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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT
		Study Code:	M016455A_4145
Generic drug name:	Fexofenadine	**Date:**	11/Mar/2008

Title:	A Comparison of Fexofenadine HCl 180 mg, Desloratadine 5 mg and Placebo in Suppression of Wheal and Flare Induced by Histamine
Investigator(s), study site(s):	Dr Eli Meltzer; San Diego, CA, USA and Dr Sherwin A. Gillman; Orange, CA, USA

Study duration and dates: The first subject was enrolled on 23 December 2002 and the last subject completed the study on 27 July 2003	**Phase of development:** IV

Objectives:	<u>Primary objective</u> The primary objective of the study was to compare the effects of a single dose of fexofenadine HCl 180 mg (Allegra®), desloratadine 5 mg (Clarinex®), and placebo on the change from baseline (pre-dose) in histamine 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. <u>Secondary objectives</u> The secondary objectives of the study were the comparison of the effects of study drug 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 histamine wheal and flare data following study drug administration; . Duration of action based on histamine skin wheal and flare data; . Time to maximum percent suppression based on histamine skin wheal and flare data. The safety of the drug was evaluated by monitoring for serious adverse events and treatment emergent non-serious adverse events and vital signs.
Study design:	This was a two-center, randomized, double-dummy, placebo-controlled, complete 3 x 3 crossover design 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 histamine skin prick testing at selected intervals for a period of 24 hours. Each treatment period was to be followed by a 14 (10-28) day washout period.
Number of subjects planned:	A total of 36 (up to 42 planned) healthy male and female subjects who were 12 to 55 years of age and had a positive skin test to histamine were to complete the study.
Inclusion criteria:	Male or female; subjects 12 to 55 years of age, with positive histamine skin prick tests (or duplicate histamine skin prick test) with a 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 . Desloratadine 5 mg tablet . Placebo tablet A 14 (10-28) day washout period separated treatment periods.

Efficacy data:	Primary Endpoint: . Size of change in summation 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). Secondary endpoints: . Size of change in summation 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 histamine skin prick challenge. At baseline, subjects received a physical examination, and had skin prick testing (histamine, duplicate histamine and diluent control) to assess eligibility. At each of the treatment visits, subjects had baseline skin prick testing, followed by repeat skin prick testing at the times noted above. Each crossover was separated by a period of 14 (10-28) days.
Safety data:	Safety data included serious and non-serious adverse events, urine pregnancy testing (for all female subjects at Visits 1, 2, 4, and 6), and vital signs.

Statistical procedures:	**Efficacy:** Primary efficacy variable: The difference between pre-dose skin flare and subsequent skin flare measurements within each subject (summation flare [SF] difference from diluent control). Secondary: The difference between pre-dose skin wheal and subsequent skin wheal summation measurements within each subject (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). There was a small change in the analysis of the primary efficacy parameter from the original statistical analysis plan such that the model that best fit the data was consistently used across all analysis time points. The primary efficacy parameter was to be analyzed in two steps. First, the carry-over effect was to be tested at all time points, using a Generalized Linear Model with factors for treatment, sequence, period, and first order carry-over effects. If more than 20% of time points had carry-over effect detected at 0.10 significance level, then the carry-over effect was to be considered present for the study and the crossover design model was to be considered invalid. Hence, only the data collected from the first period was to be used and a simple one-way ANOVA was to be performed at all time points. The between treatment comparisons were also to be performed using only the first-period data. If no more than 20% of the time points had significant carry-over effect detected at 0.10 significance level, then a reduced one-way repeated measure ANOVA model without carry-over factor was to be considered valid and was not to be used at all time points. In particular, a model based comparison between two active treatments was to be carried out. If the comparison test was significant at the level of $a = 0.05$ in favor of fexofenadine 180 mg, then fexofenadine 180 mg would be declared to be superior to desloratadine 5 mg. **Safety:** 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:	No interim analysis was performed for this study.

