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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT
		Study Code:	M016455A_4146
Generic drug name:	Fexofenadine	**Date:**	11/Mar/2008

Title:	A Comparison of Fexofenadine HCl 180 mg, Montelukast Sodium 10 mg and Placebo in Suppression of Wheal and Flare Induced by Seasonal Allergen
Investigator(s), study site(s):	Dr Martha White; Wheaton, MD, USA
Study duration and dates: The first subject was enrolled on 27 February 2003 and the last subject completed the study on 02 May 2003	**Phase of development:** IV
Objectives:	Primary objective The primary objective of the study was to compare the effect of a single dose of fexofenadine HCl 180 mg (Allegra), montelukast sodium 10 mg (Singulair) and placebo on the change from baseline (pre-dose) in seasonal allergen-induced skin flares at 20, 40, and 60 minutes post-dose; then hourly through the first 12 hours post-dose; and 23 and 24 hours post-dose. Secondary objectives The secondary objectives of the study were the comparisons of the effects of fexofenadine, montelukast, and placebo on the following parameters: . The change from baseline (pre-dose) in skin wheals at 20, 40, and 60 minutes post-dose; then hourly through the first 12 hours post-dose; and at 23 and 24 hours post-dose. . Onset of action based on seasonal allergen wheal and flare data following study drug administration; . Duration of action based on seasonal allergen skin wheal and flare data; . Time to maximum percent suppression based on seasonal allergen skin wheal and flare data. The safety of the drug was evaluated by monitoring for serious adverse events (SAE) and non-serious adverse events and vital signs.
Study design:	This was a single-center, randomized, placebo-controlled, complete 3x3 crossover study. Each of the three treatment periods consisted of 2 visits on consecutive days. During each treatment period, a single dose of one of the three study treatments was to be administered to the subject, followed by seasonal allergen skin prick testing at selected intervals for a period of 24 hours. Each treatment period was to be followed by a 14 (±4) day washout period.
Number of subjects planned:	A total of 48 (up to 54) healthy male and female subjects who were 15 to 55 years of age and had a positive skin test to histamine with a history of allergy symptoms were to complete the study.

Inclusion criteria:	Male or female; subjects 15 to 55 years of age, with positive histamine skin prick tests (or duplicate seasonal allergen skin prick test) of summation flare (SF) =20 mm larger than diluent control, and summation wheal (SW) =6 mm larger than diluent control at the screening Visit 1
Treatments:	Qualified subjects were to be randomized and crossed over to the following treatments: . Fexofenadine HCl 180 mg tablet . Montelukast sodium 10 mg tablet . Placebo tablet A 14 (±4) day washout period separated treatment periods.
Efficacy data:	<u>Primary Endpoint:</u> . Size of change in skin flares (the primary endpoint) from baseline was measured at pre-specified times post-dose (20 min, 40 min, 60 min, and hourly through 12 hours with an additional 2 time points obtained at Hours 23 and 24). <u>Secondary endpoints:</u> . Size of change in skin wheals from baseline was measured at pre-specified times post-dose (20 min, 40 min, 60 min, and hourly through 12 hours with an additional 2 time points obtained at Hours 23 and 24). . Onset of action: the first time when the difference in summation diameters between active treatment and placebo was =5 mm change from baseline on 2 consecutive measurements for flares, or =1 mm on 2 consecutive measurements for wheals. . Duration of action: the time when the change from baseline between placebo and active treatment became less than 5 mm on 2 consecutive measurements for flares (unless at Hour 24 when 1 measurement was sufficient), or became less than 1 mm on 2 consecutive measurements for wheals (unless at Hour 24 when 1 measurement was sufficient). . Time to maximum percent suppression: based on skin wheal and flare data. These analyses were to be performed based on measures from seasonal allergen skin prick challenge. At baseline, subjects had a physical examination, and had skin prick testing (seasonal allergens of ragweed, a tree mix, and a grass mix; and histamine and diluent control) to assess eligibility. At each of the treatment visits, subjects had pre-dose skin prick testing, followed by repeat skin prick testing at the times noted above. Each crossover was separated by a period of 14 (±4) days.
Safety data:	Safety data included serious and non-serious adverse events, urine pregnancy testing (for all female subjects at Visits 1, 2, 4, 6 early discontinuation visit), and vital signs.

Statistical procedures:	**<u>Efficacy:</u>** Primary efficacy variable: Summation flare [SF] difference from diluent control. Secondary: Summation wheal [SW] difference from diluent control along with other end points listed under efficacy data. The efficacy analyses were to be based on the per-protocol population (all randomized subjects without a major protocol violation who completed the study). The primary efficacy parameter was to be analyzed in two steps. First, a Generalized Linear Model with terms of (at least, but not limited to) sequence, period, treatment, and first order carry-over effect were to be used to analyze data to detect if any carry-over, period or sequence effect existed. If there was any unwanted effect (sequence or carry-over) for which an adjustment could not be made, then only the data collected from the first period was to be combined and a simple one-way ANOVA was to be performed. The pairwise comparisons between three treatment groups were also to be conducted using only the first period data. If no carry-over or sequence effects existed, then a reduced one-way repeated measure ANOVA was to be performed. In particular, a one-way repeated measures contrast was to be carried out to compare the two active treatments. If the comparison test was significant at 0.05 level in favor of fexofenadine 180 mg, then fexofenadine 180 mg was declared to be superior to montelukast 10 mg treatment. The histamine wheal and flare data were summarized descriptively by treatment group at each available time point and analyzed using statistical methods similar to that of the primary endpoint. **<u>Safety:</u>** Serious adverse events, non-serious adverse events and vital signs were collected. The safety analyses were based on the safety evaluable population (all randomized subjects who consumed study medication(s)).
Interim analysis:	There was no interim analysis for this study.

