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Proprietary Drug Name: ALLEGRA®	**INN:** fexofenadine HCl capsules and tablets	**Therapeutic area and FDA approved indications:** for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery red eyes. ALLEGRA is also indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. It significantly reduces pruritus and the number of wheals.
Name of Sponsor/Company:	Aventis Pharmaceutical Member of the sanofi-aventis group	

Title of Study: (M016455A/4143) Comparative study evaluating the effects of fexofenadine HCl 180 mg with grapefruit juice versus placebo with grapefruit juice in a skin wheal and flare challenge model

Principal Study Investigators: Michael Kaliner, MD

Study centre: one U.S. site: The Institute for Asthma and Allergy, P. C.
Wheaton Tower South
11160 Veirs Mill Road, Suite 414
Wheaton, MD 20902

Publication: Kaliner MA, MV, Rothrock S, Meeves S, Liao Y, Georges G. Effect of grapefruit juice and orange juice on fexofenadine vs placebo in a skin wheal-and-flare model. Abstract presentation at the American College of Allergy, Asthma and Immunology (November 7 - 12, 2003 New Orleans, Louisiana).

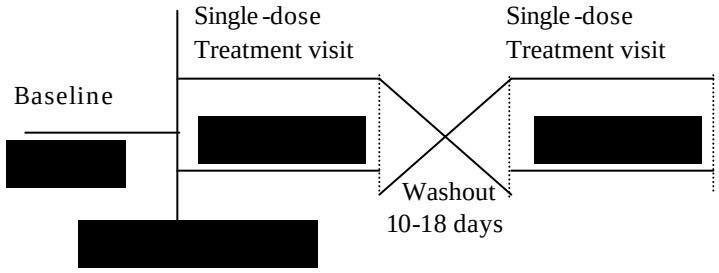
Study period (years): (date of first enrolment) (date of last completed): 3 September, 2002 to 4 October, 2002.	**Phase of development:** Phase IV

Objectives: The primary objective of the study was to compare the effect of a single dose of fexofenadine HCl 180 mg plus grapefruit juice versus placebo plus grapefruit juice 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.

The secondary objectives of the study were the comparison of the effects of fexofenadine plus grapefruit juice versus placebo plus grapefruit juice on:

- 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 of maximum percent suppression based on histamine skin wheal and flare data.

Methodology:
This is a single-center, randomized, placebo-controlled, complete crossover design study. The following is a schematic of the study design:



Number of patients (planned and analyzed):
34 subjects were to be enrolled and treated in this study.
The number of subjects screened for this study was 35. Of these, 1 subject passed screening but never returned for Visit 2 for randomization, did not receive study drug, and was lost to follow-up. The remainder, 34 subjects, were randomized to either Sequence 1 (fexofenadine plus grapefruit juice, followed by placebo plus grapefruit juice) or Sequence 2 (placebo plus grapefruit juice, followed by fexofenadine plus grapefruit juice) and comprised the safety population. Of these 34 subjects, 16 were randomized to Sequence 1 and 18 were randomized to Sequence 2. None of these subjects discontinued the study early.
All 34 subjects were also considered protocol correct.

Diagnosis and main criteria for inclusion: Male or female; subjects 18-55 years of age, with positive histamine skin prick tests (or duplicate histamine 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

Test product, dose and mode of administration, batch number: Fexofenadine HCl 180 mg, PO tablet x 1 dose with 8 oz regular strength grapefruit juice. Batch number not available.

Duration of treatment: 1 dose with 8 oz regular strength grapefruit juice. A 14 ±4 day washout period separated treatment periods.

Reference therapy, dose and mode of administration, batch number : Matching placebo , oral tablet x 1 dose with 8 oz regular strength grapefruit juice. Batch Number not available.

Criteria for evaluation:

Efficacy Primary endpoint:

- Size of change in skin flares 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).

Efficacy Secondary endpoints:

- 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 $\geq$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 of maximum percent suppression: based on skin wheal and flare data.

Safety data included serious and non-serious adverse events, urine pregnancy testing, and vital signs.

STATISTICAL METHODS:

The primary analysis variable is the difference between pre-dose skin flare and subsequent skin flare summation measurements within each subject as described in Appendix A.