Results – Study subjects and conduct:	The number of subjects screened for this study was 65. Of these, 11 subjects were not randomized. The remaining 54 subjects comprised the safety population and were randomized to one of the following six sequences: . 9 randomized to Sequence 1 (fexofenadine, desloratadine, placebo) . 8 randomized to Sequence 2 (fexofenadine, placebo, desloratadine) . 8 randomized to Sequence 3 (desloratadine, fexofenadine, placebo) . 10 randomized to Sequence 4 (desloratadine, placebo, fexofenadine) . 10 randomized to Sequence 5 (placebo, fexofenadine, desloratadine) . 9 randomized to Sequence 6 (placebo, desloratadine, fexofenadine) Of the 54 subjects, 23 were enrolled at site 1 and 31 were enrolled at site 2. Seven subjects discontinued the study early due to major protocol violations and consent withdrawals. Forty-seven (47) subjects completed the study; however, only 45 subjects were included in the per-protocol population, on which all efficacy analyses were based. For the safety population, the mean age was 30.5±11.7 (S.D.) years. The mean age ranged across sequences from 27.3±13.2 (S.D.) to 37.1±11.4 (S.D.). Overall, approximately 1.5 times more females than males were included, with each sequence group ranging from 1.3 to 3 times more females than males except for Sequence 5 with 1.5 more males than females. The majority of subjects were White, followed by Asian/Pacific Islander for each Sequence, except for Sequences 2 and 5 that had an equal number of White and Asian/Pacific Islander subjects. The mean body weight overall was 155.1±30.5 (S.D.) pounds and body mass index (BMI, kg/m2) was 25.0±3.7 (S.D.). No statistically significant differences in demographic parameters (age, sex, race, weight, height, and BMI) were found among sequence groups. Demographics for the per-protocol population yielded similar results as that for the safety population.

Results – Efficacy:	Fexofenadine 180 mg demonstrated significantly greater suppression of histamine-induced flares and wheals compared to desloratadine 5 mg at several time points measured. Compared to placebo, fexofenadine had significantly greater suppression for histamine-induced flares at most time points evaluated and for the majority of wheal time points measured. Desloratadine had a significantly greater suppression than placebo for histamine-induced flares at several time points measured and for wheals at only one time point measured. In response to histamine skin prick tests, fexofenadine 180 mg had a significantly greater suppression of histamine-induced flares (from 2 to 6 hours post-treatment) and wheals (from 2 to 4 hours, 6 to 9 hours, and 12 hours post-treatment) when compared to desloratadine. Compared to placebo, fexofenadine had a significantly greater suppression at most time points evaluated for histamine-induced flares (from 2 to 24 hours) and wheals (from 2 to 12 hours post-treatment). Desloratadine had a significantly greater suppression than placebo at several time points for histamine-induced flares (from 6 to 10 hours, 12, and 24 hours post-dose), but only at one time point (10 hours post-dose) for wheals. The onset of suppression of histamine-induced skin flares occurred at 60 minutes post-dose for fexofenadine with duration of action being 23 hours (offset was not observed). Following treatment with desloratadine, the onset of suppression of histamine-induced skin flares occurred at 5 hours post-dose with duration of action of 19 hours (offset not observed). The onset of suppression of histamine-induced skin wheals was observed at 60 minutes post-fexofenadine with duration of action of 23 hours (offset was not observed). At 60 minutes post-dose with desloratadine, the onset of suppression of histamine-induced skin wheals was observed with duration of action of 23 hours (offset not observed). The maximum flare and wheal suppression for fexofenadine were both reached at 6 hours post-dose and were 84.7% and 67.8%, respectively. The maximum flare suppression for desloratadine was 51.4% and was reached at 10 hours post-dose. The maximum wheal suppression for desloratadine was reached at 7 hours post-dose and was 30.6%. At 11 hours post-treatment with placebo, maximum skin flare suppression was 15.1%. Following placebo, maximum wheal suppression was 10.5% and was reached at 7 hours.

Results – Safety:	The incidence of adverse events was low for fexofenadine, desloratadine, and placebo. There was one pre-treatment adverse event of mild body pain secondary to overexertion. Nine of the 54 (17%) subjects reported 16 treatment emergent adverse events. Of these nine subjects, one subject each was in Sequence 1, 2, 4 and 5, two subjects were in Sequence 6, and three subjects were in Sequence 3. Four subjects had six adverse events during fexofenadine treatment. One of these four subjects was in Sequence 2 and had moderate drowsiness and moderate lactose intolerance. Three of the four subjects were in Sequence 3 and had the following adverse events: insomnia, laceration of the right shin and cellulitis, and bladder infection. Six adverse events in five subjects occurred during desloratadine treatment and included an injured finger (Sequence 1), diarrhea and gastroenteritis (both in one subject in Sequence 3), fainting (Sequence 4), infected gland and head cold (both Sequence 6). Four adverse events were reported in three subjects during placebo treatment including conjunctivitis and cold sore (both in one subject in Sequence 4) and headache (occurred in both Sequences 5 and 6). For any treatment group (and across every sequence), all events were assessed as unrelated to study medication and all subjects continued in the trial. Twelve of the 16 events were treated with counteractive medications. Eleven of the 16 adverse events were noted as recovered without sequelae while the other 5 adverse events were noted as ongoing. 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:	21-Oct-2003