CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:	**20786**
Trade Name:	**Allegra-D**
Generic Name:	**Fenofenadine/pseudoephedrine**
Sponsor:	**Hoechst Marion Roussel**
Approval Date:	**December 24, 1997**
Indication:	**Seasonal allergic rhinitis in adults and children 12 years of age and older**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20786

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20786

APPROVAL LETTER

NDA 20-786

DEC 24

Hoechst Marion Roussel, Inc.
P.O Box 9627
Kansas City, MO 64134-0627

Attention: Elaine Waller, Pharm.D.
Vice President,
North American Regulatory Affairs

Dear Dr. Waller:

Please refer to your new drug application dated December 20, 1996, received December 20, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Allegra-D (fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) Extended-Release Tablets.

We acknowledge receipt of your submissions dated January 9 and 17, February 5, 11, and 12, March 10, 14, and 31, April 30, May 20, June 2 and 26, July 2, 21, and 25, August 15 and 19, September 15, 25, and 30, November 4, 5, 13, 14, and 17, and December 5, 11, 12, 15, 17, and 19, 1997. The user fee goal date for this application is January 2, 1998.

This new drug application provides for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 year of age and older.

We have completed the review of this application, as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated December 19, 1997, with the revisions listed below. Accordingly, the application is approved effective on the date of this letter. The revisions are as follows.

1. The immediate carton and container labeling should contain the lot or control number.

2. In the last paragraph of the "Pharmacokinetics" subsection, the reference to "Dosage and Administration" should be capitalized.

3. In the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection, third paragraph, the sentence reading "(approximately 1/2 and 1/3, respectively...)" should read "(approximately 1/3 and 1/2, respectively...)." In addition, the word "times" should be deleted from this sentence.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-786." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated December 5, 1997. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4

commitments must be clearly designated "Phase 4 Commitments."

In addition, we remind you of the following agreements.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20786

MEDICAL REVIEW(S)

NOV 26 1997

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

Application #:	20-786	Application Type:	NDA
Sponsor:	Hoechst Marion Roussel, Inc.	Product/Proprietary Name:	ALLEGRA-D Extended Release Tablet
Principal Investigator:	Not Applicable	USAN/Established Name:	Fexofenadine HCl 60 mg/Pseudoephedrine HCl 120 mg Extended Release Tablets
Category of Drug:	Histamine H_1 Receptor Antagonist/Decongestant	Route of Administration:	Oral
Reviewer:	Alexandra S. Worobec, M.D.	Review Date:	11/10/97, revised 11/18/97

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
December 20, 1996	December 20, 1996	NDA 20-786	
April 30, 1997	May 1, 1997	NDA 20-786	120 Day Safety Update
May 20, 1997	May 21, 1997	NDA 20-786	Protocol PR0035
November 13, 1997	November 17, 1997	NDA 20-786	Protocol PR0035

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
July 31, 1995	NDA 20-625	NDA Application for ALLEGRA
August 8, 1995	IND	IND Application for ALLEGRA-D

Overview of Application/Review: This is an NDA for ALLEGRA-D (fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg tablet combination) administered twice a day for the treatment of symptoms of SAR (including nasal congestion) in adults and children 12 years of age and older. One clinical ragweed SAR trial (PO0035) and 5 human PK trials were evaluated to assess the efficacy of this combination treatment with respect to each individual component of ALLEGRA-D. While bioequivalence was not demonstrated for the pseudoephedrine HCl component at the end-of dosing interval (but was for the fexofenadine HCl component), statistically significant reduction in nasal congestion (the pseudoephedrine mediated symptom) was shown in the study PR0035 at the end-of-dosing interval. ALLEGRA-D likewise maintained an adequate duration of effect and was shown to reduce most SAR symptoms 1-3 hours after dosing. No outstanding safety concerns were seen with ALLEGRA-D, with no evidence of cardiac arrhythmias or QT_c prolongation. Headache, insomnia, and nausea were the most frequent AEs based on an safety evaluable combination group population of 215 patients. Based on a review of the data presented in the submission for NDA 20-786, the medical reviewer recommends approval of ALLEGRA-D in adults and children 12 years of age and older, for the treatment of symptoms of SAR and nasal congestion.

Outstanding Issues: None

Recommended Regulatory Action: Approvable

N drive location:n:\NDA\20786\clin\97-11-18.rev

New Clinical Studies: ___NA___ Clinical Hold ___NA___ Study May Proceed

NDAs:

Efficacy/Label Supp.: ___NA___ Approvable ___NA___ Not Approvable

Signed: Medical Reviewer: Alexandra S. Worobec, M.D. Date: 11/18/97

Medical Team Leader: [signature] Date: 11/20/97

cc: orig NDA 20 786
Div File
Worobec
Himmel
Trout
Elashoff
Wilson

MEDA_APTX03505103

PTX0126-00008

Medical Officer's Review

NDA #:	20-786	Submission Date: December 20, 1996
Medical Officer Review:	20-786	Filing Date: January 2, 1997
		Review Completed:

1.2. Drug Name:

1.2.1. Generic Name: Fexofenadine HCl 60 mg/Pseudoephedrine HCl 120 mg Extended Release Tablet

1.2.2. Proposed Trade Name: ALLEGRA-D™ Extended Release Tablet

1.2.3. Chemical Name: Fexofenadine HCl: (±)-4-[1[Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α-α-dimethylbenzenacetic acid HCl (MDL 16,455A)
Pseudoephedrine HCl: [S-(R*,R*)-α-[1-(Methylamino)ethyl]-benzenemethanol HCl

1.3. Sponsor: Hoechst Marion Roussel, Inc.

1.4. Pharmacologic Category: Histamine H_1-receptor antagonist/decongestant combination

1.5. Proposed Indication: Treatment of symptoms due to seasonal allergic rhinitis

1.6. Dosage form and route of administration: Fexofenadine HCl 60 mg/Pseudoephedrine HCl 120 mg Extended Release tablet twice a day.

1.7. NDA Drug Classification: S

1.8. Related Drugs: NDA 20-625: ALLEGRA™ (Fexofenadine 60 mg capsules), Approved July 25, 1996.

1.9. Related Reviews: Chemistry review #1 dated: 04/14/97
Chemistry review #2 dated: 07/31/97
Chemistry review #3 dated:
Pharmacology/Toxicology review dated: 03/14/97
Pharmacology/Toxicology
Environmental Assessment dated: 03/12/97
Statistical review dated: 11/05/97
Biopharmaceutics review dated: 10/17/97

2.0. TABLE OF CONTENTS

3.0. CONDUCT OF THE REVIEW

The clinical review of NDA 20-786 (ALLEGRA-D) was conducted using volume 1.1 of the NDA submission [S2-V1.1], along with volumes S9-V1 to S9-V33 of the 120 Day Safety Update for NDA 20-786, and volumes 4.1-4.4: the supporting statistical analysis programs data-sets and documentation (for analysis of weekly scores).

The one pivotal clinical study was reviewed after determination by the Agency that bioequivalence for the combination product: fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg was not demonstrable for the pseudoephedrine component. The only clinical indication for this combination product in this NDA submission is the treatment of the symptoms of SAR in adults and children age 12 years and older. Line listings were reviewed for all efficacy endpoints, demographic subgroups, and the efficacy results for the intent-to-treat population were compared to the efficacy evaluable population in order to evaluate any potential discrepancies. The safety review also consisted of a review of all adverse events by summary tables and line listings, along with review of the physical examination line listings. Particular importance was placed on cardiac adverse events and evaluation of electrocardiographic evaluation of patients' ECG tracings before and after treatment with the combination drug. Laboratory tests were likewise reviewed, with special attention to trends in mean values post-treatment with the combination drug, compared with the 2 active comparators and patient outlier values for liver function tests, white blood count and absolute neutrophil count. 'Clinically significant' or 'outlier' liver function elevations or white blood cell count changes were defined as falling outside the 'normal' range values for the clinical parameter by a specified amount [S9-V1-p. 139-140] defined in the study report by the sponsor.

Pertinent positive and negative safety and efficacy findings are discussed in the clinical study review, with the appropriate volumes indexed from the NDA or 120 Day Safety Update [Submission Number-Volume of Submission-pages]. An integrated summary of efficacy and safety was not appropriate for the analysis of the 1 clinical study reviewed in this NDA, although additional human safety information derived from human PK studies with ALLEGRA-D are discussed in the integrated summary of safety section. The medical reviewer's recommendations for approval are summarized in the Conclusion-'Executive summary of efficacy and safety' section (section 12.0.).

4.0. CHEMISTRY, MANUFACTURING, AND CONTROLS

ALLEGRA-D is a fixed combination coated tablet consisting of 60 mg immediate release fexofenadine HCl and 120 mg of sustained release pseudoephedrine HCl. The daily recommended dose of ALLEGRA-D is one tablet twice a day. The formulation of ALLEGRA-D is an engraved, bi-layer tablet form containing a white fexofenadine HCl layer and a second tan pseudoephedrine HCl layer in a for extended release [CMC Review #

1, Dr. Brian Rogers, 04/15/97, NDA 20-786, p. 15]. The fexofenadine HCl layer also contains microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, and magnesium stearate. The pseudoephedrine layer also contains carnauba wax, stearic acid, and colloidal silicon dioxide. The individual components of ALLEGRA-D are listed in Figure 1. below.

Figure 1: **INGREDIENTS of ALLEGRA-D:**

INGREDIENT	Mg/Tablet
Fexofenadine HCl layer	
--Fexofenadine HCl	60
--Microcrystalline Cellulose	
--Pregelatinized Starch	
--Microcrystalline Cellulose	
--Croscarmellose Sodium	
--Magnesium Stearate	
Pseudoephedrine HCl layer	
--Pseudoephedrine HCl	120
--Carnauba Wax	
--Stearic Acid Flakes	
--Colloidal Silicon Dioxide	

Of note, the drug lot for the 'to-be-marketed' ALLEGRA-D (lot RC9614) represents the same lot used in the pivotal clinical trial PR0035 and in all the bioavailability studies (with the exception of the fexofenadine-pseudoephedrine interaction study (Study PJPR0043) which used commercially available fexofenadine HCl and pseudoephedrine HCl [Biopharmaceutics Review, Dr. Bradley Gillespie, NDA 20-786, 10/17/97, p. 4 and S3.V1.2-p. 58].

On review of NDA 20-786, the amount of magnesium stearate in the 'to-be-marketed' product was noted to have been changed by the sponsor, with the final 'to-be-marketed' formulation delivering approximately less magnesium stearate and therefore a substantially lower dose of pseudoephedrine HCl. This change in formulation prompted the requirement for additional pharmacokinetic data by the Agency in order demonstrate bioequivalence of the combination product with the 2 separate single ingredients; in particular in this case, the pseudoephedrine HCl component.

Another CMC issue for the ALLEGRA-D application was that of the NDA submission for ALLEGRA-D containing 6 months accelerated and 6 months regular stability data on the primary stability batches. While the sponsor submitted some supporting data for up to 12 months, these were not for the 'to-be-marketed' formulation and/or the 'to-be-marketed' packaging., As per the ICH

Stability Guidelines, current recommendations at the time of approval for the application were provision by the sponsor of at least 12 month stability data at the time of the submission of the NDA. Since the 6/6 month stability data submitted by the sponsor only became available in November, 1996, the earliest the 12 month data became available to the Agency was June, 1997. Hence, the application for ALLEGRA-D would be approved on review of the 12 month data, since the expiration dating that the 6 month data would support would be too short for the sponsor to distribute and market the product.

5.0. ANIMAL PHARMACOLOGY/TOXICOLOGY

As the individual components of ALLEGRA-D--fexofenadine HCl 60 mg (NDA 20-625) and pseudoephedrine HCl 120 mg (Final Monograph for OTC Nasal Decongestant Products) are already approved drugs by the oral route and the pharmacology and toxicology of both components is well known, preclinical data was not required for the approval of ALLEGRA-D, a combination product of fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg.

The toxicity profile of fexofenadine HCl in animals was based on that of its pro-drug, terfenadine, during the approval of ALLEGRA (approved July 26, 1996). Pseudoephedrine HCl is considered safe and effective under the Final Tentative Monograph for OTC Cold, Cough, Allergy Bronchodilator, and Antihistaminic Combination Drug Products. Furthermore, the doses of fexofenadine HCl and pseudoephedrine HCl for this combination product are the same as those in the respective individual marketed products.

Environmental assessment of ALLEGRA-D indicated that no environmental impact was anticipated, hence no alternatives to manufacturing practices were recommended by the Agency.

6.0. CLINICAL BACKGROUND

Relevant Human Experience

Two adequate and well-controlled efficacy and safety phase III clinical trials were not required by the Agency as a basis for approval of ALLEGRA-D, as this application represents a combination of 2 approved products. Based on the 1992 FDA Guidance 'Statistical Procedures for Bioequivalence Studies Using the Standard Two-Treatment Crossover Design', the sponsor elected to follow the bioequivalence approach as the basis for approval of this combination product. Because the results of the single-dose bioequivalence study for the 'to-be-marketed' product (study DDPR0005) failed to demonstrate bioequivalence (C_{max} significantly lower for the pseudoephedrine HCl component of ALLEGRA-D), the sponsor, at the request of the Agency, submitted the results of a double-blind, active-controlled clinical trial (study PR0035) in order to evaluate the reduction in nasal congestion at the end-of dosing interval for ALLEGRA-D, as compared to

ALLEGRA and SUDAFED. This one Canadian study (study PR0035) constituted the pivotal clinical trial for ALLEGRA-D (NDA 20-786).

Important Information from related INDs and NDAs

Information about the combination product and its rationale for development is provided in IND (ALLEGRA-D). Information about the safety and efficacy of fexofenadine HCl alone was provided by the medical officer review of NDA 20-625 (ALLEGRA) in which 4 adequate and well-controlled phase III trials provided evidence of efficacy of fexofenadine HCl in the reduction of SAR related symptom scores, as compared with placebo. The safety database for ALLEGRA includes data available in NDA 20-625 from over 2800 patients with allergic rhinitis and normal volunteers treated with doses of ALLEGRA up to 690 mg po bid. Since fexofenadine HCl (MDL 16,455) is the major human metabolite of terfenadine (Seldane, NDA 18-949 and Seldane-D, NDA 19-664), the safety database also includes the extensive clinical exposure to fexofenadine HCl which has occurred in patients treated with terfenadine.

