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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT
		Study Code:	M016455A_4149
Generic drug name:	Fexofenadine	**Date:**	11/Mar/2008

Title:	Single-center, double-blind, randomized, parallel study comparing onset of action, efficacy and safety of a single-dose of fexofenadine hydrochloride (HCL) 180 mg versus montelukast Na 10 mg and placebo in treating seasonal allergic rhinitis subjects in an allergen exposure unit (Study I).
Investigator(s), study site(s):	Robert B. Berkowitz, M.D., Woodstock, GA
Study duration and dates: 18 February 2003 - 27 March 2003	**Phase of development:** IV
Objectives:	**Primary objective** The primary objective of the study was to determine the efficacy and onset of action of single-dose fexofenadine HCL 180 mg and montelukast sodium 10 mg, relative to placebo. **Secondary objectives** The secondary objectives were to assess onset of action versus placebo, and to compare safety and efficacy among the 3 treatment groups.
Study design:	This was a single-center, single-dose, double-blind, randomized, placebo-controlled, parallel-group study. The study consisted of a Screening visit, one or two 2-hour Priming visits, and a Treatment Visit.
Number of subjects planned:	A minimum of 597 subjects (199 per treatment group) was to be enrolled into the study. The estimated number of subjects to be screened was 1010 subjects.
Inclusion criteria:	Male or female subjects who were 15 years of age, had a positive skin test to ragweed allergen within the previous 15 months and had at least a 2-year history of allergy symptoms during the past two fall seasons wee eligible for enrollment into the study.
Treatments:	Treatments administered: . Fexofenadine HCl 180 mg tablet . Fexofenadine HCl placebo tablet . Montelukast sodium capsule 10 mg (blinded tablet) . Montelukast sodium placebo capsule (blinded tablet) Single-dose treatment groups: . Fexofenadine HCl 180 mg tablet + a placebo capsule (identical in appearance to montelukast sodium) . Montelukast sodium capsule 10 mg (overencapsulated tablet) + a placebo tablet (identical in appearance to fexofenadine HCL) . Placebo tablet (identical in appearance to fexofenadine HCL 180 mg) + a placebo capsule (identical in appearance to montelukast sodium)

Efficacy data:	The primary efficacy variable was the absolute change in MSC from baseline (0900 and 0915 predose baseline diary cards). The Major Symptoms Complex (MSC) was defined as the sum of the scores for the subjects' assessments of the following symptoms: • Sneezes • Itchy nose (average of left and right nostrils) • Runny nose (average of left and right nostrils) • Watery eyes • Itchy eyes • Itchy ears/throat The primary study endpoint was the determination of the onset of action of fexofenadine HCL 180mg and montelukast sodium 10 mg, and was based on the absolute change in MSC relative to the mean MSC during the predose baseline symptom evaluation (0900 and 0915 predose baseline diary cards). Onset of action for fexofenadine HCL 180 mg and montelukast sodium 10 mg was defined as the first time (between 15 minutes and 6 hours postdosing) at which consistent, statistically significant change in MSC was achieved for fexofenadine HCL 180 mg relative to placebo and montelukast sodium 10 mg relative to placebo. Consistent was defined as two consecutive measurements, with onset being the start of that interval. The secondary efficacy variables for the secondary endpoint, comparison of onset of action versus placebo, and efficacy among 3 treatment groups, included the following: • Absolute and percent change in MSC plus stuffy nose • Percent change in MSC • Absolute and percent change in individual symptoms as well as stuffy nose • Absolute and percent change in Itching Symptom Complex (ISC, defined as the sum of the scores for itchy nose, itchy eyes, and itchy ears/throat) • Absolute and percent change in MSC, ISC and individual symptoms on all diary cards at 1 to 5 hours (inclusive) postdose relative to the mean predose baseline symptom evaluation (0900 and 0915 predose baseline diary cards) • Time at which a 7-point reduction in absolute MSC (i.e., clinically meaningful change, as defined in the Clinical Study Protocol was obtained and the number of subjects having a 7-point reduction in absolute MSC • A measure of sustainability of effect (i.e., absolute reduction in MSC did not fall out of significance at two consecutive time points after onset of action (fexofenadine HCL or montelukast) and durability of effect (i.e., the absolute reduction in MSC did not fall out of significance for any time point after onset of action of a treatment was achieved) • Time at which subjects in either group achieved pre-specified reductions (10%, 20%, 30%, 40%, 50%, 60%, 70% and 80%) in MSC and ISC relative to the individual subject's mean baseline MSC and ISC, respectively.
Safety data:	The safety of fexofenadine HCL 180 mg and montelukast sodium 10 mg was evaluated by monitoring for serious and non-serious adverse events.