Results – Study subjects and conduct:	The number of subjects screened for this study was 70. Of these, twenty subjects were not randomized. The remainder, 50 subjects, comprised the safety population and were randomized to one of the following six sequences: . 8 randomized to Sequence 1 (placebo, montelukast, fexofenadine) . 8 randomized to Sequence 2 (placebo, fexofenadine, montelukast) . 8 randomized to Sequence 3 (montelukast, placebo, fexofenadine) . 8 randomized to Sequence 4 (montelukast, fexofenadine, placebo) . 9 randomized to Sequence 5 (fexofenadine, placebo, montelukast) . 9 randomized to Sequence 6 (fexofenadine, montelukast, placebo) Two subjects discontinued the study early. Specifically, Subject 26 (Sequence 6) was discontinued prior to receiving placebo because of a major protocol violation and Subject 48 (Sequence 5) was discontinued prior to receiving montelukast because of the sponsor's request. Therefore, all 50 randomized subjects comprised the safety population and 48 subjects comprised the per protocol population. For the safety population, the mean age ranged across sequences from 27.0 ±4.1 (S.D.) years (Sequence 1) to 33.8 ± 13.8 (S.D.) years (Sequence 4). Overall, there were approximately twice as many females than males, with each sequence group ranging from 1.6 to 7 times more females than males except for Sequence 5 where there were 3.5 times more males than females. The majority of subjects were Black, followed by White for each Sequence, except for Sequence 1 which had a majority of White followed by Black subjects. The mean body weight overall was 166.5 ±29.6 (S.D.) pounds and body mass index (BMI, kg/m2) was 26.2 ±3.3 (S.D.). There were not any statistically significant differences among sequence groups in demographic parameters (age, sex, race, weight, height, and BMI). The per protocol population yielded similar results.

Results – Efficacy:	Fexofenadine 180 mg had significantly greater suppression of seasonal allergen-induced flares than montelukast 10 mg or placebo beginning at 40 minutes and lasting through 24 hours post-treatment for mean change from pre-dose. Mean changes in seasonal allergen skin flare from pre-dose throughout all time points from 20 minutes to 24 hours post-treatment were not significant between montelukast 10 mg and placebo. At 6, 12, and 24 hours post-dose, fexofenadine significantly suppressed histamine-induced skin flares greater than montelukast or placebo. There were no significant differences between montelukast and placebo in histamine-induced skin flares at all 3 measured time points. Fexofenadine 180 mg had significantly greater suppression of seasonal allergen-induced wheals compared to montelukast 10 mg, beginning at 40 minutes and at all time points through 24 hours post-dose. Significant differences in wheal suppression between fexofenadine 180 mg and placebo were also observed beginning at 1 hour and at all time points through 24 hours post-dose. There were no significant differences between montelukast and placebo in suppression of seasonal allergen induced-wheals at any time point, except placebo had significantly greater suppression than montelukast at 2 and 11 hours post-treatment. Fexofenadine suppressed histamine-induced skin wheals to a greater extent than montelukast or placebo at 6, 12, and 24 hours post-dose. There were no significant differences between montelukast and placebo at all 3 measured time points. The onset of suppression of seasonal allergen-induced skin and wheal flares occurred at 40 minutes post-dose for fexofenadine with a duration of action being 23.33 hours (offset was not observed for either flares or wheals). Montelukast did not demonstrate significant seasonal allergen-induced skin flare and wheal suppression, so no onset or duration was observed. The maximum percent suppression of skin flares was reached at 4 hours post-dose for fexofenadine and was 79%. The maximum wheal suppression for fexofenadine was 72.3% and was reached at 3 hours post-dose. The maximum flare and wheal suppression for montelukast 10 mg were both reached at 60 minutes post-dose and were 7.3% and 9.6%, respectively. Following placebo, maximum flare suppression of 10.3% and wheal suppression of 18%, were reached at 40 minutes post-dose.
Results – Safety:	There were no pre-treatment adverse events and five of the 50 (10%) subjects reported six treatment emergent adverse events. All of the adverse events were of moderate intensity and none were assessed as related to study drug. None of the subjects receiving placebo had adverse events. Adverse events during fexofenadine treatment included rash on forearms and viral infection; the viral infection required medication. Adverse events during montelukast treatment included hyperthyroidism, rash on forearms, low back pain, and nausea. The hyperthyroidism required medication and was noted as the only ongoing event of the six adverse events; otherwise, the subjects recovered without sequelae. No deaths, serious adverse events, discontinuations from the study due to adverse events, overdoses, or pregnancies occurred in this study. Mean vital signs at baseline and throughout the study (Visits 2, 4, and 6) appeared to be similar among sequence groups and the changes were considered not clinically significant.
Date of report:	14-Aug-2003