestants if they are not stopped 3 days before the inclusion visit.

Within 1 week prior to the day of registration:

- Intranasal or oral: Antiallergic drugs, antihistamines, anticholinergic agents, vasoconstrictor, antihistamine-containing cold remedies, agents that can be expected to have an antiallergic/antihistaminic effect (including Chinese medicines and glycyrrhizin), and other agents that are indicated for allergic symptoms (sneezing, rhinorrhea, nasal congestion, etc.);
- Agents that may affect the blood concentration of FEX (macrolide antibiotics, azole fungicides, and preparations containing aluminum hydroxide / magnesium hydroxide).

Within 2 week prior to the day of registration: Steroids, immunosuppressant, and nonspecific alternative therapy (histamine-containing gamma-globulin preparations etc.).

Within 4 week prior to the day of registration:

- Oral, nasal, inhaled corticosteroids;
- Depot steroid preparations.

6. Patients using sodium cromoglycate/nedocromil or leukotriene modifiers if they are not stopped 14 days before the inclusion.
7. Patients under immunotherapy if specific immunotherapy has been started or dose changed approximately 1 month preceding enrolment in the study, (doses should maintain the same dose throughout the trial).
8. Patients suffering from Upper Respiratory Tract Infection, sinusitis or acute otitis media within 30 days before the inclusion visit.
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 registration.
10. Patients who are considered by the Investigator/Sub-investigator to be unsuitable for enrolment in the study for any other criterion or previously participated in this study.
11. Patients with a history of hypersensitivity to antihistamines or antiallergic agents including FEX.
12. 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).
13. Patients receiving monoamine oxidase (MAO) inhibitor therapy or within 2 weeks prior to the day of registration.
14. Women who are pregnant, possibly pregnant, or breast-feeding.
15. Patients with underlying hepatobiliary disease.

Study treatments

Investigational medicinal product(s): Fixed Dose Combination drug product containing 60 mg of fexofenadine hydrochloride and 10 mg of phenylephrine hydrochloride (FEX 60 mg/PE 10 mg tablet)

Formulation: Tablets

Route(s) of administration: Oral

Dose regimen: One tablet of FEX 60 mg/PE 10 mg administered in the morning and evening

Duration of treatment: Treatment Period (2 weeks [± 2 days])

On the first day of the Treatment Period, subjects started study treatment from the evening dose. On the last day of the Treatment Period, subjects received the morning dose and then visited study sites.

Duration of observation: Study participation began with signature of written informed consent.

The observation period after the first dose of study drug in this study consisted of the following 3 Periods with a duration of 25 days (up to 40 days):

- Screening Period: 1 week (± 2 days)*
  From 7 (± 2) days before Visit 3 (Day 1) through Visit 3 (Day 1)
- Treatment Period: 2 weeks (± 2 days)
  From Visit 3 (Day 1) through Visit 4 (Day 15 [± 2])
- Post-treatment Period: From Visit 4 (Day 15 [± 2]) through Visit 5 (Post-treatment Day 3 [+ 2])

*For subjects who did not meet criteria for the nasal symptoms score at the end of the 1-week Screening Period, observation for additional 1 week (± 2 days) was allowed.