The secondary efficacy parameters are:

- The onset of histamine flare block is the first time when the difference in summation diameters between active treatment and placebo is $\geq$5 mm change from baseline on 2 consecutive measurements.
- The duration of histamine flare block is the difference between the onset of histamine flare block and the time when the change from baseline between placebo and active treatment becomes less than 5 mm on 2 consecutive measurements, unless occurrence is at Hour 24, when one measurement is sufficient.
- The onset of histamine wheal block is the first time when the difference in summation diameters between active treatment and placebo is $\geq$1 mm change from baseline on 2 consecutive measurements.
- The duration of histamine wheal block is the difference between the onset of histamine wheal block and the time when the change from baseline between placebo and active treatment becomes less than 1 mm on 2 consecutive measurements, unless occurrence is at Hour 24, when one measurement is sufficient.
- The time of maximum percent suppression based on skin flare data. Percent suppression is the ratio of change within each subject between baseline (pre-dose) and subsequent summation measurements to baseline (pre-dose) measurement;
- The time of maximum percent suppression based on skin wheal data.

To minimize within subject data variability, duplicate histamine skin prick tests were conducted at baseline (pre-dose), 6 hours, 12 hours and 24 hours. Appropriate statistical methodology was used to describe and make inference on the reliability of the wheal and flare measurements.

The average of the two histamine-induced wheal (flare) measurements was used for efficacy analyses at previously identified time points.

SUMMARY – CONCLUSIONS

The mean age was 33.4 years for Sequence 1 subjects and 30.7 for Sequence 2 subjects. There were approximately 10% more females than males within each sequence group. The majority of subjects in Sequence 1 were White (10/16, 62.5%), followed by Black (6/16, 37.5%). For Sequence 2 subjects, the majority was Black (9/18, 50.0%), followed by White (5/18, 27.8%). No statistically significant differences were found between sequence groups in these parameters.

EFFICACY RESULTS:

Skin Flares: Fexofenadine 180 mg plus grapefruit juice had significantly greater suppression of histamine-induced flares than placebo plus grapefruit juice at all timepoints beginning at 2 hours and lasting through 24 hours post-treatment for mean change from pre-dose. These results are similar to those observed from a previous trial of fexofenadine HCl 180 mg versus loratadine 10 mg or placebo.

Skin Wheals: Fexofenadine 180 mg plus grapefruit juice had significantly greater suppression of histamine-induced wheals than placebo plus grapefruit juice at all timepoints beginning at 2 hours and lasting through 12 hours post-treatment for mean change from the pre-dose value. Mean changes from pre-dose trended toward significance at 23 and 24 hours post-dose for fexofenadine plus grapefruit juice ($p<0.10$).

Onset & Duration of Action: The onset of suppression of histamine-induced skin flares occurred at 2 hours post-dose for fexofenadine 180 mg plus grapefruit juice. The duration of action was 22 hours (no offset was observed). The onset of suppression of histamine-induced skin wheals occurred at 3 hours post-fexofenadine plus grapefruit juice with a duration of action of 21 hours (no offset was observed).

Max % Suppression: The maximum percent suppression of skin flares was reached at 8 hours post-dose for fexofenadine plus grapefruit juice and was 84.8%; maximum wheal suppression was reached at 4 hours post-dose and was 64.0%. For placebo, the maximum percent suppression of skin flares was reached at 20 minutes post-dose and was 5.1%; maximum wheal suppression was reached at 2 hours post-dose and was 7.1%.

SAFETY RESULTS:

Two of the thirty-four (5.9%) subjects reported treatment emergent adverse events overall (n=1 for headache, n=1 for drowsiness), both possibly related to study drug. Both subjects were in the Sequence 1 group (fexofenadine first), but had crossed-over and were receiving placebo at the time of the events. No countermeasures such as medications were given and both subjects recovered without sequelae and continued in the study.

No deaths, serious adverse events, discontinuations from the study due to adverse events, overdoses, or pregnancies occurred in this study. Baseline values for vital signs were similar regardless of sequence or treatment group. Overall changes from baseline were also similar regardless of sequence or treatment group, were small and not clinically relevant.

Date of the report: 12 February 2003