Pseudoephedrine HCl is generally recognized as safe and effective for the relief of nasal congestion under the Final Monograph for OTC Nasal Decongestant Drug Products [S2-V1.1-p. 144, S8-V1.33-p. 8]. The recommended dose is not to exceed 240 mg of pseudoephedrine HCl in 24 hours.

An antihistamine and oral nasal decongestant combination product is listed as Category I (generally recognized as safe and effective) under the Tentative Final Monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products [S2-V1.1-p.145].

Foreign Experience

ALLEGRA-D is currently not approved in any country. Furthermore, there have not been any commercial marketing experiences or foreign regulatory actions taken with the combination product. ALLEGRA was approved in the U.S. on 07/25/96 (NDA 20-625) and was more recently approved in the U.K. The various formulations of immediate and sustained release pseudoephedrine HCl products comprise USP Monograph drugs whose safety and efficacy are well established.

Human Pharmacology, pharmacokinetics, pharmacodynamics

A total of 4 pharmacokinetic studies were submitted by the sponsor in support of ALLEGRA-D at the time of filing of the NDA: (1) a single-dose formulation screen (protocol PJPR0038), (2) a multiple-dose bioequivalence study comparing the proposed product to the approved reference products (DDPR0001), (3) a food effect study (DDPR0002), and (4) a fexofenadine HCl/pseudoephedrine HCl interaction study (PJPR00430 [S2-V1.1-p. 72-134]. At the 45 Day Planning Meeting, a single-dose bioequivalence study (study DDPR0005) was requested by the Agency in support of the application for ALLEGRA-D, since a single-dose

bioequivalence study comparing the 'to-be-marketed' product to an approved reference was not included in the NDA at the time of filing.

In this single-dose bioequivalence study (n=48 subjects), bioequivalence was not demonstrated between the proposed tablet and reference treatments (ALLEGRA capsule and SUDAFED extended release tablet). While the AUC and plasma concentration at the end of the dosing interval were equivalent in both comparisons, C_{max} was significantly lower for the pseudoephedrine HCl component of the combination product (90% confidence interval: 0.78-0.83) and higher for fexofenadine HCl (90% confidence interval: 1.04-1.34). Failure to demonstrate bioequivalence is nonetheless offset by review of the clinical efficacy data in study PR0035 and in particular, the reduction in nasal congestion at the end-of dosing interval by the combination product, in which the combination product demonstrated a statistically significant decrease in symptom scores, as compared with fexofenadine HCl alone (p=.0007, refer to section 8.1.4.2. of the Medical Officer Review, Table IX.).

The multiple-dose bioequivalence study (DDPR0001) demonstrated bioequivalence of the combination product with the reference products.

After administration of a single dose of the combination product, the mean fexofenadine HCl C_{max} was 191.5 ng/mL (CV 52%), the mean $AUC_{0-\infty}$=1369 ng•hr/mL (CV 39%), the median T_{max}=2 (range:) hours, the mean plasma elimination half-life=16.48 hours (CV 47%), and oral clearance=47.24 L/hr (CV 43%). The mean pseudoephedrine HCl C_{max} for the combination product was 206.4 ng/mL (CV 16%), the mean $AUC_{0-\infty}$=3576 ng•hr/mL (CV 23%), the median T_{max}=6 (range: 2-8) hours, the mean plasma elimination half-life=7.82 hours (CV 18%), and oral clearance=28.51 L/hr (CV 24%).

After multiple-dose administration of the combination product (1 tablet q 12 for 11 doses) the mean fexofenadine HCl $C_{max,ss}$ was 254.5 ng/mL (CV 48%), the mean $AUC_{0-12,ss}$=1525.1 ng•hr/mL (CV 41%), and T_{maxss}=2 (range: hours. The mean pseudoephedrine HCl $C_{max,ss}$ was 410.8 ng/mL (CV 20%), $C_{minx,ss}$ was 224.5 ng/mL (CV 27%), the mean $AUC_{0-12,ss}$=4060.5 ng•hr/mL (CV 20%), and T_{maxss}=5 (range: 3-6) hours.

A food effect study (DDPR0002) showed that when the combination product is given with food, a substantial decrease in fexofenadine HCl bioavailability (C_{max} -46%, $AUC_{0-\infty}$ -42%) can be expected with no appreciable effect on the absorption of pseudoephedrine HCl. These data are in contrast to those of fexofenadine hydrochloride given alone [ALLEGRA, NDA 20-625, Biopharmaceutics Review, Dr. Bradley Gillespie, 03/15/96, study PJPR0026] where relative bioavailability in the fed group was deemed slightly lower (drug administration following a stanadardized high fat breakfast) than that of the fasted group when subjects were given a single 80 mg (2 x 40 mg 'to-be-marketed' capsules) ($AUC_{0-\infty}$: -21%; p=0.007; C_{max} : -14%; p=0.098). Time to maximal concentrations (T_{max}) was delayed only slightly (+7%) [ALLEGRA, NDA20-625,

Biopharmaceutics Review, Dr. Bradley Gillespie, 03/15/96, study PJPR0026, p. 4].

A drug interaction study (PJPR0043) failed to demonstrate a pharmacokinetic interaction between fexofenadine HCl and pseudoephedrine HCl when given at therapeutic doses in healthy, male volunteers. Based on these data, these 2 compounds may be safety formulated into a combination product.

An additional pharmacokinetic trial was performed by the sponsor for various prototype fexofenadine HCl/pseudoephedrine HCl formulations (protocol PJPR0038) in support of ALLEGRA-D, and was reviewed by the biopharmaceutics reviewer and medical officer at the 45 Day Planning Meeting. Since these formulations did not represent the 'to-be-marketed product, the data from this study was not summarized in this NDA review.

Directions for use

ALLEGRA-D is indicated for the relief of symptoms associated with SAR in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes, and temporary relief of nasal congestion.

ALLEGRA-D should be administered when both the antihistaminic properties of fexofenadine HCl and the nasal decongestant properties of pseudoephedrine HCl are desired.

The recommended dose of ALLEGRA-D is 1 tablet twice daily for adults and children 12 years of age and older. ALLEGRA-D should be taken on an empty stomach. A dose of 1 tablet once daily is recommended as the starting dose in patients with decreased renal function.

7.0. DESCRIPTION OF CLINICAL DATA SOURCES

The clinical data sources for NDA 20-786 comprised the efficacy and safety data for fexofenadine HCl (ALLEGRA NDA 20-625), along with post-marketing safety data for fexofenadine HCl (Medical Officer Review of Adverse Events for the first-fourth quarterly periods,), Dr. Alexandra Worobec, ALLEGRA (NDA 20-625) and the wealth of published literature on both fexofenadine HCl and pseudoephedrine HCl.

Aside from the pivotal clinical trial PR0035 and the human safety data from the pharmacokinetic studies with ALLEGRA-D, no additional human clinical studies of safety or efficacy for the combination product were reviewed for the approval of this application.

8.0. CLINICAL STUDIES:

SEASONAL ALLERGIC RHINITIS (Pivotal Trial):

8.1. Protocol No. 016455PR0035: A comparative study of the safety and efficacy of twice-daily fexofenadine HCl 60 mg-pseudoephedrine HCl 120 mg combination vs. its components alone in the management of ragweed seasonal allergy.

Principal Investigator: None, multi-center study.

Participating Centers: 17 Canadian centers

8.1.1. Objective

The primary objective of this study was to investigate the safety and efficacy of the fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg po bid combination vs. its individual components (fexofenadine HCl 60 mg po bid and vs. pseudoephedrine HCl 120 mg po bid, respectively) in the treatment of symptoms of seasonal allergic rhinitis (SAR).

Secondary objectives were: (1) to evaluate the effect of the 3 treatments on patient productivity at work and school, (2) to assess patient's health state preferences in allergy, and (3) to study the population pharmacokinetics of fexofenadine plus pseudoephedrine.

8.1.1. Study Design

The study was a phase III, multi-center, randomized, double-blind, parallel group with 3-5 day placebo lead-in, safety and efficacy study of the combination treatment of fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg po bid vs. its individual components (fexofenadine HCl 60 mg po bid and vs. pseudoephedrine HCl 120 mg po bid, respectively) in 600 ragweed allergic patients. The study consisted of 4 subject visits: 2 screening/baseline visits (visits 1 and 2; weeks 1 and 2) and 2 treatment visits (visits 3 and 4; weeks 3 and 4) such that patients received study medication for 2 weeks. The duration of the study for a given patient was approximately 3 weeks.

8.1.1. Protocol

8.1.3.1.a. Population: Male or female patients, 12-65 years of age, with SAR documented by a positive response to ragweed allergen [S9-V1-p. 28, S9-V2-p. 16].

(I) Inclusion Criteria [S9-V1-p. 28-29, S9-V2-p.16-18]:

1. History of seasonal allergies due to ragweed allergy for at least 2 seasons.
2. A positive skin prick test to a standardized ragweed extract (diluent not specified in the protocol) performed within the previous 15 months at the investigator's site and recorded in the patient's medical record. A positive skin test was defined as a wheal diameter at least 3 mm greater than diluent within 15 minutes after placement of the allergen.
3. History of a positive response of SAR symptoms to antihistamines.
4. Clinical evidence of active SAR symptoms at both screening and baseline. At visit 1 (=screening visit), the patient's reflective total symptom score (TSS) for the previous 12 hours had to be ≥ 6, nasal congestion and 2 or more additional SAR symptoms were to be rated as 'moderate' or 'severe', and no SAR symptom was to be rated as 'very severe'. At visit 2 (=baseline visit), the reflective allergy symptom assessment from the placebo lead-in period had to meet the following criteria: a total symptom score (TSS) ≥ 6 for 2 of the 3 most recent p.m. assessments, and 2 or more SAR symptoms, other than nasal congestion, rated as 'moderate' and severe' for 2 of the 3 most recent p.m. assessments, and no symptom rated as 'very severe' at any p.m. assessment.
5. Sexually active females or females of childbearing potential were expected to use an effective form of birth control throughout the study, (defined as: continuous use of oral or long-acting injected contraceptives for at least 2 months prior to study entry, use of an IUD, use of an implantable contraceptive, or use of a barrier method) and were to have a negative serum pregnancy test prior to study enrollment (visit 1, week 1).

(II) Exclusion Criteria [S9-V1-p. 30, S9-V2-p.18-20]:

1. Upper respiratory tract infection within 30 days prior to visit 1.
2. Evidence of sinusitis within 30 days prior to visit 1.
3. Presence of any disease state or surgery known to affect the gastrointestinal absorption of drugs.
4. Known or suspected presence of any of the following medical conditions: renal or hepatic insufficiency, malnutrition, malabsorption, malignancy, chronic infection, blood dyscrasia, drug abuse or alcoholism.

5. Clinically significant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease which would make interpretation of the protocol results difficult.
6. Patients on immunotherapy to ragweed allergen, except those on stable maintenance immunotherapy for at least 6 months prior to visit 1.
7. Any laboratory abnormalities on screening blood work that might compromise the safety of the patient, or jeopardize study results, as determined by the clinical investigator.
8. Patients with moderate to severe asthma, as defined by an $FEV_1 < 70\%$ predicted and/or ≥ 3 asthma attacks/week.
9. At visit 2, a QT interval > 440 msec on ECG.
10. Use of any investigational new drug within 30 days prior to visit 1.
11. Hypersensitivity to terfenadine, fexofenadine HCl, pseudoephedrine HCl or the tablet/capsule ingredients (e.g. cellulose, lactose, cornstarch, gelatin, croscarmellose) in either of these medications.
12. At visit 2, patients who had been < 80% compliant with the single-blind medication during the placebo lead-in period.
13. Females who are pregnant, lactating, or not using a medically acceptable form of birth control.

Reviewer's Note: The clinical criteria (e.g. radiographic findings, culture results) for defining 'sinusitis' were not discussed in the study protocol, thus leaving potential for including inappropriate study patients in the trial.

(III). Concurrent Medication Restrictions [S9-V1-p. 30-31, S9-V2-p. 18-20]:
The following medications were to be discontinued within the indicated time periods prior to visit 1, and were not allowed throughout the study duration:

	Medication	Time Discontinued Prior to Visit 1
1.	Long-acting corticosteroids (e.g. I.M.)	≥ 90 days
2.	Short-acting I.V. corticosteroids	≥ 14 days
3.	Oral corticosteroids	≥ 30 days
4.	Nasal corticosteroids	≥ 14 days
5.	Nasal cromolyn sodium	≥ 14 days
6.	Ketotifen	≥ 14 days

	Medication	Time Discontinued Prior to Visit 1
7.	Astemizole	≥ 90 days
8.	Loratadine	≥ 5 days
9.	Terfenadine	≥ 5 days
10.	Cetirizine	≥ 5 days
11.	Other antihistamines (H1 and H2 antagonists)	≥ 2 days
12.	Hydroxyzine	≥ 3 days
13.	Allergy eye drops/rinses (e.g. saline, vasoconstricting agents, topical antihistamines)	> 1 day
14.	Oral decongestants, decongestant nasal sprays or drops, including all OTC preparations-cough/cold and sleep aids.	≥ 2 days
15.	α-adrenergics (e.g. decongestants or drugs which produce adrenergic activity)	≥ 2 days
16.	Anticholinergic agents, sedatives, or hypnotics	≥ 3 days
17.	Antidepressant medications (serotonin-noradrenaline reuptake inhibitors and tricyclics), MAO inhibitors	≥ 21 days
18.	Reserpine or reserpine products (i.e. SER-AP-ES®, Hydropres®)	> 14 days

Patients on inhaled steroids and/or on inhaled cromolyn/nedocromil could participate in the trial if they were on a stable dose for at least 2 weeks prior to study entry (visit 1), and expected to continue treatment at this dose throughout the study.

Additionally, patients taking antacids were counseled to take their dose of study medication either 2 hours before or 1 hour after the antacid because of potential drug binding interactions.

Reviewer's Note: Regarding astemizole use, a contradictory statement by the sponsor is given in the 'Use of Prohibited Medications' in the study report for PR0035 [S9-V1-p. 47] which disallows use of astemizole within 30 (and not 90) days before of during study entry.

8.1.3.1.b. Procedure

(I) Screening Visit (Visit 1) [S9-V1-p. 41, S9-V2-p. 15, 21, 29]:

A complete medical history, physical examination, laboratory evaluation, and confirmation of the patient's ragweed hypersensitivity with skin prick testing (if not performed within the past 15 months) was performed at the screening visit. The study was conducted during the ragweed season.

