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Proprietary Drug Name: ALLEGRA-D® 12 HOUR	**INN:** fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg extended-release tablets	**Therapeutic area and FDA approved indications:** for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/and or throat, itchy/watery red eyes and nasal congestion. ALLEGRA-D 12 HOUR should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the decongestant properties of pseudoephedrine hydrochloride are desired.
Name of Sponsor/Company:	Aventis Pharmaceuticals, Inc. Member of the sanofi-aventis group	

Title of Study: M016455/4001 Single-center double-blind, randomized, parallel study comparing onset of action, efficacy and safety of a single-dose of Allegra-D® (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) and placebo in treating seasonal allergic rhinitis subjects in an allergen exposure unit II

Principal Study Investigator: Robert B. Berkowitz, MD

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Publication:

Berkowitz RB, McCafferty F, Lutz C, Bazelmans D, Godfrey P, Meeves S, Liao Y, Georges G. Fexofenadine HCl 60 mg/ pseudoephedrine HCl 120 mg has a 60-minute onset of action in the treatment of seasonal allergic rhinitis symptoms, as assessed in an allergen exposure unit. *Allergy Asthma Proc*. 2004 Sep-Oct;25(5):335-43.

Study period (years): (date of first enrolment) (date of last completed)	**Phase of development:** Phase IV
July 16, 2002 to October 19, 2002	

Objectives:

Primary: To determine the onset of action of Allegra-D (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) in the treatment of subjects with moderately severe seasonal allergic rhinitis (SAR) in a controlled setting.

Secondary: To compare the safety and efficacy of Allegra-D and placebo.

Methodology:

This was a single-center, single-dose, randomized, double-blind, placebo-controlled, parallel-group study. The study consisted of a screening visit, one or two 3-hour priming visits, and a treatment visit, all occurring within approximately 4 weeks.

Number of patients (planned and analyzed):

- A minimum of 480 subjects (240 per treatment group) were to be enrolled and treated with study medication. The estimated number of subjects screened was to be 620.
- A total of 1122 subjects were screened for enrollment at 1 investigative site in the United States. Of these 1122 subjects, 634 were considered screen failures and 488 subjects were randomized. Two subjects withdrew their consent and discontinued from the study prior to receiving any double-blind study medication

Diagnosis and main criteria for inclusion:

Male or female subjects 12 years of age or older with a history of SAR during the fall pollen season for at least the previous 2 years and a positive skin test to ragweed within the last 15 months.

Test product, dose and mode of administration, batch number:

Allegra-D® oral tablet every 12 hours (60 mg fexofenadine HCl and 120 mg pseudoephedrine HCl. Batch # KE2002028.

Duration of treatment: The study consisted of a screening visit, one or two 3-hour priming visits, and a treatment visit, all occurring within approximately 4 weeks. This was a single dose study.

Reference therapy, dose and mode of administration, batch number

Placebo tablet, identical in appearance to Allegra-D®, every 12 hours. Batch # KE2002025.

Criteria for evaluation:

Efficacy was to be evaluated at 15- to 30-minute intervals based on subject assessments of SAR symptoms recorded on diary cards during exposure to ragweed pollen in an allergen exposure unit. Certain symptoms were combined to form the major symptom complex (MSC) (primary) and the total symptom complex (TSC). One symptom, headache, was not included in the MSC or TSC.

Safety: Adverse events reported by the subject or noted by the investigator.

Statistical methods:

The primary efficacy analysis, conducted in the intent-to-treat population (ITT), investigated the onset of action of Allegra-D based on change from baseline in MSC score (the sum of the symptom scores for subjects' assessments of sneezes, itchy nose, runny nose, watery eyes, itchy eyes, itchy ears/throat, and stuffy nose). Onset of action was defined as the first (between 15 minutes and 6 hours postdose) of 2 consecutive measurements at which a statistically significant change in the MSC was achieved for Allegra-D relative to placebo.
Treatment comparisons for each time point were conducted using an analysis of variance model with fixed terms for treatment group and replication, and a random term for block (block of 6 consecutive treatment assignment numbers [TANs] assigned to 6 subjects with similar baselines). Adjusted treatment means with standard errors, adjusted mean treatment difference with standard error, a 95% confidence interval for the adjusted mean treatment difference, and p-value testing the adjusted mean treatment difference were provided at each time point. A two-tailed p-value less than 0.05 at 2 consecutive post baseline time points would be required to declare onset of action and efficacy of Allegra-D.
Supportive analyses of the primary endpoint were conducted using the protocol-correct and modified intent-to-treat populations.
If onset of action was not observed using this definition, the primary analysis was to be the change in mean MSC across all diary cards at 1 to 5 hours postdose relative to the predose mean baseline MSC (defined as the mean of the data recorded on the 2 predose baseline diary cards).
Secondary analyses included the following:

- Onset of action based on
  - Absolute and percent change in TSC
  - Percent change in MSC
  - Absolute and percent change in individual symptoms;
- Absolute and percent change in TSC, MSC, and individual symptoms across all diary cards at 1 to 5 hours (inclusive) relative to mean predose baseline symptom evaluation;
- Time at which a 7-point reduction in absolute MSC is achieved and number of subjects experiencing a 7-point reduction in absolute MSC;
- Sustainability/durability of effect;
- Time at which prespecified reductions in MSC and TSC scores are achieved.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Onset of action based on reduction in MSC scores for Allegra-D subjects relative to placebo (the primary efficacy endpoint) first occurred at 1 hour post-dose. Similarly, onset of action for Allegra-D subjects based on percent reduction in MSC scores and both absolute and percent reduction in TSC scores relative to placebo also occurred at 1 hour post-dose. The significant differences lasted through 6 hours post-dose for all endpoints, which confirmed both sustainability and durability of effect. Other significant differences noted in the Allegra-D treatment group when compared to placebo
included:

- Mean change-from-baseline scores during the 1- to 5-hour post-dose interval for MSC, TSC, and many individual symptoms were significantly lower;
- A greater number of subjects achieved a 7-point reduction in MSC (it took an average of 74.9 minutes in the Allegra-D group compared to an average of 91.8 minutes in the placebo group);
- Reductions in MSC and TSC scores of 50%, 60%, 70%, and 80% occurred generally in more subjects receiving Allegra-D and in a shorter period of time.

SAFETY RESULTS:

The safety-evaluable population consisted of 486 subjects, 243 in the Allegra-D treatment group and 243 in the placebo treatment group. All safety-evaluable subjects received a single dose of double-blind study medication on the morning of the treatment visit (Visit 3).

- The overall frequency of treatment-emergent adverse events was low (Allegra-D: 1.6%; placebo: 3.3%) in both the Allegra-D and placebo treatment groups;
- The only event reported in more than 1 subject was somnolence, which occurred more frequently in the placebo group then in the Allegra-D group;
- All treatment-emergent adverse events were mild or moderate in intensity except for 1 event of somnolence in the placebo group, and all were possibly related to study medication;
- There were no deaths or serious adverse events, and no discontinuations due to adverse events;
- Overall, there were no meaningful differences in the incidence, pattern, or intensity of treatment-emergent adverse events for the Allegra-D and placebo treatment groups.

Date of the report: 7 March, 2003