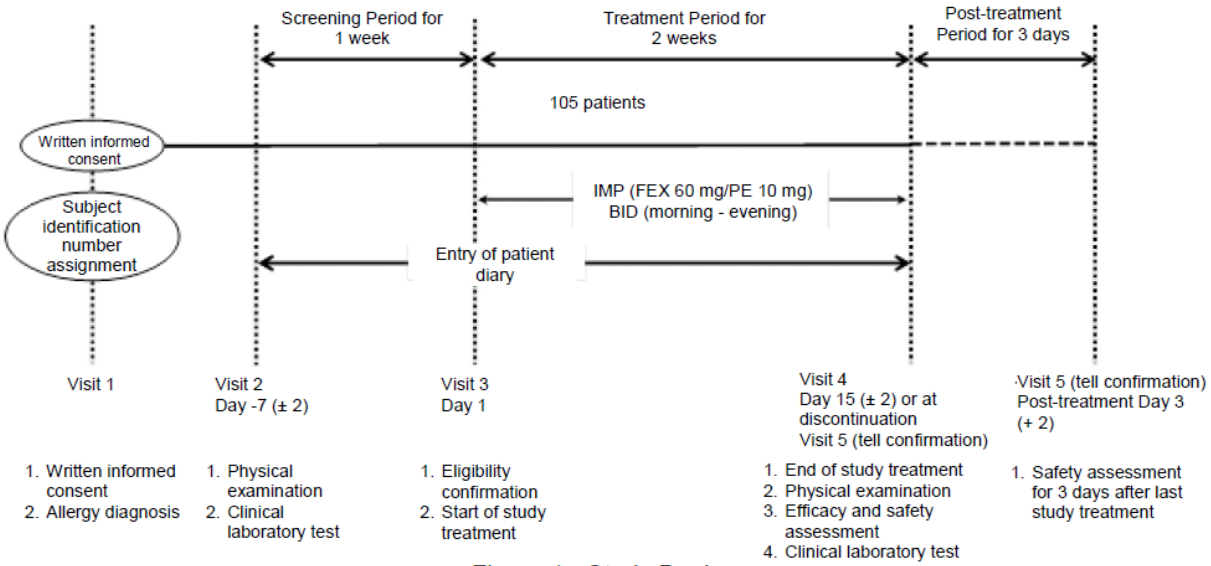

Figure 1 - Study Design

Criteria for evaluation:

Efficacy:

Primary endpoint: Change from baseline in the period average of the nasal congestion score derived from a patient diary following 2-week treatment.

Secondary endpoints

- Change from baseline and longitudinal changes in the total score for 3 nasal symptoms (sneezing, nasal discharge, nasal congestion) following 2-week treatment.
- Change from baseline and longitudinal changes in the daytime and nighttime scores of 3 nasal symptoms (sneezing, nasal discharge, nasal congestion) following 2-week treatment.
- Change from baseline and longitudinal changes in the total score for individual symptoms (sneezing, nasal discharge, and disability in activities of daily living [ADL]) following 2-week treatment.
- Change from baseline and longitudinal changes in the daytime and nighttime scores of individual symptoms (sneezing, nasal discharge, and disability in ADL) following 2-week treatment.
- Change from baseline in nasal cavity findings (swelling of inferior turbinate mucosa, color of inferior turbinate mucosa, amount of watery discharge, characteristics of nasal discharge) following 2-week treatment.
- Impression of subjects.
- Change in the severity of allergic rhinitis symptoms over time.

Safety:

Primary endpoint: Incidence of treatment-related adverse events (AEs) reported during the study.

Secondary endpoints

- AEs in the Treatment Period.
- Laboratory findings.
- Vital signs.

Statistical methods:

Efficacy analysis set:

The modified Intent-to-Treat (mITT) population was defined as all subjects of the ITT population who received at least 1 dose of study drug and had available data on change in the nasal congestion score.

Safety analysis set:

The safety analysis set was defined as all subjects of the ITT population who received at least 1 dose of study drug.

Effectiveness analysis approaches:

Based on the mITT population, descriptive statistics of efficacy endpoints for each period were provided with their changes over time shown graphically. Changes from baseline were also summarized using descriptive statistics.

Safety analysis approaches:

The safety analysis was performed in the safety data analysis set.
AEs which were coded with MedDRA/J ver 18.1 were used for summarization and analysis.

- The frequencies and incidence rates of AEs and adverse drug reactions (ADRs) were provided.
- The frequencies and incidence rates of AEs and ADRs by preferred term were provided.

For clinical laboratory data, descriptive statistics and the number of subjects with abnormal values were provided by period. Vital signs were summarized by period using descriptive statistics.

Summary: Among 158 subjects who provided a written informed consent, 105 (66.5%) of the ITT population were treated; all of these subjects were included in the safety analysis set and mITT population.