During visit 1, it was determined whether the 12 hour reflective allergy symptom scores (see Tables I and II) qualified a patient for entry into the single-blind placebo lead-in period of the study, as per the inclusion criteria discussed above (i.e. at visit 1 (screening visit), the patient's reflective total symptom score (TSS) for the previous 12 hours had to be ≥ 6, nasal congestion and 2 or more additional SAR symptoms were to be rated as 'moderate' or 'severe', and no SAR symptom was to be rated as 'very severe').

Patients who fulfilled the SAR symptom score criteria based on this 12 hour reflective assessment then entered into a 3-5 day single-blind placebo lead-in period to establish baseline allergy symptoms that would determine study qualification.

Reviewer's Note: A single-blind placebo lead-in was used to reduce the number of 'placebo responders' in the double-blind period of the study.

The single-blind treatment utilized a double-dummy blinding method--1 placebo capsule identical in appearance to the 'marketed' fexofenadine 60 mg capsule and 1 placebo tablet identical in appearance to the 'to-be-marketed' fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg tablet combination were both to be taken twice daily by patients. Patients were asked to score their allergy symptoms daily at 7:00 p.m. (± 1 hour) prior to taking the study medication. SAR symptoms were assessed 'reflectively' (over the previous 12 hour period), 'instantaneously' (over the previous 1 hour period immediately prior to taking study medication), and again 'at bedtime' (i.e. an instantaneous assessment 1-3 hours after the 7:00 p.m. dose) in a daily symptom diary. The bedtime assessment was performed only after the first dose of single-blind (and double-blind) medication. Also at visit 1, patients were assigned in sequential order (e.g. 001)—a number that would be utilized at visit 2 for purposes of patient randomization to the 3 treatment groups.

A total of 5 SAR symptoms were assessed:

Table I: SAR Symptoms
(1) nasal congestion
(2) sneezing
(3) rhinorrhea
(4) itchy nose, palate and/or throat
(5) itchy, watery, red eyes

Each SAR symptom was rated on a 0-5 scale:

Table II: SAR Symptom Severity Scale:	
0	**Absent** (symptom not present)
1	**Mild** (symptom present, but not annoying or troublesome)
2	**Moderate** (symptom frequently troublesome, but does not interfere with normal daily activity or sleep)
3	**Severe** (symptom is sufficiently troublesome to interfere with normal daily activity or sleep)
4	**Very Severe** (symptom is so severe as to warrant 'an immediate visit to the physician')

In order to qualify for enrollment into the double-blind portion of the study, patients were to be symptomatic at both the screening and baseline visits using the 'reflective' allergy symptom assessment for the previous 12 hours.

(II) Visit 2 (Week 2, 3-5 days after Visit 1) [S9-V1-p. 42-43, S9-V2-p. 22, 29-30]:

After completion of the single-blind placebo lead-in portion of the study, patients underwent re-evaluation of SAR symptomatology via review of the patient symptom diary and assessment of compliance with study medication for the lead-in period.

Patients whose baseline allergy symptoms were sufficiently severe to qualify for randomization to double-blind medication were randomly assigned a treatment assignment number (TAN). This computer generated number was used to stratify the randomized patients into the 3 treatment groups and assure similar numbers of patients with a similar severity of allergy symptoms between the 3 treatment groups. The TAN was based on the sum of the 3 most recent 12 hour p.m. total symptom scores (TSS) during the placebo lead-in period and placed patients into one of 2 categories of symptom severity:

an 'A' or 'low' sum baseline 12-hour p.m. reflective TSS of ≤ 32 ('low' baseline symptom severity) and
a 'B' of high sum baseline 12-hour p.m. reflective TSS of ≥ 33 ('high' baseline symptom severity) .

The TAN, along with patients' sequential number, and the site's study number was used for patient identification. Additionally, the TAN was used to randomize study enrollable patients into 1 of the following 3 treatment groups:

Double Blind Treatment Groups:	
STUDY GROUPS	**DOSING**
(1) **Fexofenadine HCl 60 mg po bid**	**1 capsule (fexofenadine HCl 60 mg) + 1 tablet (placebo**; identical in appearance to the fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg combination tablet) **q a.m. and p.m.**
(2) **Pseudoephedrine HCl 120 mg po bid**	**1 capsule (pseudoephedrine HCl 120mg;** re-encapsulated to appear identical to fexofenadine HCl 60 mg capsules) + **1 tablet (placebo;** identical in appearance to the fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg combination tablet) **q a.m. and p.m.**
(3) **Fexofenadine HCl 60 mg/ Pseudoephedrine HCl 120 mg po bid**	**1 tablet (fexofenadine HCl 60mg/pseudoephedrine 120 mg) + 1 capsule (placebo**; identical in appearance to fexofenadine HCl 60 mg capsules) **q a.m. and p.m.**

Patients were instructed to take their initial dose of double-blind study medication at 7:00 p.m. (± 1 hour) after completing their p.m. diary scores the evening of visit 2. Similar to visit 1, SAR symptoms were assessed instantaneously 'at bedtime' (i.e. an instantaneous assessment 1-3 hours after the 7:00 p.m. dose) in a daily symptom diary, in addition to 'reflective' (over the previous 12 hour period) and 'instantaneous' (over the previous 1 hour period immediately prior to taking study medication) scoring.

After visit 2, patients continued to receive study medication twice daily at 7:00 a.m. (± 1 hour) and 7:00 p.m. (± 1 hour) and were to assess their SAR symptoms immediately prior to taking study medication 'instantaneously' and 'reflectively' once daily at approximately 7:00 p.m. Patients were furthermore reminded to take the 7:00 a.m. medication prior to visit 3.

(III) Visit 3 (Week 3, 7-10 days after Visit 2) [S9-V1-p. 42-43, S9-V2-p. 30-31]:

During visit 3 of the study, SAR symptoms were assessed by the investigator via review of patient diaries and concomitant medications were recorded. Blood samples to evaluate the plasma concentration of fexofenadine HCl and pseudoephedrine HCl were collected at a random time during this visit. Patients were advised to take the 7:00 a.m. medication prior to visit 4.

(IV) Visit 4 (Week 4, 7-10 days after Visit 3) [S9-V1-p. 43, S9-V2-p. 31]:

During visit 4 of the study, patients underwent repeat physical examination, along with a review of SAR symptoms and concomitant medications by the investigator. The WPAI questionnaire was completed by patients.

A 12 lead ECG was performed along with routine laboratory tests, and plasma fexofenadine HCl and HCl levels were collected.

(V) Collection of ragweed pollen counts [S9-V1-o. 41, S9-V2-p. 27]:

Ragweed pollen counts were collected on a daily basis by the sponsor and recorded in a log, beginning at least 1 week prior to the day the first patient qualified at visit 1 for study enrollment and ending until the last patient completed visit 4 of the study.

Ragweed pollen counts were collected for every region of the participating study centers, which were to include the following 5 regions: Montreal, Toronto, Quebec City, Sherbrooke, and London but were not collected at each individual study center. For the purpose of covariate analysis of the treatment-by-pollen count interaction, a ragweed pollen count of < 100 grains/m^3 (an average during the peak period of the ragweed season) was arbitrarily designated by the sponsor as a 'low' pollen count and a ragweed pollen count $>$ 100 grains/m^3 was arbitrarily designated as a 'high' pollen count [S9-V1-p. 102].

8.1.3.2. Clinical Endpoints

Primary and secondary efficacy variables, were based on a determination of the total symptom score or **TSS** (=sum of the individual SAR symptom scores), the nasal congestion score or **NCS**, and the total symptom score-the nasal congestion score or **TSS-NCS**.

Reviewer's Note: Given a symptom score range of 0-4 for any individual SAR symptom, patients could achieve a TSS ranging from 0-20, a NCS ranging from 0-4, and a TSS-NCS ranging from 0-16.

Based on these scores the following primary and secondary efficacy variables were assessed in this SAR study:

Primary Efficacy Variables [S9-V1-p. 36, 55, S9-V2-p. 24, 35]:

(1) The change from baseline in the average 7:00 p.m. reflective TSS-NCS; where the primary comparison of interest was the fexofenadine-pseudoephedrine combination vs. pseudoephedrine alone.
(2) The change from baseline in the average 7:00 p.m. reflective NCS; where the primary comparison of interest was the fexofenadine-pseudoephedrine combination vs. fexofenadine alone.

Reviewer's Note: The above 2 primary efficacy variables were selected in order to demonstrate that each active component of the fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg po bid combination makes a contribution to the claimed effects. The purpose of this comparison with the appropriate individual component was to demonstrate that: (1) the combination treatment is more effective than the decongestant pseudoephedrine for histamine-mediated SAR symptoms (TSS-NCS) and (2) the combination treatment is more effective than the antihistamine component (fexofenadine alone) for the non-histamine mediated symptom of nasal congestion (NCS).

Secondary Efficacy Variables [S9-V1-p. 37, 55, S9-V2-p. 25, 35]:

(1) Change from baseline in the average daily 7:00 p.m. reflective TSS.
(2) Change from baseline in the average daily 7:00 p.m. instantaneous TSS.
(3) Change from baseline in the average daily 7:00 p.m. instantaneous NCS.
(4) Change from baseline in the average daily 7:00 p.m. instantaneous TSS-NCS.
(5) Change from baseline in the bedtime instantaneous TSS.
(6) Change from baseline in the bedtime instantaneous NCS.
(7) Change from baseline in the bedtime instantaneous TSS-NCS.
(8) Change from baseline in the average daily 7:00 p.m. reflective individual SAR symptom scores, which consisted of the following:
    (i) Sneezing,
    (ii) Rhinorrhea,
    (iii) Itchy nose, palate, and/or throat,
    (iv) Itchy, watery, red eyes, and
    (v) Nasal congestion.

Reviewer's Note: The secondary efficacy endpoints were acceptable and the change from baseline in the average daily 7:00 p.m. instantaneous NCS represented the end of dosing interval. The change from baseline in the bedtime instantaneous NCS was used to provide information about the onset of action of the pseudoephedrine component of Allegra-D. These latter 2 secondary efficacy endpoints (endpoints (3) and (6) above) were considered by the medical reviewer to be the most important secondary efficacy endpoints for assessing the clinical efficacy of the combination product.

Table IX.
Efficacy of Allegra-D vs. Allegra vs. Pseudoephedrine
Secondary Efficacy Variables: Intent-to-Treat (ITT) Population [S9-V1-p. 80-88]

Secondary Efficacy Variables	TREATMENT GROUP (A) Fexofenadine (n=218)	(B) Pseudoephedrine (n=218)	(C) Combination (n=215)	[1]P-value A-C	B-C
(1) 7 p.m. reflective Total Symptom Score (TSS; Mean ± Standard Error)					
Baseline TSS	10.56 ± 0.156	10.31 ± 0.153	10.15 ± 0.152	[2]NA	NA
Double-blind Treatment Period TSS	7.98 ± 0.177	8.38 ± 0.191	7.30 ± 0.199	NA	NA
Change from baseline in average 7 p.m. reflective TSS	-2.41 ± 0.167	-1.88 ± 0.167	-2.88 ± 0.169	.0468	.0001
(2) 7 p.m. Instantaneous Total Symptom Score (TSS; Mean ± Standard Error)					
Baseline TSS	9.61 ± 0.196	9.11 ± 0.198	9.08 ± 0.199	NA	NA
Double-blind Treatment Period TSS	7.38 ± 0.193	7.73 ± 0.204	6.62 ± 0.209	NA	NA
Change from baseline in average 7 p.m. reflective TSS	-1.98 ± 0.171	-1.37 ± 0.171	-2.47 ± 0.173	.0389	.0001
(3) 7 p.m. Instantaneous Nasal Congestion Score (NCS; Mean ± Standard Error)					
Baseline NCS	2.19 ± .042	2.11 ± .042	2.11 ± .044	NA	NA
Double-blind Treatment Period NCS	1.86 ± .043	1.76 ± .044	1.63 ± .049	NA	NA
Change from baseline in average 7 p.m. NCS	-0.29 ± .040	**-0.35 ± .040**	-0.48 ± .040	.0007	.0186
(4) 7 p.m. Instantaneous TSS-NCS (Mean ± Standard Error)					
Baseline TSS-NCS	7.42 ± 0.166	7.01 ± 0.169	6.97 ± 0.169	NA	NA
Double-blind Treatment Period TSS-NCS	5.52 ± .161	5.97 ±.172	4.99 ±.171	NA	NA
Change from baseline in average 7 p.m. TSS-NCS	-1.69 ± 0.141	-1.03 ± 0.141	-1.99 ± 0.142	.1206	.0001
(5) Bedtime Instantaneous TSS (Mean ± Standard Error)					
Baseline TSS	8.77 ± 0.268	8.18 ± 0.248	8.20 ±0.252	NA	NA
Double-blind Treatment Period bedtime TSS	7.35 ± 0.249	7.26 ± 0.249	6.77 ±0.243	NA	NA
Change from baseline in bedtime TSS	-1.23 ±0.203 (n=209)	-1.03 ±0.203 (n=211)	-1.53 ± 0.203 (n=210)	.2986	.0772
(6) Bedtime Instantaneous NCS (Mean ± Standard Error)					
Baseline NCS	2.00 ±0.057	1.95 ±0.058	1.97 ±0.059	NA	NA
Double-blind Treatment Period NCS	1.79 ± 0.054	1.67 ± 0.058	1.68 ±0.061	NA	NA
Change from baseline in bedtime NCS	-0.20 ± 0.053 (n=209)	-0.30 ± 0.053 (n=211)	-0.30 ± 0.053 (n=210)	.1939	.9595
(7) Bedtime Instantaneous TSS-NCS (Mean ± Standard Error)					
Baseline TSS-NCS	6.77 ± 0.179	6.23 ± 0.206	6.23 ± 0.209	NA	NA
Double-blind Treatment Period TSS-NCS	5.56 ± 0.202	5.58 ± 0.209	5.09 ± 0.201	NA	NA
Change from baseline in bedtime TSS-NCS	**-1.04 ±0.170 (n=209)**	-0.74 ±0.170 (n=211)	**-1.24 ±0.170 (n=210)**	.3921	.0341

[1]P-value obtained from an ANCOVA model containing adjustment for site, treatment, and baseline symptom severity score (defined as a TSS < 33 (less severe disease) or a TSS > 33 (more severe disease), as based on the total of 3 TSS for the 3 days prior to study randomization (the placebo lead-in period).
[2]NA=Not Available (Data not provided by the sponsor).

