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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:	Aventic Pharmaceuticals, Inc. Member of the sanofi-aventis group	

Title of Study: (M016455A/4144) Comparative study evaluating the effects of fexofenadine HCl 180 mg with orange juice versus placebo with orange juice in a skin wheal and flare challenge model

Principal Study Investigator: Michael Kaliner, MD

Study centre: one U.S. site: The Institute for Asthma and Allergy, P. C.
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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 meeting (November 7 - 12, 2003 New Orleans, Louisiana).

Study period (years): (date of first enrolment) (date of last completed): 4 November, 2002, to 6 December, 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 orange juice versus placebo plus orange 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 at 23 and 24 hours post-dose.

The secondary objectives were the comparison of the effects of fexofenadine plus orange juice versus placebo plus orange juice on the following:

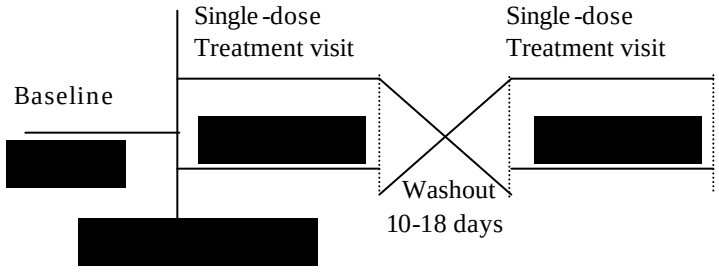
- Change from baseline (pre-dose) in skin wheals at 20, 40, and 60 minutes post-dose, then hourly through the first 12 hours post dose, and at 23 and 24 hours post-dose;
- Onset of action based on histamine wheal and flare data following study drug administration;
- Duration of action based on histamine skin wheal and flare data; and
- Time of maximum percent suppression based on histamine skin wheal and flare data.

An additional secondary objective was to evaluate the population pharmacokinetics of fexofenadine by analyzing plasma samples; these data are included in a separate report.

The safety of the study medication was evaluated by monitoring for serious adverse events (SAE), non-serious adverse events, and vital signs.

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 planned to be enrolled. The number of subjects screened for this study was 40. Of these, 3 subjects (# 9, 11, and 29) were considered screening failures; subject 9 withdrew consent prior to receiving study drug. One

subject was discontinued from the study prior to receiving study drug due to a pretreatment adverse event, high blood pressure. Two (2) subjects were granted a waiver from the sponsor and allowed to participate in the study. The remainder, 36 subjects, were randomized to either Sequence 1 (fexofenadine + orange juice followed by placebo + orange juice) or Sequence 2 (placebo + orange juice followed by fexofenadine + orange juice) and comprised the safety population. Of these 36 subjects, 18 subjects each were randomized to Sequence 1 and Sequence 2, respectively. None of these subjects discontinued the study early. All 36 subjects were also considered protocol correct.

Diagnosis and main criteria for inclusion: Healthy male or non-pregnant, non-lactating female subjects; 12-55 years of age; within 15% of normal body weight for their height or had a body mass index (BMI) less than 29.9 kg/m^2; positive histamine skin prick tests (or a 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 HCI 180 mg oral tablet x 1 dose with 8 oz orange juice. Batch number not available

Duration of treatment: x 1 dose with 8 oz orange juice

Reference therapy, dose and mode of administration, batch number: Placebo, PO tablet (matching to fexofenadine). Batch number not available

Criteria for evaluation:

Efficacy Primary endpoint:

- Size of change in skin flares from baseline 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 and change in skin wheals from baseline measured at pre-specified time points (20 min, 40 min, 60 min, and hourly through 12 hours, with an additional 2 time points obtained at 23 and 24 hours post-dose).
- Onset of action, defined as the first time the difference in summation diameters between active treatment and placebo represented a =5 mm change from baseline on 2 consecutive measurements for flares, or a =1 mm change on 2 consecutive measurements for wheals
- Duration of action, defined as the point at which the change from baseline between placebo and active treatment became <5 mm on 2 consecutive measurements for flares, or <1 mm on 2 consecutive measurements for wheals (except at 24 hours, when 1 measurement was sufficient).
- Time of 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 had a medical history taken, received a physical examination, and had skin prick testing (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 (± 4) days.

Safety: Safety was assessed by monitoring serious and non-serious adverse events (AE), vital signs, and urine pregnancy tests.