Population characteristics: Slightly more subjects were male (56 subjects, 53.3%). The mean age was 38.9 years, with mean height of 165.06 cm, body weight of 60.11 kg, and body mass index (BMI) of 21.966 kg/m^2. The allergy diagnosis was seasonal allergic rhinitis in 48 subjects (45.7%), perennial allergic rhinitis in 25 (23.8%), and mixed (seasonal and perennial) allergic rhinitis in 32 (30.5%). The mean daily scores of paroxysmal sneezing, nasal discharge, nasal congestion, and disability in ADL at baseline were 2.178 (0.67 to 3.33), 2.443, 2.246 and 2.033, respectively.

Table 1. Demographic Characteristics

		N=105
Age (years)		
	Mean (± standard deviation)	38.9 (±12.3)
	Median	40.0
	Minimum, maximum	17,67
Height (cm)		
	Mean (± standard deviation)	165.06 (±8.87)
	Median	165.20
	Minimum, maximum	147.0,184.2
Body weight (kg)		
	Mean (± standard deviation)	60.11 (±11.64)
	Median	59.60
	Minimum, maximum	40.3,110.1
BMI (kg/m2)		
	Mean (± standard deviation)	21.966 (±3.256)
	Median	21.530
	Minimum, maximum	16.18,33.31
Gender, No. of subjects (%)		
	Male	56 (53.3)
	Female	49 (46.7)
Allergy diagnosis, No. of subjects (%)		
	Seasonal	48 (45.7)
	Perennial	25 (23.8)
	Mixed	32 (30.5)

Table 2. Nasal scores at baselines

		N=105
Nasal congestion score		
	Mean (± standard deviation)	2.246 (±0.287)
	Median	2.170
	Minimum, maximum	2.00, 3.00
Sneezing score		
	Mean (± standard deviation)	2.178(±0.496)
	Median	2.170
	Minimum, maximum	0.67, 3.33
Rhinorrhea score		
	Mean (± standard deviation)	2.443(±0.440)
	Median	2.500
	Minimum, maximum	1.50, 3.33

Table 3. Nasal findings at baseline

		N=105 Number (%)
Swelling of inferior turbinate mucosa		
	-	5(4.8)
	+	29(27.6)
	++	48(45.7)
	+++	23(21.9)
Color of inferior turbinate mucosa		
	-	19(18.1)
	+	36(34.3)
	++	33(31.4)
	+++	17(16.2)
Amount of watery discharge		
	-	43(41.0)
	+	49(46.7)
	++	13(12.4)
	+++	0(0.0)
Characteristics of nasal discharge		
	-	42(40.0)
	+	0(0.0)
	++	3(2.9)
	+++	60(57.1)

Efficacy results:
For the primary analysis, change in the period average of the daily nasal congestion score (Treatment Period - Baseline) was -0.798, showing a statistically significant difference relative to the baseline.
For the secondary endpoints, comparison of change in the period average of the daily score for individual symptoms yielded the following results: -0.875 for sneezing, -0.857 for nasal discharge, -0.798 for nasal congestion, and -0.721 for disability in ADL.

Table 4. Baseline Scores by Symptom and Change from Baseline in the Period Average (mITT Population)

Daily score	Baseline Screening Period (last 3 days)	Week 1 of treatment (Day 2 to Day 8)	Change Week 2 of treatment (Day 9 to Day 14)	Overall for 2 weeks of treatment (Day 2 to Day 14)
Nasal congestion	2.246 ± 0.287	-0.721 ± 0.596**	-0.888 ± 0.642**	-0.798 ± 0.595**
Sneezing	2.178 ± 0.496	-0.802 ± 0.545**	-0.960 ± 0.595**	-0.875 ± 0.546**
Nasal discharge	2.443 ± 0.440	-0.780 ± 0.584**	-0.946 ± 0.602**	-0.857 ± 0.571**
Disability in activities of daily living	2.033 ± 0.358	-0.647 ± 0.621**	-0.806 ± 0.705**	-0.721 ± 0.635**

Mean ± standard deviation
**: p<0.05 for comparison versus baseline using paired t-test

For nasal findings, the magnitude of swelling and color of inferior turbinate mucosa, amount of watery discharge, and characteristics of nasal discharge generally tended to improve.