Table X.
Efficacy of Allegra-D vs. Allegra vs. Pseudoephedrine
Secondary Efficacy Variables-continued:
Individual 7:00 p.m. Reflective SAR Symptom Scores
Intent-to-Treat (ITT) Population [S9-V1-p. 90]

	TREATMENT GROUP				
Secondary Efficacy Variables-Individual Reflective SAR Symptoms	**(A) Fexofenadine (n=218)**	**(B) Pseudoephedrine (n=218)**	**(C) Combination (n=215)**	**[1]P-value A-C**	**B-C**
(1) 7 p.m. Reflective Sneezing Score (Mean ± Standard Error)					
Change from baseline in average 7 p.m. reflective Sneezing Score	-0.49 ± 0.039	-0.34 ± 0.039	-0.59 ± 0.039	.0609	.0001
(2) 7 p.m. Reflective Rhinorrhea Score (Mean ± Standard Error)					
Change from baseline in average 7 p.m. reflective TSS	-0.42 ± 0.040	-0.30 ± 0.040	-0.51 ± 0.040	.1031	.0002
(3) 7 p.m. Reflective Itchy Nose, Palate, and/or Throat Score (Mean ± Standard Error)					
Change from baseline in average 7 p.m. instantaneous NCS	-0.61± .043	-0.41± .043	-0.64 ±.043	.6365	.0002
(4) 7 p.m. Reflective Itchy, Watery, Red Eyes (Mean ± Standard Error)					
Change from baseline in average 7 p.m. instantaneous TSS-NCS	-0.52 ± 0.043	-0.38 ± 0.043	-0.59 ± 0.044	.2998	.0006
(5) 7 p.m. Reflective Nasal Congestion Score (Mean ± Standard Error)					
Change from baseline in bedtime instantaneous TSS	-0.36 ±0.40	-0.45 ±0.040	-0.56 ± 0.40	.0005	.0590

[1]P-value obtained from an ANCOVA model containing adjustment for site, treatment, and baseline symptom severity score (defined as a TSS < 33 (less severe disease) or a TSS > 33 (more severe disease), as based on the total of 3 TSS for the 3 days prior to study randomization (the placebo lead-in period).

Analysis of the Secondary Efficacy Variables by Week 1 and Week 2 of Treatment:

All 8 secondary efficacy variables (including the individual 7:00 p.m. reflective SAR symptoms) were evaluated separately for Week 1 vs. Week 2 of the double-blind treatment period and are summarized in Table XII. below. These data revealed an additive effect of the 3 treatments in decreasing the respective clinical endpoint during the second week of treatment which was greater in numerical value than those recorded during the first week of treatment.

Subgroup Analysis of the Secondary Efficacy Variables:

Subgroup analysis of the secondary efficacy variables was not performed by the sponsor.

Table XI.

Analysis of Treatment Effect of Allegra-D vs. Allegra vs. Pseudoephedrine
Secondary Efficacy Variables: Intent-to-Treat (ITT) Population
[Biostatistics Review, Barbara Elashoff, HFD-715]

	TREATMENT GROUP COMPARISONS			
Secondary Efficacy Variables	**(A) Combination vs. Fexofenadine Treatment Effect**	**(B) Combination vs. Pseudoephedrine Treatment Effect**	**[1]P-value A**	**B**
(1) 7 p.m. reflective Total Symptom Score (TSS; Double-blind Treatment Period)				
Change from baseline in average 7 p.m. reflective TSS	0.47	1.00	.0468	<.0001
(2) 7 p.m. instantaneous Total Symptom Score (TSS; Double-blind Treatment Period)				
Change from baseline in average 7 p.m. reflective TSS	0.50	1.10	.0389	<.0001
(3) 7 p.m. instantaneous Nasal Congestion Score (NCS; Double-blind Treatment Period)				
Change from baseline in average 7 p.m. NCS	0.19	0.13	.0007	.0186
(4) 7 p.m. instantaneous TSS-NCS (Double-blind Treatment Period)				
Change from baseline in average 7 p.m. TSS-NCS	0.31	0.96	.1206	<.0001
(5) 7 p.m. Sneezing (Double-blind Treatment Period)				
–Change from baseline in Sneezing: **Reflective**	0.10	0.25	.0609	<.0001
–Change from baseline in Sneezing: **Instant.**	0.12	0.26	.0346	<.0001
(6) 7 p.m. Rhinorrhea (Double-blind Treatment Period)				
–Change from baseline in Rhinorrhea: **Reflective**	0.09	0.21	.1031	.0002
–Change from baseline in Rhinorrhea: **Instant.**	0.13	0.23	.0217	<.0001
(7) 7 p.m. Itchy Nose/Palate and/or Throat (Double-blind Treatment Period)				
–Change from baseline: **Reflective**	0.03	0.23	0.6365	.0002
–Change from baseline: **Instant.**	0.03	0.24	.6731	<.0001
(8) 7 p.m. Itchy, Watery, Red Eyes (Double-blind Treatment Period)				
–Change from baseline: **Reflective**	0.06	0.21	.2998	.0006
–Change from baseline: **Instant.**	0.05	0.24	.4388	.0001

[1]P-values are pairwise comparisons between each component (fexofenadine HCl and pseudoephedrine HCl) and the c combination treatment. Computationally, the treatment effect is the difference between the 2 least square means (not shown in this table) from an ANCOVA with adjustment for site, treatment, and symptom severity at baseline.

Table XII.
Efficacy of Allegra-D vs. Allegra vs. Pseudoephedrine
Secondary Efficacy Variables: **WEEK 1 vs. WEEK 2 of Treatment**
ITT Population; [HMR Response to FDA Request 05/20/97-V4.1-p. 14-21]

Secondary Efficacy Variables	TREATMENT GROUP (A) Fexofenadine (n=218)	(B) Pseudoephedrine (n=218)	(C) Combination (n=215)	[1]P-value A-C	B-C
(1) 7 p.m. reflective Total Symptom Score (TSS; Mean ± Standard Error)					
Change from baseline in average 7 p.m. reflective TSS-Week 1	-1.96 ± 0.161	-1.49 ± 0.161	-2.37 ± 0.163	.0677	.0001
Change from baseline in average 7 p.m. reflective TSS-Week 2	-3.05 ± 0.206 (n=204)	-2.47 ± 0.216 (n=186)	-3.49 ± 0.207 (n=202)	.1244	.0006
(2) 7 p.m. Instantaneous Total Symptom Score (TSS; Mean ± Standard Error)					
Change from baseline in average 7 p.m. reflective TSS- Week 1	-1.46 ± 0.166	-0.94 ± 0.166	-1.99 ± 0.168	.0241	.0001
Change from baseline in average 7 p.m. reflective TSS- Week 2	-2.68 ± 0.208 (n=204)	-2.05 ± 0.219 (n=186)	-3.07 ± 0.209 (n=202)	.1720	.0006
(3) 7 p.m. Instantaneous Nasal Congestion Score (NCS; Mean ± Standard Error)					
Change from baseline in average 7 p.m. NCS- Week 1	-0.19 ± 0.039	-0.26 ± 0.039	-0.39 ± 0.040	.0003	.0206
Change from baseline in average 7 p.m. NCS- Week 2	-0.44 ± 0.050 (n=204)	-0.49 ± 0.052 (n=186)	-0.59 ± 0.050 (n=202)	.0252	.1641
(4) 7 p.m. Instantaneous TSS-NCS (Mean ± Standard Error)					
Change from baseline in average 7 p.m. TSS-NCS- Week 1	-1.27 ± 0.137	-0.68 ± 0.137	-1.60 ± 0.138	.0889	.0001
Change from baseline in average 7 p.m. TSS-NCS- Week 2	-2.24 ± 0.170 (n=204)	-1.56 ± 0.179 (n=186)	-2.48 ± 0.170 (n=202)	.3093	.0001
(5) Change from baseline in average daily 7 p.m. individual symptom scores					
Sneezing:					
–WEEK 1	-0.44 ± 0.040	-0.26 ± 0.039	-0.51 ± 0.040	.2016	.0001
–WEEK 2	-0.56 ± 0.047	-0.44 ± 0.049	-0.68 ± 0.047	.0705	.0003
Rhinorrhea:					
–WEEK 1	-0.33 ± 0.040	-0.24 ± 0.040	-0.41 ± 0.041	.1381	.0028
–WEEK 2	-0.54 ± 0.049	-0.40 ± 0.052	-0.63 ± 0.049	.2374	.0012
Itchy nose, palate, throat:					
–WEEK 1	-0.48 ± 0.043	-0.33 ± 0.043	-0.53 ± 0.043	.4262	.0009
–WEEK 2	-0.77 ± 0.051	-0.52 ± 0.054	-0.77 ± 0.052	.9728	.0005
Itchy, watery, red eyes:					
–WEEK 1	-0.41 ± 0.042	-0.29 ± 0.042	-0.47 ± 0.042	.3222	.0019
–WEEK 2	-0.68 ± 0.052	-0.54 ± 0.055	-0.73 ± 0.052	.4873	.0114
Nasal congestion:					
–WEEK 1	-0.29 ± 0.039	-0.38 ± 0.039	-0.46 ± 0.040	.0017	.1330
–WEEK 2	-0.49 ± 0.049	-0.58 ± 0.052	-0.68 ± 0.050	.0056	.1596

[1]P-value obtained from an ANCOVA model containing adjustment for site, treatment, and baseline symptom severity score (defined as a TSS < 33 (less severe disease) or a TSS ≥ 33 (more severe disease), as based on the total of 3 TSS for the 3 days prior to study randomization (the placebo lead-in period).

8.1.4.2.1. Additional Efficacy Outcomes: Health Economic Analyses

Impairment of performance was measured using an allergy-specific 'Work Productivity and Activity Impairment' instrument (WPAI) [S9-V2-p. 96-100]. This unvalidated instrument attempted to measure the overall impact of patients' subjective allergy symptoms (and consequently the control of these symptoms) on patients' subjective perceptions of their daily activities and degree (or lack thereof) of work/school impairment. A summary of the instrument is provided in Appendix A1 of the 120 Day Safety Update for NDA 20-786, p. 149. While information acquired from this analysis was not utilized in the assessment of efficacy or patients' 'quality of life' evaluation in this NDA, a summary of the sponsor's findings (with attached data) is presented below. Tables 55-57 from the sponsor's analysis on health economics is included in Appendix II of the review for study PR0035.

An evaluation of patients' baseline characteristics after the placebo lead-in period indicates that overall, patients reported an average of 44% impairment in daily activities. Employed patients reported missing 1.8% days of work time, with 38.7% work impairment and 39.3% overall work impairment during the 7 days of placebo treatment. No significant differences between the 3 treatment groups were noted for these measures. Of note, the sample size for the classroom productivity data was smaller than 20 patients and hence the associated results were deemed inconclusive by the sponsor.

Outcome analysis after the double-blind treatment period indicated that the mean activity impairment score decreased significantly (by 13% for the combination treatment group, 9.8% for the fexofenadine HCl group, and 7.9% for the pseudoephedrine group, $p< .0001$) [S9-V1-p. 145, 148]. A significant difference between the combination group and the pseudoephedrine HCl group was noted in the change in the percent of activity impairment ($p=.006$) [S9-V1-p. 148]. The change in the percent activity impairment was not statistically significant between the combination group and the fexofenadine HCl group ($p=.075$) [S9-V1-p. 148]. Among employed patients, no significant decrease in % work time missed was noted for all 3 groups. Nonetheless, there was a significant improvement in the work productivity of 9.3% for the combination, 8.1% for the fexofenadine HCl group and 6.2% for the pseudoephedrine HCl groups ($p<.05$) [S9-V1-p. 147]. A statistically significant difference between the pseudoephedrine HCl group and the combination group was noted for the change in productivity at work ($p< .05$) but no significant difference was noted between the combination group and the fexofenadine HCl group ($p=.492$) [S9-V1-p. 148]. There was a significant improvement ($p< .001$) in the overall work productivity for the combination group (8.5%) and fexofenadine HCl group (8%) but not for the pseudoephedrine HCl group (4.9%, $p=.12$) [S9-V1-p. 148].

Reviewer's Note: Based on these health economic analyses, which use an instrument whose validity, sensitivity, reliability, and responsiveness for the particular disease state (SAR) is not discussed in any detail by the sponsor and does not specify a clinically meaningful change in percent, a modest improvement was nonetheless seen in the global functioning of patients treated with the combination product; which to varying degrees is also manifest in the individual components—fexofenadine HCl and pseudoephedrine HCl.

8.1.4.3. Safety Analysis

Safety analysis for protocol PR0035 consisted of an evaluation of adverse events, standard laboratory tests, vital signs, and 12-lead ECG pre-and post-treatment in patients randomized into the study and 'exposed' to study medication (the safety evaluable population). Two hundred and eighteen patients comprised the fexofenadine HCl and pseudoephedrine HCl safety evaluable populations, respectively, and 215 patients comprised the combination treatment safety evaluable population [S9-V1-p. 61, 104]. In this trial, the safety evaluable population was the same as the ITT population.

8.1.4.3.1. Demographics of the Exposed Population

Demographics of the exposed population (which is the same as the ITT population) was presented in section 8.1.4.1 ('Patient Demographics') of the medical officer review of NDA 20-786. All 3 treatment groups were similar in baseline characteristics with the exception of a marginally statistically significant difference in mean age between the 3 treatment groups (p=.0503). Patient composition for this study is reiterated in Table XIII. below.