Statistical procedures:	Primary efficacy analysis: Pairwise comparisons among the 3 treatment groups for absolute change in MSC relative to mean baseline MSC were conducted at each postdose time point using analysis of covariance (ANCOVA), with fixed terms for treatment group and session, and baseline slope and level of MSC score as covariates. Ninety-five percent confidence intervals for the adjusted mean treatment differences were computed and examined. Secondary efficacy analysis: Pairwise comparisons among the 3 treatment groups were conducted at each postdose time point, using the same model described above for the primary efficacy analysis, for changes from baseline in the secondary endpoints, as follows: absolute percent and changes in MSC plus stuffy nose; percent in change of MSC; absolute and percent change in individual symptoms as well as stuffy nose; absolute and percent change in ISC; and absolute and percent change in MSC, ISC and individual symptoms on all diary cards at 1 to 5 hours (inclusive). Comparisons among the 3 treatment groups for time to achieve a 7-point reduction in MSC were conducted via proportional hazards regression [Kalbfleisch and Prentice, 1980], adjusting for session, baseline slope and level (used as covariates), with cases not achieving criterion treated as censored at their last observation time. Kaplan-Meier curves presented to help visualize the differences. In addition, the number of subjects who experienced a 7-point reduction in absolute MSC was summarized descriptively and compared between groups using a Fisher's exact test. The results of the primary efficacy analysis for each study time point were examined to determine whether the criteria for sustainability of effect (a two-tailed p-value of < 0.05 at time points such that no two consecutive time points had a p-value = p 0.05 after onset of action was achieved) and durability of effect (a two-tailed p-value < 0.05 at all time points after onset of action was achieved) were met for fexofenadine HCL or montelukast sodium. The time at which subjects achieved prespecified reductions (10%, 20%, 30%, 40%, 50%, 60%, 70% and 80% reductions) in MSC and ISC relative to the individual subject's mean baseline MSC and ISC scores, respectively, was compared among treatment groups via proportional hazards regression, adjusting for session, baseline slope and level (used as covariates), with cases not achieving criterion treated as censored at their last observation time. Kaplan-Meier curves were presented to help visualize the differences. The number of subjects achieving prespecified reductions in MSC and ISC was compared among treatment groups using a Fisher's exact test. Safety analysis: The number and frequency of subjects with adverse events, treatment-emergent adverse events (TEAEs) and serious adverse events were calculated for each treatment group and summarized by MedDRA (version 6.0) system organ class and preferred term within each system organ class.
Interim analysis:	No interim analysis was performed.

Results – Study subjects and conduct:	Subject disposition: One thousand and twenty-one subjects were screened. The screen failure rate was 40.7% (416 of 1021 subjects). The most common reason for screen failure was failure to meet the study inclusion/exclusion criteria (153 subjects, 36.8%), followed by insufficient SAR symptoms (106 subjects, 25.2%). Of the total subjects who were screened, 605 subjects (59.3%) were randomized. Two hundred and two, 203, and 200 subjects were randomized to the placebo, fexofenadine HCL, and montelukast sodium groups, respectively. No subjects discontinued the study prior the completion. Demographics: The treatment groups were similar in terms of demographic and baseline characteristics for the safety and ITT subjects. The mean (SD) ages for the placebo, fexofenadine, and montelukast subjects were similar [35.3(12.3), 33.2(12.3), and 34.2(11.8) years-of-age, respectively]. The groups were predominantly female (140/202, 69.3%; 137/203, 67.5%; 133/200, 66.5%) and black (150/202, 74.3%; 150/203, 73.9%; 151/200, 75.5%). Primary disease: The subjects were similar at baseline in terms of allergic rhinitis history in the placebo, fexofenadine and montelukast groups [mean (SD) years with allergic rhinitis: 16.4 (10.2), 16.6 (11.4), and 15.4 (10.5), respectively], and all subjects had a positive allergy test at baseline. No statistically significant differences overall between treatment groups were observed with respect to baseline MSC score (mean of data recorded on the two predose baseline diary cards completed at 0900 and 0915 by subjects on the day of the Treatment Visit prior to randomization), MSC plus stuffy nose, ISC score, sneezes, itchy nose, runny nose, watery eyes, itchy eyes, itchy ears/throat, or stuffy nose.