Table 5. Nasal findings after 2 weeks treatment

		N=105 Number (%)
Swelling of inferior turbinate mucosa		
	-	20(19.0)
	+	42(38.0)
	++	38(34.5)
	+++	5(4.8)
Color of inferior turbinate mucosa		
	-	38(34.5)
	+	46(43.8)
	++	12(11.4)
	+++	9(8.6)
Amount of watery discharge		
	-	68(64.8)
	+	31(29.5)
	++	5(4.8)
	+++	1 (1.0)
Characteristics of nasal discharge		
	-	68(64.8)
	+	0(0.0)
	++	1(1.0)
	+++	36(34.3)

The proportion of subjects with impression of “good” or better was 53.3%, with as high as 92.4% of subjects rating “a bit good” or better, demonstrating favorable impression.

Table 6. Subject Impression (mITT Population)

	FEX60 / PE10	
No. of subjects analyzed	105	
Impression of subjects		
very good	17	(16.2)
good	39	(37.1)
a bit good	41	(39.0)
no change	8	(7.6)
a bid bad	0	(0.0)
bad	0	(0.0)
very bad	0	(0.0)
Impression of subjects Proportion of "a bit good” or better	97	(92.4)
Proportion of “good” or better	56	(53.3)

The shift table for the severity classification of allergic rhinitis symptoms showed a tendency toward milder magnitude and severity of nasal congestion, and paroxysmal sneezing or nasal discharge at the end of the Treatment Period.

			FEX60 / PE10									
		Magnitude and severity	Paroxysmal sneezing or nasal discharge*									
			4 (%)		3 (%)		2 (%)		1 (%)		0 (%)	
Baseline	Nasal congestion	4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		3	7	(6.7)	45	(42.9)	10	(9.5)	0	(0.0)	0	(0.0)
		2	4	(3.8)	34	(32.4)	5	(4.8)	0	(0.0)	0	(0.0)
		1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		0	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

*Sneezing or nasal discharge, which is more severe

			FEX60 / PE10									
		Magnitude and severity	Paroxysmal sneezing or nasal discharge*									
			4 (%)		3 (%)		2 (%)		1 (%)		0 (%)	
After 2 weeks treatment	Nasal congestion	4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		3	0	(0.0)	5	(4.8)	7	(6.7)	0	(0.0)	0	(0.0)
		2	2	(1.9)	13	(12.4)	32	(30.5)	3	(2.9)	0	(0.0)
		1	0	(0.0)	3	(2.9)	6	(5.7)	29	(27.6)	0	(0.0)
		0	0	(0.0)	0	(0.0)	4	(3.8)	1	(1.0)	0	(0.0)

*Sneezing or nasal discharge, which is more severe

Safety results: Adverse events were reported by 7 subjects (6.67%). Of these subjects, 2 (1.90%) were assessed by Investigators/Sub-investigators to experience ADRs. Adverse drug reactions were hepatic steatosis and somnolence. The most common AE was nasopharyngitis in 4 subjects (3.81%), followed by diarrhea, hepatic steatosis, and somnolence in 1 subject (0.95%) each. Hepatic steatosis was diagnosed by imaging findings (echo). All AEs and ADRs were mild in severity. The incidence rates of AEs and ADRs were similar among allergy diagnoses. Hepatic steatosis was resolving, and other AEs were confirmed to have resolved. There were no serious adverse events, fatal AEs, or AEs leading to treatment discontinuation of study drug. Regarding laboratory test, increase of total-cholesterol of 1 subject (251mg/dL to 308mg/dL) and increase of hematocrit level of 1subject (31.0% to 31.9%) fell into PCSA. Both were judged by Investigators as non-AEs and without clinical problems. Although it was observed some outlier in alanine aminotransferase/aspartate aminotransferase (ALT/AST) no case suggesting a potential liver injury was identified according to the Investigators.
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