Table XIII. Patient Demographics for the ITT Population [S9-V1-p. 64]:

Variable	Fexofenadine (n=218)	Pseudoephedrine (n=218)	Combination (n=215)	P-Value
Gender: (n, (%))				
Male	94 (43.1%)	90 (41.3%)	91 (42.3%)	
Female	124 (56.9%)	128 (58.7%)	124 (57.7%)	.9270[1]
Race: (n, (%))				
Caucasian	186 (85.3%)	194 (89.0%)	186 (86.5%)	
Black	13 (6.0%)	9 (4.1%)	13 (6.0%)	
Asian	18 (8.3%)	12 (5.5%)	12 (5.6%)	
Multiracial	1 (0.5%)	3 (1.4%)	4 (1.9%)	.5100[1] (Caucasian vs. Other)
Age: (yrs.)				
Mean ± SD	34.9 ± 12.35 yrs.	31.7 ± 11.12 yrs.	33.0 ± 11.41 yrs.	
Range	12-64 yrs.	12-66 yrs.	13-66 yrs.	.0503[2]
Weight: (kg)				
Mean ± SD	74.0 ± 17.33 kg.	72.3 ± 15.09 kg	71.0 ± 15.35 kg	
Range	42.2-144.0 kg	36.5-123.5 kg	38.8-126.0 kg	.2685[2]
Height: (cm)				
Mean ± SD	168.0-9.01 cm	168.3 ± 9.11 cm	168.2 ± 8.86 cm	
Range	145-195 cm	146-190 cm	148-193 cm	.8744[2]
Years since first episode of SAR occurred:				
Mean ± SD	15.2 ± 9.79 yrs.	15.9 ± 10.06 yrs.	14.9 ± 9.65 yrs.	
Range	2.0-46.2 yrs.	1.0-46.0 yrs.	14.10 2.0-55.0 yrs.	.5333[2]

[1]P-value comparing the 3 treatment groups using the Chi-square test.
[2]P-value comparing the 3 treatment groups using ANOVA on ranked observations, adjusting for site.

8.1.4.3.2. Duration of Patient Exposure/Patient Disposition

Also reiterated in Section 8.1.4.1 of the NDA review, the mean duration of double-blind exposure to study treatment for the safety population was 16 days (± 2 days) for the fexofenadine HCl and combination treatment groups and 15 days (± 3 days) for the pseudoephedrine HCl treatment group, although the range in duration of treatment for these 3 treatments was from 1-26 days [S9-V1-p. 70].

8.1.4.4. Adverse Events (AE's)

The overall incidence of all 'treatment emergent' adverse events (i.e. those AE's occurring during treatment) were generally similar for the combination (51.2%) and pseudoephedrine HCl (45.5%) treatment groups, but somewhat lower for the fexofenadine HCl (32.6%) treatment group. The most frequent adverse event for all 3 treatment groups consisted of headache (with an incidence of 11.5% in the fexofenadine HCl group, an incidence of 17.4% in the pseudoephedrine HCl group, and an incidence of 13.0% in the combination group), followed by insomnia (an incidence of 3.2% in the fexofenadine HCl group, an incidence of 13.3% in the pseudoephedrine HCl group, and an incidence of 12.6% in the combination group) [S9-V1-p. 105]. Other adverse events slightly more prevalent in combination treated patients than in either of the active comparators were nausea, throat irritation, dyspepsia, and agitation. These other recorded adverse events (see Table XIV. below) were significantly less frequent for all 3 treatment groups than headache and insomnia. With the exception of nausea, these latter 4 adverse events were present at an incidence of < 5.0% in the combination treatment group.

Compared with the labeling for ALLEGRA™ (fexofenadine hydrochloride 60 mg capsules, n=679), which listed viral infection as the most frequent adverse event (as compared with placebo, n=671), the AE analysis for study PR0035 did not specifically report or tabulate viral infection as an adverse event, hence it was not listed in the safety database for this study. In a teleconferenance with the sponsor, HMR, I was notified that different versions of the WHO Adverse Event Dictionary were utilized in assessing AEs for the clinical study(ies) in the ALLEGRA-D NDA and ALLEGRA NDA, respectively [Telecon with HMR, Dr. Paul Niehouse, Regualatory Affairs, 11/10/97].

A summary of all reported adverse events ('treatment emergent') for the combination treatment, as compared with the fexofenadine HCl and pseudoephedrine HCl comparators in trial PR0035 is presented in Table XIV.

Table XIV. Adverse Event (AE) Frequency:
AE's ≥ 1% for ALLEGRA-D
(Fexofenadine HCl/Pseudoephedrine HCl Combination Treatment), by Organ System and Preferred Term; Safety Evaluable Population [S9-V1-p. 106-112]

BODY SYSTEM	Preferred Term	Fexofenadine HCl 60 mg/ Pseudoephedrine HCl 120 mg Combination (n=215) n (%)	Fexofenadine HCl 60 mg (n=218) n (%)	Pseudoephedrine HCl 120 mg (n=218) n (%)
All Systems	Any AE	110 (51.2%)	71 (32.6%)	99 (45.5%)
Neurologic	**Headache**	**28 (13.0%)**	**25 (11.5%)**	**38 (17.4%)**
	Dizziness	4 (1.9%)	0 (0%)	7 (3.2%)
Psychiatric	**Insomnia**	**27 (12.6%)**	**7 (3.2%)**	**29 (13.3%)**
	Nervousness	3 (1.4%)	1 (0.5%)	4 (1.8%)
	Agitation	4 (1.9%)	0 (0%)	3 (1.4%)
	Anxiety	3 (1.4%)	0 (0%)	3 (1.4%)
Gastrointestinal	**Nausea**	**16 (7.4%)**	**1 (0.5%)**	**11 (5.0%)**
	Dry Mouth	6 (2.8%)	1 (0.5%)	12 (5.5%)
	Dyspepsia	6 (2.8%)	1 (0.5%)	2 (0.9%)
Respiratory	Throat Irritation	5 (2.3%)	4 (1.8%)	1 (0.5%)
	Upper Respiratory Infection	3 (1.4%)	2 (0.9%)	2 (0.9%)
Body as a Whole-General	Back Pain	4 (1.9%)	1 (0.5%)	1(0.5%)
	Abdominal Pain	3 (1.4%)	1 (0.5%)	1 (0.5%)
Cardiovascular	Palpitation	4 (1.9%)	0 (0%)	2 (0.9%)
Hematologic	Eosinophilia	4 (1.9%)	0 (0%)	2 (0.9%)
	Hemoglobin/Hematocrit	3 (1.4%)	2 (0.9%)	0 (0%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.

8.1.4.4.1. Cardiac Adverse Events

Cardiovascular adverse events in the Allegra-D safety database were specifically recorded for the clinical endpoints of: palpitation, tachycardia, heart murmur, hypertension, and syncope; however the additional adverse events of: dizziness, chest pain, and chest tightness were added to the list of cardiovascular adverse events by the medical reviewer (see Table XV. below). Incidence of arrhythmia (ventricular or atrial), QT_c prolongation, and sudden cardiac death were not specifically recorded or tabulated in the cardiac adverse event database by the sponsor, although ECGs pre- and post-treatment with the 3 study medications were evaluated as a separate safety endpoint (refer to Section 8.1.4.10.).

A total of 30 patients experienced cardiac adverse events during study PR0035 [S9-V1-p. 120]. Cardiac adverse events for the combination treatment group were infrequent for all AEs; tabulated with an overall incidence of 3.7%. Only one case of syncope was recorded (0.5% incidence) for the combination treatment, along with 4 cases of 'dizziness' (1.9% incidence). In general, patients in the pseudoephedrine HCl treatment group tended to have a higher incidence of

cardiac adverse events than patients in either the combination treatment group or patients in the fexofenadine HCl group.

Evaluation of the one case of syncope in the combination treatment group (patient 0567-0060), which occurred in a 22 year old female with a previous history of light-headedness accompanied by nausea (prior to study randomization) revealed that the patient had developed an episode of nausea on day 12 of therapy with the combination treatment which was followed approximately 25 minutes later by a fainting spell in the patient's bathroom [S9-V.25-p. 255]. It was noted that the patient had not eaten any breakfast on the day of the event which occurred approximately 11:00 a.m. Neither an ECG nor any laboratory tests were performed at the time of this event. Despite this fainting episode, the combination treatment was continued and the patient completed the study with no recurrence of nausea or syncope.

Reviewer's Note: Based on the patient's clinical presentation, which could be consistent with either syncope due to hypoglycemia or a vasovagal episode secondary to nausea; in the opinion of the medical reviewer, it is not likely that this event was a result of an acute ventricular arrhythmia, such as TdP.

A review of the 4 additional cases of 'dizziness' in patients receiving the combination treatment (patient 0568-0027, 0569-0009, 0569-0031, and 0574-0538) revealed that none of these cases resulted in pre-syncope or outright syncope; and in all 4 cases, medication was continued to completion of the study, the patient did not discontinue treatment, and the adverse event resolved without sequelae despite continuation of treatment [S9-V25-p. 256-259]. As reports of dizziness were likewise reported in the pseudoephedrine HCl treatment group and this AE has been previously described with pseudoephedrine HCl use, reports of dizziness most likely represent AEs related to the pseudoephedrine HCl component of the combination treatment, rather than to fexofenadine HCl alone.

Two combination treatment patients (patient 0567-0058 and 0567-0056) [S9-V25-p. 246, 259] were reported to experience tachycardia (see Table XV. below). In one case, (patient 0567-0058) the tachycardia occurred in the setting of severe 'hyperness' and insomnia which led the patient to discontinue treatment and in the second, symptoms were mild and the patient completed the study. In both cases, the patients experienced no clinical sequelae and the symptom of tachycardia was not accompanied by chest pain or syncope.

And finally, one combination treatment patient (patient 0567-0066) experienced insomnia with severe palpitations 2 days after starting therapy which lead to the patient's discontinuation of treatment on day 6 of therapy [S9-V25-p. 246]. This patient likewise experienced no clinical sequelae as a result of this adverse event.

In summary, the cardiac adverse events tabulated for the combination treatment group did not differ qualitatively from those for the pseudoephedrine

HCl group and overall were similar quantitatively (e.g. dizziness, tachycardia) to the pseudoephedrine HCl treatment group (although they were slightly greater in frequency than in the fexofenadine HCl treated patients) [S9-V1-p.121-122]. Based on these data, the cardiac adverse events associated with combination treatment of fexofenadine HCl with decongestant appear to be primarily the result of the decongestant's cardiac adverse event profile.

Table XV. Cardiac Adverse Event (AE) Frequency: ALLEGRA-D
(Fexofenadine HCl/Pseudoephedrine HCl Combination Treatment),
by Organ System and Preferred Term; Safety Evaluable Population [S9-V1-p. 106-112]

Cardiovascular Adverse Events	Fexofenadine HCl 60 mg/ Pseudoephedrine HCl 120 mg Combination (n=215) n (%)	Fexofenadine HCl 60 mg (n=218) n (%)	Pseudoephedrine HCl 120 mg (n=218) n (%)	TOTAL (n=651) n (%)
[1]All Cardiovascular	8 (3.7%)	1 (0.5%)	7 (3.2%)	16 (2.5%)
Palpitation	4 (1.9%)	0 (0%)	2 (0.9%)	6 (0.9%)
Tachycardia	2 (0.9%)	0 (0%)	4 (1.8%)	6 (0.9%)
Heart Murmur	1 (0.5%)	1 (0.5%)	0 (0%)	2 (0.3%)
Hypertension	0 (0%)	0 (0%)	1 (0.5%)	1 (0.2%)
Syncope	1 (0.5%)	0 (0%)	0 (0%)	1 (0.2%)
Dizziness	4 (1.9%)	0 (0%)	7 (3.2%)	11 (1.7%)
Chest Pain	0 (0%)	0 (0%)	1 (0.5%)	1 (0.2%)
Chest Tightness	2 (0.9%)	0 (0%)	1 (0.5%)	3 (0.5%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.
[1]All cardiovascular adverse events comprise the first 5 cardiac AEs in this table: palpitation, tachycardia, heart murmur, hypertension, and syncope.

8.1.4.5. Adverse Event Stratification by Duration of Treatment

Although adverse event stratification by duration of treatment was not performed by the sponsor, given the study's entire duration of 2 weeks, performance of AE stratification by duration of treatment would not be deemed clinically relevant for a combination product whose onset of action is well within 12 hours. Many of the adverse events described in the safety database for study PR0035 are ones which would not be anticipated to occur with drug accumulation (i.e. liver function abnormalities) but rather AEs related to the drug's direct pharmacologic activity (e.g. insomnia, agitation, hypertension or headache associated with pseudoephedrine HCl use due to α-adrenergic effects) [Hoffman, B. B. and Lefkowitz, R. J., Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagonists in *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, Ninth Edition, McGraw-Hill Publishing, New York, 1996, p. 219-224].

8.1.4.6. Adverse Event Stratification by Demographics (Age, Gender, Race)

Adverse event stratification by demographics was not performed in this study.

8.1.4.7. Patient Discontinuation due to Adverse Events

A total of 25 patients discontinued treatment prematurely due to adverse events. Eight of these patients were receiving treatment with the fexofenadine HCl/pseudoephedrine HCl combination drug, 3 were receiving fexofenadine HCl, and 14 were receiving pseudoephedrine HCl [S9-V1-p. 111]. The reasons for discontinuation of medication due to adverse events are summarized in Table 48 of the study report for PR0035 in the 120 Day Safety Update for NDA 20-786 [S9-V1-p. 121-122] but for the combination treatment group these generally comprised AEs such as insomnia (patients 0567-0037, 0567-0058, 0570-0027, 0576-0022, 0576-0030), nausea (patients 0576-0030, 0579-0003), headache (patients 0570-0027, 0576-0022, 0576-0030), irritability (patient 0576-0018), agitation (patient 0576-0027), and nervousness (patient 0579-0003) [S9-V1-p. 121-122]. Oftentimes these patients manifested more than one adverse event which lead to their premature discontinuation in the study. Furthermore, these AEs were similar to those reported in patients in the pseudoephedrine HCl treatment group who discontinued treatment (especially insomnia) [S9-V1-p. 121-122]. Several adverse cardiac events were reported in patients in the combination treatment group which likewise led to their premature discontinuation of the study and these individual cases were previously discussed in Section 8.1.4.4.1. of the medical officer review: 'Cardiac Adverse Events'.

Reviewer's Note: On review of the number of patients who discontinued treatment prematurely due to adverse events, a discrepancy in patient number was noted for the 3 treatment groups. In the patient disposition table in the NDA 20-786, Table 9 [S9-V1-p. 63], the number of patients who discontinued treatment was 18, while the number of patients who discontinued treatment in Table 48 of NDA 20-786 was 25 [S9-V1-p. 121-122]. The reason for this discrepancy, as clarified in the tables and on discussion with Mr. Paul Niehouse of HMR, [Telephone message by Mr. Paul Niehouse, HMR, Regulatory Affairs, 11/06/97] was that per Table 9, the patients tabulated were those who discontinued treatment 'primarily' due to occurrence of an adverse event, while the patients who discontinued treatment listed in Table 48 included those who discontinued 'primarily' or 'secondarily' due to an adverse event (i.e. an AE might not have been the primary reason for discontinuation of treatment but the patient additionally experienced an adverse event). Of note, this discrepancy in patient number did not affect the combination group—the treatment group of interest, where 8 patients were noted to have discontinued treatment prematurely in both tables solely due to an adverse event and not another reason.