Pharmacokinetics: Plasma samples for population pharmacokinetic analysis were collected for measurement of maximum plasma concentration (Cmax) and area under the concentration time curve (AUC). Four samples were required per subject and included one sample between 0.5 and 6 hours post-dose during Visit 2, one sample at 22-24 hours post-dose on Visit 3, one sample between 0.5 and 6 hours post-dose during Visit 4, and one sample at 22-24 hours post-dose on Visit 5. Additional samples were optional and were allowable between 0.5 to 6 hours post-dose and/or between 8 and 24 hours post-dose. Sample times and dates were recorded

Statistical methods:
The primary efficacy variable was the summation flare (SF).
Secondary variables were the summation wheal (SW) and other endpoints summarized under efficacy data above. Primary and secondary efficacy variables were analyzed in the protocol correct population (all subjects who completed the study without a major protocol violation) using a one-way, repeated measure ANOVA method with terms of (at least, but not limited to) sequence (confounded with carryover effect), period, and treatment, and model-based comparisons to detect treatment difference at the significance level of 0.05 for both skin flares and skin wheals, conducted at all time points.

SUMMARY – CONCLUSIONS

The mean age was 32.8 years for Sequence 1 subjects and 33.4 years for Sequence 2 subjects. There were twice as many females than males within Sequence 1 group (12 versus 6 subjects) and 8 times more females in Sequence 2 (16 versus 2 subjects). There were equal numbers of black and white subjects in Sequence 1 (7/18 each, 38.9%). For Sequence 2, the majority of subjects were Black (10/18, 55.6%), followed by White (5/18, 27.8%). The mean weight (lb) and BMI (kg/m2), respectively, were 170.3 and 26.6 for Sequence 1 and 149.0 and 24.2 for Sequence 2. There were no statistically significant differences between sequence groups in these parameters.

EFFICACY RESULTS:
Skin Flares: Fexofenadine 180 mg plus orange juice was significantly greater than placebo plus orange juice for mean change from pre-dose suppression of histamine-induced flares at all time points beginning at 60 minutes and lasting through 24 hours post-treatment. No significant differences were seen at 20 or 40 minutes post-dose. These results are similar to those observed from two previous trials: Protocol M016455A/4143 – fexofenadine HCl 180 mg plus grapefruit juice versus placebo and grapefruit juice; and Protocol M016455/4120 – fexofenadine HCl 180 mg versus loratadine 10 mg or placebo.
Skin Wheals: Fexofenadine 180 mg plus orange juice was significantly greater than placebo plus orange juice for mean change from pre-dose suppression of histamine-induced wheals at all time points beginning at 2 hours and lasting through 10 hours post-treatment and again at 23 hours post-treatment. No significant differences were seen at 20, 40, and 60 minutes, or at 11, 12, or 24 hours post-treatment.
Onset & Duration of Action: The onset of suppression of histamine-induced skin flares occurred at 60 minutes post-dose for fexofenadine 180 mg plus orange juice. The duration of

action was 23 hours (offset was not observed). The onset of suppression of histamine-induced skin wheals occurred at 3 hours post-fexofenadine plus orange juice with a duration of action of 8 hours. Even though the duration of action for suppression of histamine-induced wheals was only 8 hours (based on protocol definition), the mean change from pre-dose for fexofenadine 180 mg plus orange juice were significantly greater for suppression of histamine-induced wheals than placebo plus orange juice at 23 hours post-treatment.

Max % Suppression: The maximum percent suppression of skin flares was reached at 8 hours post-dose for fexofenadine plus orange juice and was 91.5%; maximum wheal suppression was reached at 4 hours post-dose and was 33.1%. For placebo, the maximum percent suppression of skin flares was reached at 20 minutes post-dose and was -1.4% (always larger than the baseline value); maximum wheal suppression was reached at 60 minutes post-dose and was 6.9%.

SAFETY RESULTS:

Five of the thirty-six (13.9%) subjects reported treatment-emergent adverse events overall. Two of 36 subjects (5.6%) reported headache with fexofenadine 180 mg plus orange juice, whereas 3 of 36 subjects (8.3%) reported headache with placebo plus orange juice. Adverse events were similar regardless of sequence. Only one of five reports of headache was considered related to study drug (subject received placebo plus orange juice). One subject who received fexofenadine 180 mg plus orange juice and two subjects who received placebo plus orange juice experienced headache that required treatment. All five 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.

Pharmacokinetics Results: reported elsewhere.

Date of the report: 07 August, 2003