Results – Efficacy:	• The primary analysis of absolute change from baseline in MSC revealed a onset of action for fexofenadine HCL at the 2:30 hour (hr) postdose time point [LS (least squares) mean difference (fexofenadine – placebo) in change from baseline (95% CI) = 1.0 (0.2, 1.8), p=0.0160] and for montelukast sodium at the 3:00 hr postdose time point [LS mean difference in change from baseline (95% CI) = 0.9 (0.1, 1.8), p=0.0284] • Sustainability and durability of the treatment effect were observed for the primary efficacy variable, absolute change from baseline in MSC, for both fexofenadine HCL and montelukast sodium • No consistent differences between the fexofenadine and montelukast groups were observed for absolute change in MSC (range of probabilities for all time points from 0.3469 to 0.9925), absolute change in ISC (range of probabilities for all time points from 0.2980 to 0.9532), absolute changes in MSC plus stuffy nose (range of probabilities from 0.3074 to 0.9989) or absolute changes in individual symptoms: sneeze [significance at the 2:30 hr, 4:30 hr and 6:00 hr time points (p=0.0055, p=0.0041, and p=0.0110, respectively); range of probabilities for all other time points from p=0.0629 to p=0.9884]; itchy nose (range of probabilities from 0.2602 to 0.9974), runny nose (range of probabilities from 0.4118 to 0.9838); watery eyes (range of probabilities from 0.0604 to 0.8716); itchy eyes (range of probabilities from 0.3957 to 0.9726); itchy ears/throat (range of probabilities from 0.3257 to 0.9729); and stuffy nose (range of probabilities from 0.2479 to 0.9770) • Fexofenadine HCL treatment led to improvements in absolute change from baseline in the individual symptoms sneeze averaged over all diary cards at 1 to 5 hours, that were statistically better than those of montelukast sodium [LS mean difference (fexofenadine – montelukast) in change from baseline (95% CI) = 0.1 (0.0, 0.1), p=0.0230]. In contrast, there were no statistically significant differences between treatment groups for the comparison of MSC score, MSC plus stuffy nose (p=0.9989, p=0.9286, p= 0.9278, p=0.7506, p=0.8312, p=0.1619, p=0.9201, p=0.9575, and p=0.5784, respectively). • The most robust treatment effects observed for the assessment of the individual symptoms were for the assessments of absolute changes from baseline for the symptom sneeze, for the fexofenadine subjects (range of probabilities for placebo versus fexofenadine, from the time of treatment onset of p<0.0001 to p=0.0262), and this effect exhibited sustainability and durability. • The most robust treatment effects observed among the individual symptoms for the montelukast group were for the assessment of watery eyes (range of probabilities from 0.0008 to 0.1681). • A significant higher percentage of subjects in the fexofenadine group achieved a 7-point reduction in absolute MSC in comparison to placebo subjects [142/203 subjects (70.0%) for the fexofenadine group versus 120/202 subjects (59.4%) for the placebo group, p=0.0292]. In contrast, the comparison between the percentage of subjects in the montelukast group [136/200 subjects (68.0%)] and placebo group [120/202 subjects (59.4%)] who achieved a 7-point reduction in absolute MSC was not significant (p=0.0786). • The time to which subjects in the fexofenadine group achieved 7-point reductions in MSC was significantly less than that of the placebo group (75.0 versus 90.0 minutes, respectively; p=0.0489); there were no significant differences observed for the comparisons of montelukast to placebo (p=0.0516) or fexofenadine to montelukast (p=0.9933). • No pattern was discerned among the results of the comparisons of placebo and fexofenadine or montelukast groups in terms of the number of subjects achieving prespecified reductions, or time to prespecified reductions, in MSC and ISC.

Results – Safety:	• The overall incidence of adverse events was low (16/605 subjects, 31%); a majority of subjects experienced adverse events that were of moderate intensity (12/19 subjects, 63.2%); and only 1 subject who received treatment with fexofenadine HCL (5.3%), among the total safety subjects, experienced adverse events that were assessed by the investigator as severe (eye irritation and sore throat, assessed by the investigator as possibly related to study medication) • The adverse event profile of the fexofenadine group (8 adverse events, 1, 5, and 2 of which were assessed as possibly related to study medication) was comparable to that of the montelukast group (8 adverse events, 4, 4, and 0 of which were assessed as mild, moderate, and severe, respectively, and all of which were assessed as possibly related to study medication) and placebo groups (8 events, 3, 5, and 0 of which assessed as mild, moderate, and severe, respectively, 7 of which were assessed as possibly related to study medication, and one of which was assessed as not related to study medication). • Drowsiness was the only adverse event that occurred in more than one subject in each group [3/202 placebo-treated subjects (1.5%); 5/203 fexofenadine-treated subjects (2.5%); and 4/200 montelukast-treated subjects (2.0%)] and each occurrence of the event was assessed as possibly related to study medication. • No deaths, serious adverse events, discontinuations due to adverse events or other clinically significant events occurred. A significant (accidental) overdose for one subject in the montelukast group was the only noteworthy event that occurred during the study.
Date of report:	25-Mar-2004