8.1.4.8. Serious Adverse Events and Death

Neither any [1]serious treatment emergent adverse events nor any deaths were reported during this SAR trial for any of the 3 treatment groups. An assessment of treatment emergent adverse events in safety evaluable patients using a subjective severity rating scale of 'mild', 'moderate', or 'severe' by the principal investigator and/or patient indicated that the majority of patients for all 3 treatment groups subjectively experienced AEs 'moderate' in severity (51.8% of combination treated patients, 55.1% of fexofenadine HCl treated patients, and 63.6% of pseudoephedrine HCl treated patients) [S9-V1-p. 119]. In general, pseudoephedrine HCl treated patients experienced more severe AE's ('moderate' and 'severe' categories of AEs, combined) than the other 2 (fexofenadine) treatment groups, although the combination treatment group experienced the highest percentage of 'severe' AEs (19.1%), as compared with the other 2 treatment groups (14.5% for the fexofenadine HCl treatment group and 16.2% for the pseudoephedrine HCl treatment group) [S9-V1-p. 119]. The differences in severity between the 3 treatment groups were small and not deemed clinically significant by the medical reviewer.

8.1.4.9. Laboratory Test Results

Laboratory tests performed during visit 1 (pre-randomization) and visit 4 (completion of treatment) of the study and which consisted of a complete blood count with differential count, blood chemistries, liver function tests (SGOT, SGPT, alkaline phosphatase, total protein, albumin, and total bilirubin), urinalysis, and serum pregnancy test (for all women) did not reveal any unexpected abnormalities in combination treated patients, as compared with fexofenadine HCl or pseudoephedrine HCl treated patients. The effects of the 3 treatments on laboratory parameters were analyzed (with the exception of serum pregnancy tests) using the change from baseline (end-study value minus the baseline value), shift tables, and a tabulation of outlier values for individual patients [S9-V1-p. 123]. The sponsor's criteria for an abnormal laboratory value was a value outside the limits of normal for that parameter, as defined by the principal investigator. Summary statistics for each laboratory value were computed using an ANOVA model with adjustment for site [S9-V1-p. 125] and based on these several statistically significant differences between the 3 treatment groups were noted which are listed in Table XVI.

Statistically significant mean changes from baseline to end-study were observed for the WBC, RBC, hemoglobin, SGPT (ALT), albumin, chloride, and total cholesterol [S9-V1-p. 125-132]. Importantly, these minor numerical

[1] Serious Adverse Event-defined as any of the following AEs: (1) death due to an adverse event, (2) death due to any cause, (3) immediate risk of death, (4) an adverse event which resulted in, or prolonged in-patient hospitalization, (5) an adverse event which resulted in permanent disability, (6) congenital abnormality, (7) cancer, or (8) overdose.

differences were not deemed clinically significant by the principal investigator for any of the laboratory tests and are not considered clinically significant by the medical reviewer of NDA 20-786.

Analysis of laboratory tests by shift tables (from baseline to end-study) failed to reveal any significant differences between the 3 treatment groups [S9-V1-p. 134-138].

An evaluation of individual outliers (marked abnormalities in laboratory parameters, as based on a set percentage of the lower/higher limit of normal for a given laboratory value and a set decrease/increase from the baseline value [S9-V1-p. 139-140]) for each laboratory test showed no obvious difference in the number of patients with outliers between the 3 treatment groups. These data are summarized in Table 52 of study report of PR0035, as presented in the 120 Day Safety Update for NDA 20-786 [S9-V1-p. 141] and attached as Appendix III of this review and listed separately by patient identifier in Appendix M of the 120 Day Safety Update [S9-V1-p. 240-241]. High outlier values were reported in 5 combination treatment patients (n=207, 2.42% of total combination group patients) for the eosinophil count, in 2 combination treatment patients for the neutrophil count (n=207, 0.97% of total combination group patients), in 1 combination treatment patient for the WBC count (n=207, 0.48% of total combination group patients), 1 combination treatment patient for the band count (n=207, 0.97% of total combination group patients), 1 combination treatment patient for the LDH, SGPT, and serum magnesium, respectively (n=207, 0.48% of total combination group patients for each parameter [S9-V1-p. 141]. Low outlier values were reported in 3 combination group patients for the hemoglobin (1.45% incidence in combination group patients) and 1 combination group patient for the lymphocyte count (0.48% incidence) [S9-V1-p. 141].

Reviewer's Note: Slight discrepancies in the percentages between the various laboratory values (for laboratory outliers) was noted by the medical officer. Additional information was provided by the sponsor to explain these discrepancies [Response to FDA Questions, Mr. Paul Niehouse, HMR, 11/13/97, p. 1]. Per the sponsor, the denominator used for the laboratory outliers was defined as the number (#) of patients with both a baseline and post-baseline value for a particular analyte. Therefore, the denominator was potentially different for each of the individual analytes. The sponsor also stated that the denominator could also be different than the total number of safety evaluable patients for each treatment group.

Table XVI. Descriptive Statistics for Laboratory Parameters: ALLEGRA-D (Fexofenadine HCl/Pseudoephedrine HCl Combination Treatment); Safety Evaluable Population [S9-V1-p. 125-133]

Laboratory Test	Fexofenadine HCl 60 mg/ Pseudoephedrine HCl 120 mg Combination (n=215)		Fexofenadine HCl 60 mg (n=218)		Pseudoephedrine HCl 120 mg (n=218)		[1]P-Value
WBC (x 10^3u/L)	PRE	6.558	PRE	6.448	PRE	6.717	.0257
	POST	6.383	POST	6.571	POST	6.456	
	Mean [2]Δ=	-0.276	Mean Δ=	0.123	Mean Δ=	-0.260	
	[3]Std. Dev.=	1.416	Std. Dev.=	1.420	Std. Dev.=	1.496	
RBC (x 10^6 u/L)	PRE	4.820	PRE	4.774	PRE	4.779	.0143
	POST	4.703	POST	4.636	POST	4.703	
	Mean Δ=	0.117	Mean Δ=	-0.136	Mean Δ=	-0.076	
	Std. Dev.=	0.221	Std. Dev.=	0.236	Std. Dev.=	0.248	
Hemoglobin (g/dL)	PRE	142.618	PRE	141.349	PRE	141.730	.0230
	POST	139.845	POST	138.010	POST	139.968	
	Mean Δ=	-2.773	Mean Δ=	-3.340	Mean Δ=	-1.762	
	Std. Dev.=	5.656	Std. Dev.=	6.744	Std. Dev.=	6.625	
SGPT (ALT, U/L)	PRE	21.565	PRE	20.909	PRE	21.347	.0029
	POST	19.304	POST	21.392	POST	21.674	
	Mean Δ=	-2.261	Mean Δ=	0.483	Mean Δ=	0.326	
	Std. Dev.=	10.042	Std. Dev.=	7.218	Std. Dev.=	9.930	
Albumin (g/dL)	PRE	42.845	PRE	42.531	PRE	43.032	.0095
	POST	43.140	POST	42.316	POST	43.526	
	Mean Δ=	0.295	Mean Δ=	-0.215	Mean Δ=	0.495	
	Std. Dev.=	2.486	Std. Dev.=	2.610	Std. Dev.=	2.300	
Chloride (mEq/L)	PRE	106.038	PRE	106.143	PRE	105.885	.0464
	POST	105.572	POST	106.324	POST	105.333	
	Mean Δ=	-0.466	Mean Δ=	0.181	Mean Δ=	-0.552	
	Std. Dev.=	3.514	Std. Dev.=	3.369	Std. Dev.=	3.433	
Total Cholesterol (mg/dL)	PRE	4.678	PRE	4.739	PRE	4.717	.0001
	POST	4.507	POST	4.759	POST	4.525	
	Mean Δ=	-0.171	Mean Δ=	0.020	Mean Δ=	-0.192	
	Std. Dev.=	0.457	Std. Dev.=	0.458	Std. Dev.=	0.523	

[1] P-value for overall treatment effect from ANOVA model adjusting for site.

[2]Δ=Change, [3]Std. Dev.= Standard Deviation

8.1.4.1. Electrocardiograms

Electrocardiograms (ECGs) performed at baseline (visit 2) and at the final visit (visit 4) revealed that there was no statistically significant change in the QT_c interval from baseline to the final treatment visit for all 3 treatment groups in the safety evaluable population (p=0.6164 for the combination group vs. fexofenadine HCl alone, and p=0.4442 for the combination group vs. pseudoephedrine HCl alone) [S9-V1-p.144]. While there was a statistically significant decrease in the heart rate and a decrease in the QT (uncorrected) interval from baseline to the final visit in the combination group patients, compared to fexofenadine HCl treated patients (p <.0001 and p=.0004, respectively for heart rate and QT interval), these differences were minimal and not deemed to be clinically

significant by the principal investigator [S9-V1-p.142, 144]. A summary table of the heart rate, QT interval and QT_c interval findings for the 3 treatment groups in the safety evaluable population is presented in Table XVII. below.

Table XVII. Summary of ECG Findings (Baseline visit and Visit 4); ALLEGRA-D; Safety Evaluable Population [S9-V1-p.144, S9-V19-p.363].

ECG Parameter	(A) Fexofenadine HCl 60 mg/ Pseudoephedrine HCl 120 mg Combination (n=213 out of 215) (Mean ± SD)	(B) Fexofenadine HCl 60 mg (n=215 out of 218) (Mean ± SD)	(C) Pseudoephedrine HCl 120 mg (n=212 out of 218) (Mean ± SD)	[1]P-Value A-B	A-C
Heart Rate (bpm)	Visit 2= 69.3 ± 11.05 Visit 4= 72.9 ± 11.96 Change= 3.6 ± 9.98	Visit 2= 69.0 ± 11.19 Visit 4= 69.1 ± 10.86 Change= 0.1 ± 9.85	Visit 2= 67.5 ± 9.78 Visit 4= 72.9 ± 11.96 Change= 5.4 ± 9.85	.0001	.5205
QT Interval (msec)	Visit 2= 374.1 ± 32.60 Visit 4= 368.1 ± 28.14 Change= -6.0 ± 38.18	Visit 2= 375.2 ± 31.06 Visit 4= 374.0 ± 27.15 Change= -1.2 ± 28.14	Visit 2= 374.8 ± 26.48 Visit 4= 366.2 ± 27.70 Change= -8.6 ± 24.40	.0004	.8278
QT_c Interval (msec)	Visit 2= 391.0 ± 31.37 Visit 4= 393.2 ± 23.27 Change= 2.3 ± 34.77	Visit 2= 389.6 ± 29.03 Visit 4= 392.3 ± 23.81 Change= 2.7 ± 28.25	Visit 2= 388.4 ± 25.50 Visit 4= 388.9 ± 24.53 Change= 0.5 ± 22.18	0.6164	0.4442

[1]P-value obtained from an ANCOVA model on ranked data including treatment and site as factors and baseline value as covariate.

An evaluation of ECG outliers at the endpoint visit (the last patient visit) for QT_c interval prolongation was likewise performed by the medical reviewer for study PR0035 which defined an ECG 'outlier' as an increase in the QT_c interval by 40 msec from baseline or endpoint $QT_c \geq 450$ msec. These criteria were based on established inclusion and exclusion criteria for evaluation of QT_c interval prolongation for the ALLEGRA™ NDA review (see Medical Officer Review, NDA 20-625).

Review of the patient line listings [S9-V25-p. 35-135] revealed that for the combination treatment group, 9 ECG outliers with an increase in the $QT_c \geq 40$ msec by the endpoint visit were noted. Two (2) of these outliers had a $QT_c \geq 450$ msec by the endpoint visit which was not noted on baseline ECG. For the fexofenadine HCl treatment group, 10 ECG outliers with an increase in the $QT_c \geq 40$ msec by the endpoint visit were noted. None of the outliers had a $QT_c \geq 450$ msec at either the baseline or endpoint visit. For the pseudoephedrine HCl group, 5 ECG outliers with an increase in the $QT_c \geq 40$ msec by the endpoint visit were noted. None of these outliers had a $QT_c \geq 450$ msec at either the baseline or endpoint visit.

Review of the patient line listings [S9-V25-p. 138-200] for electrocardiographic rhythm based on a machine reading, indicated that the majority of patients for all 3 treatment groups had a normal sinus rhythm recording throughout the study duration.

8.1.4.1. Vital Signs and Weight

Vital signs (blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature) were monitored in this study at baseline and the final study visit (visit 4). Review of the mean change from baseline in all vital signs for the safety evaluable population revealed no statistically significant change at final visit from baseline for the combination treatment group, as compared with the 2 active comparators. These data are summarized in Table 53 of the study report for PR0035 of the 120 Day Safety Update of NDA 20-786 [S9-V1-p. 143].

8.1.5. Reviewer's Conclusion of Study Results (Efficacy and Safety):

(1) The results of this study support the safety of ALLEGRA-D (fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg) for the treatment of symptoms of SAR (including nasal congestion) in adults and children 12 years of age and older.

(2) A summary table of all efficacy parameters is presented below and shows that the combination treatment group demonstrated statistically significant efficacy compared to decongestant (pseudoephedrine 120 mg po bid) for histamine-mediated symptoms and statistically significant efficacy compared to antihistamine alone (fexofenadine HCl 60 mg po bid) for the non-histamine mediated symptom on nasal congestion, with the exception of 1 clinical endpoint (a secondary efficacy variable)—the change from baseline in the bedtime instantaneous NCS (nasal congestion score). Of note, pseudoephedrine HCl treated patients showed the same numerical decrease in nasal congestion as the combination group. Importantly, for this efficacy endpoint, symptom assessments were only made twice throughout the study and the study was not powered to detect a difference in day 1 bedtime scores. It was the conclusion of the medical and statistical reviewers that results for this efficacy endpoint, because of faulty study design, were inconclusive.

Results that Support Approval:

The results for all efficacy endpoints are summarized below and demonstrate statistical significance of the combination group in decreasing both histamine and non-histamine mediated SAR symptoms.

Results that do not Support Approval:

As discussed above, because of study design flaws and uninterpretability of the bedtime instantaneous nasal congestion score--the only efficacy endpoint in which statistical significance for the combination treatment was not demonstrated, all other study results support the efficacy of ALLEGRA-D in the treatment of SAR symptoms with nasal

congestion. Additionally, the combination treatment group did not demonstrate a statistically significant reduction in instantaneous TSS scores compared with the 2 active comparators, but as discussed previously, statistical significance would be difficult to demonstrate on this endpoint when compared to any active comparator given that it is a composite of both histamine and non-histamine mediated symptoms.

Summary Table: Efficacy Variables for the ITT Population and Treatment with ALLEGRA-D

EFFICACY VARIABLE	Statistically Significant Response (as compared with the appropriate active comparator) Yes/No
Primary Efficacy Variable	Yes
1. Δ from baseline in average 7 p.m. reflective TSS-NCS	Yes
2. Δ from baseline in average 7 p.m. reflective NCS	Yes
Secondary Efficacy Variables	Yes
1. Δ from baseline in average daily 7 p.m. reflective [1]TSS	Yes
2. Δ from baseline in average daily 7 p.m. instantaneous TSS	Yes
3. ***Δ from baseline in average daily 7 p.m. instantaneous NCS***	Yes
4. Δ from baseline in average daily 7 p.m. instantaneous TSS-NCS	Yes
5. Δ from baseline bedtime instantaneous TSS	No
6. ***Δ from baseline bedtime instantaneous NCS***	No
7. Δ from baseline bedtime instantaneous TSS-NCS	Yes
8. Δ from baseline in average 7 p.m. reflective individual sx scores: –Sneezing –Rhinorrhea –Itchy nose, palate, and/or throat –Itchy, watery, red eyes. –Nasal congestion	 Yes Yes Yes Yes Yes

Important efficacy variables for the approval of ALLEGRA-D are represented in **bold italics**.
There is no appropriate active comparator for the TSS score, as this composite score represents both histamine and non-histamine mediated symptoms. Hence demonstration of statistical significance on this endpoint for the combination treatment, as compared with either of the 2 active comparators is limited in clinical meaning. Thus these efficacy variables are deemed less important for demonstrating efficacy of the combination treatment vs. its individual components than the other efficacy variables listed in this summary table
Δ=Change, Sx=Symptom

Other Results:

ALLEGRA-D demonstrated adequate duration of decongestant effect, as per analysis of the end-of-dosing interval (the 7:00 p.m. instantaneous NCS) compared with fexofenadine HCl alone (p=.0007). This endpoint was critical for the approval of ALLEGRA-D, as bioequivalence of the former was not demonstrated for the pseudoephedrine component in PK studies. Analysis of onset of efficacy was not formally performed in this SAR trial, although a statistically significant decrease in histamine mediated but not non-histamine mediated SAR symptoms (i.e. nasal congestion) was noted for the combination treatment group at 1-3 hours

post-dosing, when compared to the appropriate active control. For the individual SAR symptoms (7:00 p.m. reflective), ALLEGRA-D demonstrated a statistically significant reduction in symptom scores, when compared to the appropriate active control drug.

Analysis of response of SAR symptoms to treatment separately by week 1 and week 2, indicated that ALLEGRA-D achieved a statistically significant reduction in all efficacy endpoints by week 1 of treatment but continued to provide a greater numerical reduction in SAR symptoms and nasal congestion by week 2 of treatment.

Safety:

Overall, ALLEGRA-D was safe and well-tolerated given twice a day, at a dose of 60 mg of immediate release fexofenadine HCl and 120 mg of sustained release pseudoephedrine HCl (Eltor™) in 215 patients. No serious adverse events occurred in patients treated with ALLEGRA-D, nor were any deaths reported. Similar to the 2 active comparators, headache was the most common adverse event, followed by insomnia, and nausea. Cardiac adverse events were rare, the most common being palpitations (1.9% of combination treated patients). No evidence of QT_c prolongation was demonstrated in combination treated patients and although several QT_c interval outliers were seen in the combination treated patients, numbers were comparable to the those of the 2 active comparators.

Summary:

Based on the results of this SAR trial, ALLEGRA-D demonstrated adequate evidence of efficacy and safety compared with its 2 active comparators, fexofenadine HCl and pseudoephedrine HCl, for the treatment of SAR symptoms with nasal congestion in adults and children 12 years of age and older.

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9.0. Integrated Summary of Efficacy

Since one clinical SAR trial was submitted and reviewed in this NDA application, itself not an a priori requirement for approval of ALLEGRA-D had bioequivalence of the 'to-be-marketed' product to the reference products been demonstrated, an integrated summary of clinical efficacy based on 1 SAR trial reviewed in this NDA is not feasible for this combination product. As stated previously in this review, the separate components of ALLEGRA-D have been previously shown to be effective for their respective clinical indication(s).

10.0. Integrated Summary of Safety

The integrated summary of safety for ALLEGRA-D consists of the safety analysis of the pivotal study PR0035 as previously discussed in section 8.1.5. of the medical officer review which comprised a total of 651 safety evaluable patients, of which 215 received the combination product.

Clinical Pharmacokinetic Studies

An additional safety database which was comprised of healthy non-smoking male volunteers in the 5 clinical pharmacokinetic studies initially submitted to NDA 20-786 is summarized separately in this section (and not pooled as an integrated summary of safety), as this group of subjects overall had significantly less drug exposure (received single or multiple doses of medication) than patients in the pivotal ragweed SAR trial, represented a different population (normal healthy volunteers) than those studied in the SAR trial, did not all receive treatment with the 'to-be-marketed' combination product, and underwent codification of AEs using a slightly different version of the WHO Adverse Event Dictionary than that used in study PR0035.

Three of the five clinical PK studies submitted to NDA 20-786 utilized single-dose crossover designs (studies DDPR0002, DDPR0003, PJPT0038), hence the duration of exposure to the combination of fexofenadine HCl and pseudoephedrine HCl was considered to be 1 day (n=65) [S2-V1.1-p. 154]. The remaining 2 PK studies utilized a multiple-crossover design in which the duration of exposure for fexofenadine HCl and pseudoephedrine HCl for study DDPR0001 (n=49) was 12 days and 5 days (n=22) for study PJPR0043 [S2-V1.1-p. 154]. In summary, the duration of exposure for all PK studies ranged from 1-12 days. Of note, study 0005 (the single dose bioequivalence study was not included as part of this safety database for PK studies).

Furthermore, in the PK studies, subjects in 2 of the 5 studies (PJPR0038 and PJPR0043) were exposed to different formulations of the combination treatment which did not represent the 'to-be-marketed' drug.

As in the pivotal clinical study (PR0035), lack of a placebo control group in the PK studies limited somewhat the ability to perform comparative analyses. Adverse events were collected at each study visit and tabulated using slightly different AE definitions from study PR0035 (a different 'version' of the World

Health Organization Reaction Terminology Dictionary, the MD WHO Adverse Event Dictionary or MMD WHO Adverse Event Dictionary) [S2-V1.1-p. 157, Telecon, Mr. Paul Niehouse, HMR, 11/10/97, and Amendment to NDA 20-786, Mr. Paul Niehouse, HMR, 11/13/97, p. 1]. Adverse events in the human PK studies were codified using the same version of the WHO Adverse Event Dictionary as was used in the Allegra NDA (20-625). Additionally, adverse events based on changes in clinical laboratory tests or ECGs were reported at the end of each respective study.

With the exception of 3 parameters (serum chloride, bicarbonate, and glucose), the protocol-defined criteria used to trigger clinical laboratory AE reports were identical to the outlier criteria used in study PR0035 [S2-V1.1-p. 158].

A total of 136 subjects were evaluable for safety in these 5 studies (i.e. were exposed to study medication with post-baseline AE measurements). The total number of subjects reporting AEs after exposure to the combination treatment (in all 5 PK studies) was 55 out of 136 (40.4%) [S2-V1.1-p. 158]. The total number of subjects reporting AEs in the fexofenadine HCl group was 3 out of 21 (14.3%) and in the pseudoephedrine HCl group, 8 out of 22 subjects (36.4%) [S2-V1.1-p. 158].

Adverse events (AEs) for 4 out of the 5 clinical PK studies in which subjects were exposed to combination treatment (study PJPR0038, DDPR0001, DDPR0002, and DDPR0003) are presented in 1 table, whereas AEs for study PPJPR0043 (subjects treated with fexofenadine HCl alone, pseudoephedrine HCl alone, or fexofenadine HCl taken with pseudoephedrine HCl as 2 separate tablets) are presented separately.

For the 4 combined PK studies, the most frequently reported AEs in combination treated subjects were granulocytosis (12/114 subjects or 10.5%), leukocytosis (5/114 subjects or 4.4%), hyperlipemia (5/114 subjects or 4.4%), and anemia (5/114 subjects or 4.4%). Notably, this AE profile was significantly different for the combination treatment group from that of study PR0035 (n=215 combination treatment subjects).

Reviewer's Note: This discrepancy in types and percentages of AEs between the 2 safety databases may be attributed to the fact that approximately half (39/75 of 52%) of the individual AEs reported in the 4 PK studies were for report-defined laboratory outliers and not subject reported AEs. Additionally, the issue of using slight versions of the WHO Adverse Event Dictionary may have contributed to AE reporting discrepancies, based on subtle differences in AE definitions.

A summary for AEs greater in frequency than 1% for the 4 combined PK studies in which the combination treatment group was administered to subjects is listed in Table XVIII. below.

Table XVIII. Adverse Event (AE) Frequency:
AE's ≥ 1% for ALLEGRA-D for the 4 Combined Clinical PK Studies
(Fexofenadine HCl/Pseudoephedrine HCl Combination Treatment), by Organ System and Preferred Term; Safety Evaluable Population [S2-V1.1-p. 159-161]

BODY SYSTEM	Preferred Term	Fexofenadine HCl 60 mg/ Pseudoephedrine HCl 120 mg Combination (n=114) n (%)
All Systems	Any AE	52 (45.61%)
White Blood Cells and RES	**Granulocytosis**	**12 (10.53%)**
	Leukocytosis	5 (4.39%)
Heart Rate and Rhythm	Bradycardia	3 (2.63%)
	Bundle Branch Block	3 (2.63%)
Metabolic and Nutritional	Hyperlipemia	5 (4.39%)
	Hyperglycemia	2 (1.75%)
	Increased LDH	2 (1.75%)
Red Blood Cell	Anemia	5 (4.39%)
	Polycythemia	3 (2.63%)
Urinary System	Hematuria	2 (1.75%)
	Pyuria	2 (1.75%)
	Urethral Disorder	2 (1.75%)
CNS	Headache	4 (3.51%)
	Drowsiness	2 (1.75%)
Cardiovascular, General	ECG Abnormal-Specific	4 (3.51%)
	ECG Abnormal-Non-specific	1 (0.88%)
Respiratory System	Throat Irritation	2 (1.75%)
Platelet, Bleeding and Clotting	Thrombocytopenia	2 (1.75%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.

For study PJPR0043, the most frequently reported AEs were headache (3/21 subjects, 14.3%) and viral infection (2/21 subjects, 9.5%) for fexofenadine HCl alone and throat irritation (2/22 subjects, 9.1%) for pseudoephedrine HCl alone.

Table XIX. Adverse Event (AE) Frequency:
AE's ≥ 1% for ALLEGRA-D; PK Study PJPR0043
(Fexofenadine HCl/Pseudoephedrine HCl Combination Treatment), by Organ System and Preferred Term; Safety Evaluable Population [S2-V1.1-p. 162-163]

BODY SYSTEM	Preferred Term	Fexofenadine HCl 60 mg + Pseudoephedrine HCl 120 mg (n=22) n (%)	Fexofenadine HCl 60 mg (n=21) n (%)	Pseudoephedrine HCl 120 mg (n=22) n (%)
All Systems	Any AE	3 (13.64%)	3 (14.29%)	8 (36.36%)
Respiratory System	Rhinorrhea	1 (4.55%)	0 (0%)	0 (0%)
	Throat Irritation	1 (4.55%)	0 (0%)	2 (9.09%)
Vision	Vision Abnormal	1 (4.55%)	0 (0%)	0 (0%)
CNS	Headache	1 (4.55%)	3 (14.29%)	1 (4.55%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.

Again, the AE profile for this small group of subjects was slightly different from that of the other 2 safety databases, but overall, one could conclude that AEs were infrequent for fexofenadine HCl when taken with pseudoephedrine HCl. Based on these 3 databases which could not and should not be integrated in one safety summary (for reasons previously delineated), no signals or trends in adverse events were notable, although several types of AEs (such as headache) tended to be more common in all treatment groups for all studies reviewed.

Analysis of these data by subgroups/demographics and dose range was not possible given that all the study subjects were healthy males and only one dose of each respective treatment was given in the PK studies. No deaths occurred in any of the 5 PK studies and no subject was hospitalized due to an AE or discontinued the study prematurely secondary to an AE [S2-V1.1-p. 165-167]. Of subjects who experienced 'serious' AEs (5 total for the 5 PK studies combined), the AEs consisted of: (1) moderate stomach pain (subject 001-002, DDPR0001), (2) headache (subject 002-012, DDPR0002), (3) phlebotomy site infection (002-019, DDPR0002), (4) muscle strain (subject 003-009, DDPR003), and conjunctivitis (subject 325-109, PJPR0043) [S2-V1.1-p. 168-169].

A total of 13 out of 136 safety evaluable subjects (9.6%) discontinued treatment in the 5 PK studies. Nonetheless, the most common reason to discontinue treatment was the subject's/investigator's decision to discontinue treatment (10/136 subjects, 7.4%) [S2-V1.1-p. 165]. Of these 10 subjects, 5 were discontinued by investigators due to positive drug screens [S2-V1.1-p. 166].

Regarding clinical laboratory data and taking into account that subjects receiving the combination treatment were not being exposed to the 'to-be-marketed' product, overall, the frequency of laboratory outliers was low and no trends in laboratory tests were noted. There were 35 subjects in the combination treatment group with a total of 46 laboratory outliers reported for the 5 combined PK studies [S2-V1.1-p. 175]. Of the 46 outlier laboratory values, 24 were reported in study DDPR0001 (16 subjects), including 12 high neutrophil outlier values (6 of these individuals had above normal neutrophil counts at baseline). Additionally, 5 subjects were reported with high triglyceride values (in study DDPR0001). One of these subjects had an above normal triglyceride level at baseline. Five low hematocrit outlier values were attributed by the investigators to multiple phlebotomies and not due to a drug effect [S2-V1.1-p. 175].

Other safety assessments in the clinical PK studies included evaluation of ECGs by QT_c, PR, and QRS intervals and by ECG rhythm [S2-V1.1-p. 176]. Prolongation of the QT_c interval (i.e. an outlier) was defined as per the criteria of study PR0035 and NDA 20-625 (ALLEGRA). No outliers were recorded for the heart rate, PR interval, QRS, and QT_c interval following exposure to either fexofenadine HCl alone, pseudoephedrine HCl alone, or the combination of fexofenadine HCl and pseudoephedrine HCl [S2-V1.1-p. 176-177]. Cardiac arrhythmias were recorded in 14/127 subjects (11%) and these were recorded as AEs because of a priori study design (refer to Table XVIII. above). None of these

rhythm disturbances were deemed treatment related. In 5 of the 14 cases, baseline ECGs revealed mild deviations from normal that did not preclude study enrollment and in 3 subjects with post-baseline bradycardia, baseline ECGs revealed borderline bradycardia. One subject entered the study with a borderline intraventricular conduction delay, and post-study ECG revealed a borderline first degree AV block [S2-V1.1-p. 176-177]. No cases of TdP, or any other ventricular tachycardia (the arrhythmias associated with terfenadine misuse) were reported in any study subjects for the 5 PK studies.

In terms of vital sign recordings, while a few outlier values were reported, again no discrete patterns of change in vital signs emerged and the treatments appeared to be well tolerated.

No studies for NDA 20-786 were conducted in renally or hepatically impaired subjects. Information regarding fexofenadine HCl dosing in these 2 special populations is based on data provided in the ALLEGRA NDA (20-625) where 1 PK study was performed in each of these 2 groups of patients.

In summary, based on safety evaluations of study PR0035 and data analyzed from the 5 clinical PK studies, the combination treatment of fexofenadine HCl/pseudoephedrine HCl was well tolerated with a low frequency of adverse events, the most common being headache. Importantly, aside from the sympathomimetic, and anticholinergic side effects such as palpitations and chest tightness (most likely attributable to the pseudoephedrine HCl component of ALLEGRA-D, as the incidence of these AEs was similar to the pseudoephedrine HCl alone treated patients), cardiac complaints were rare and 'clinically relevant' ECG abnormalities (defined in terms of QT_c prolongation or ventricular arrhythmias) were not detected in the combination treatment group patients, nor in either of the 2 active comparators. No significant demographic differences in adverse event reporting was appreciated, although this conclusion is based on 1 clinical SAR study. Serious adverse events with the combination treatment (ALLEGRA-D) were rare and no hospitalizations or deaths were reported with use of this antihistamine-decongestant combination drug.

Thus, ALLEGRA-D combination treatment of fexofenadine HCl and pseudoephedrine HCl appears to be safe for the treatment of SAR with nasal congestion in adults and children age 12 and older.

11.0. Data Verification (DSI Audit)

A Division of Scientific Investigations (DSI) audit of the clinical data for study PR0035 was not required for NDA approval as this was primarily a bioequivalence NDA. Hence, auditing of clinical study sites was not performed.

12.0. CONCLUSION: Executive Summary of Efficacy and Safety

Evaluation of the efficacy of ALLEGRA-D was based on the analysis of one pivotal SAR clinical trial (PR0035) and human pharmacokinetic data from 5 PK trials in order to establish bioequivalence of the combination treatment

(ALLEGRA-D) with the respective individual components of ALLEGRA-D, fexofenadine HCl and pseudoephedrine HCl, and to assess food effect and drug interaction between fexofenadine HCl and pseudoephedrine HCl. While fexofenadine HCl bioequivalence for the combination product was shown to be within the accepted confidence limits at the end-of-dosing interval, bioequivalence for the pseudoephedrine HCl component was not demonstrated. At the request of the Agency, the sponsor of ALLEGRA-D, HMR, submitted their Canadian ragweed SAR study (PR0035) which was analyzed by the medical and statistical reviewers with a primary focus on evaluation of reduction of the nasal congestion score at the end-of-dosing interval by the combination treatment vs. fexofenadine HCl alone. The change from baseline in the average daily 7:00 p.m. instantaneous NCS represented this clinical endpoint, although it was defined a priori by the sponsor as a secondary efficacy endpoint.

ALLEGRA-D demonstrated adequate duration of decongestant effect, as per analysis of the end-of-dosing interval (the 7:00 p.m. instantaneous NCS) compared with fexofenadine HCl alone (p=.0007). Analysis of the onset of efficacy was not formally performed in this SAR trial, although a statistically significant decrease in histamine mediated but not non-histamine mediated SAR symptoms (i.e. nasal congestion) was noted for the combination treatment group at 1-3 hours post-dosing, when compared to the appropriate active control. For the individual SAR symptoms (7:00 p.m. reflective), ALLEGRA-D demonstrated a statistically significant reduction in symptom scores, when compared to the appropriate active control drug. The treatment effect of ALLEGRA-D confirmed the extra reduction in both histamine and non-histamine medicated symptoms that the combination treatment provided over the individual treatments of fexofenadine HCl and pseudoephedrine HCl given alone, as already noted for the efficacy variable analyses of the individual SAR symptoms.

Analysis of response of SAR symptoms to treatment separately by week 1 and week 2, revealed that ALLEGRA-D achieved a statistically significant reduction in all efficacy endpoints by week 1 of treatment but continued to provide a greater numerical reduction in SAR symptoms by week 2 of treatment. A similar trend of added benefit by week 2 of treatment was noted for both fexofenadine HCl alone and pseudoephedrine HCl alone.

Extensive subgroup analyses by race, gender, and age were not attempted, nor was an integrated summary of efficacy appropriate for analysis of a single study. Based on the 651 ITT patients of study PR0035, with the exception of a minimal age-by-treatment interaction which most likely represents sampling effect, no significant demographic differences were noted for the combination treatment group.

The safety database for ALLEGRA-D consisted of 215 safety evaluable patients in the Canadian SAR trial who received approximately 2 weeks of treatment with combination drug, along with a total of 136 safety evaluable subjects in the 5 human PK trials submitted to NDA 20-786 where subjects

received from 1 day to a maximum of 12 days of treatment with both fexofenadine HCl and pseudoephedrine HCl (for 1 of these studies (PJPR0043) combination treatment was not given as a single tablet but rather a separate tablets of the individual components of ALLEGRA-D). These two safety databases were analyzed separately and thus an integrated summary of safety was not performed in the classic sense. Because the Canadian SAR trial was felt by the medical reviewer to provide more reliable safety information than the individual PK studies and patients consistently were exposed to a longer duration of study medication, data from this study was used to compile the adverse event frequency table for the ALLEGRA-D label.

Overall, ALLEGRA-D was safe and well-tolerated given twice a day, at a dose of 60 mg of fexofenadine HCl and 120 mg of pseudoephedrine HCl (Eltor™) in 215 patients. No serious adverse events occurred in patients treated with ALLEGRA-D, nor were any deaths reported. Similar to the 2 active comparators, headache was the most common adverse event, followed by insomnia, and nausea. Cardiac adverse events were rare, the most common being palpitations (1.9% of combination treated patients). No evidence of QT_c prolongation was demonstrated in combination treated patients and although several QT_c interval outliers were seen in the combination treated patients, numbers were comparable to the those of the 2 active comparators. No clinically significant trends in laboratory abnormalities were demonstrable in combination treated patients and no obvious difference in outlier values was noted between the 3 treatment groups. No statistically significant change in vital signs or weight was demonstrated between the 3 treatment groups. Follow-up physical examinations post-treatment in all 3 treatment groups were generally consistent with an unremarkable exam or one in which findings of SAR (e.g. nasal turbinate swelling, post-nasal drip) were demonstrable. In summary, ALLEGRA-D appears to be safe for the treatment of symptoms of SAR (including nasal congestion) at the recommended dose of fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg po bid.

12.1. Reviewer Recommendation:

ALLEGRA-D (fexofenadine HCl 60 mg immediate release/pseudoephedrine HCl 120 mg sustained release tablet) is shown to be safe and effective for the treatment of symptoms of seasonal allergic rhinitis (SAR) (including nasal congestion) in adults and children ≥ 12 years of age. The recommended dose is 1 tablet taken orally, twice a day, with adjustment in renally impaired patients to 1 tablet orally, once a day. The medical reviewer of NDA 20-786 recommends approval of ALLEGRA-D (fexofenadine HCl 60 mg/pseudoephedrine HCl 120 mg tablet) for this clinical indication.

APPENDIX I: Study Procedures for PRO035 [S9-V1-p. 45, S9-V2-p. 28]

e. Study Procedures

Table 4.				
PHASES	**Placebo lead-in**		**Treatment**	
VISITS	1	2	3	4 or ET[a]
WEEKS	1	2	3	4
Sign Consent Form	X			
Medical History	X			
Inclusion/Exclusion	X	X		
Physical Examination	X			X
Skin Test	X(t)			
Concomitant Medication	X	X	X	X
Standard Laboratory Test	X			X
Fexofenadine/Pseudoephedrine Blood Sample Collection			X	X
Pregnancy Test	X(s)	X(u)	X(u)	X(s)
Dispense Single-Blind Medication	X			
Dispense Double-Blind Medication		X	X	
Dispense Daily Symptom Diary	X	X	X	
Dispense Adverse Event Diary	X	X	X	
12-Lead ECG		X		X
Assess Adverse Events		X	X	X
Collect and Review Daily Symptom Diaries		X	X	X
Collect Medication and Assess Compliance		X	X	X
WPAI Questionnaire		X		X
Patient Health State Preferences		X		

$X_{(s)}$ = serum pregnancy test
$X_{(u)}$ = urine pregnancy test
X(t) = if not performed within the last 15 months
ET[a] = early termination visit

Table 55

Summary of Work and Productivity at Baseline
Mean (± SD)
(Intent-to-Treat Population)

Variable	*Treatment Group*		
	Fexofenadine (n=218)	Pseudoephedrine (n=218)	Combination (n=215)
% Work Time Missed	1.6 ± 5.37 (131)	2.2 ± 9.18 (145)	1.5 ± 5.90 (140)
% Productivity at Work	61.6 ± 22.73 (147)	59.7 ± 22.33 (157)	62.6 ± 23.96 (151)
% Overall Work Productivity	60.8 ± 22.97 (130)	60.2 ± 22.28 (145)	61.0 ± 24.14 (138)
% Classroom Time Missed	4.0 ± 10.09 (14)	1.2 ± 4.02 (11)	9.7 ± 25.11 (16)
% Productivity in the Classroom	62.7 ± 24.92 (15)	60.0 ± 25.69 (11)	57.2 ± 24.92 (18)
% Overall Classroom Productivity	62.4 ± 27.23 (14)	56.3 ± 25.26 (10)	51.2 ± 29.69 (16)
% Regular Daily Impairment	44.1 ± 23.07 (216)	44.6 ± 23.12 (213)	43.3 ± 22.73 (213)

Supporting Data: Appendix L1.8

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Table 56

Summary of Work and Productivity at the Final Visit Mean (± SD) Change from Baseline (Intent-to-Treat Population)

Variable	*Treatment Group*		
	Fexofenadine (n=218)	Pseudoephedrine (n=218)	Combination (n=215)
% Work Time Missed	0.1 ± 11.27 (131)	-0.4 ± 8.58 (145)	0.8 ± 11.95 (140)
% Productivity at Work	8.1 ± 23.21 (147) .0002[1]	6.2 ± 24.43 (157) .0304[1]	9.3 ± 25.47 (151) .0001[1]
% Overall Work Productivity	8.0 ± 24.12 (130) .0009[1]	4.9 ± 24.11 (145) .1178[1]	8.5 ± 26.94 (138) .0003[1]
% Classroom Time Missed	-3.3 ± 9.09 (14)	1.7 ± 10.82 (11)	-3.2 ± 31.81 (16)
% Productivity in the Classroom	3.3 ± 28.70 (15) .3474[1]	8.2 ± 29.26 (11) .1996[1]	12.8 ± 22.70 (18) .0320[1]
% Overall Classroom Productivity	5.1 ± 31.01 (14) .1358[1]	11.7 ± 29.03 (10) .1469[1]	16.9 ± 38.61 (16) .0524[1]
% Regular Daily Impairment	-9.8 ± 24.73 (216) .0001[1]	-7.9 ± 24.04 (213) .0001[1]	-13.0 ± 25.11 (213) .0001[1]

[1] Probability testing the null-hypothesis that mean change from baseline is 0

Supporting Data: Appendix L1.8

Table 57

Summary of Work and Productivity at the Final Visit Mean (± SD) Change from Baseline (Intent-to-Treat Population)

Variable	*Treatment Group* Fexofenadine (n=218)	Pseudoephedrine (n=218)	Combination (n=215)	Probability
% Work Time Missed	0.1 ± 11.27 (131)	-0.4 ± 8.58 (145)	0.8 ± 11.95 (140)	.628[a]
% Productivity at Work	8.1 ± 23.21 (147)	6.2 ± 24.43 (157)	9.3 ± 25.47 (151)	.492[b] .050[c]
% Overall Work Productivity	8.0 ± 24.12 (130)	4.9 ± 24.11 (145)	8.5 ± 26.94 (138)	.868[b] .115[c]
% Classroom Time Missed	-3.3 ± 9.09 (14)	1.7 ± 10.82 (11)	-3.2 ± 31.81 (16)	.584[d]
% Productivity in the Classroom	3.3 ± 28.70 (15)	8.2 ± 29.26 (11)	12.8 ± 22.70 (18)	.432[e] .733[f]
% Overall Classroom Productivity	5.1 ± 31.01 (14)	11.7 ± 29.02 (10)	16.9 ± 38.61 (16)	.802[e] .929[f]
% Regular Daily Impairment	-9.8 ± 24.73 (216)	-7.9 ± 24.04 (213)	-13.0 ± 25.11 (213)	.075[b] .006[c]

[a] Probability for Mantel-Haenszel Statistic controlling for site comparing the percent of patients who deteriorated on each treatment

[b] Probability for the comparison of fexofenadine versus combination from an ANCOVA model including treatment, site and baseline value

[c] Probability for the comparison of pseudoephedrine versus combination from an ANCOVA model including treatment, site and baseline value

[d] Probability for Chi-statistic comparing the percent of patients who deteriorated on each treatment

[e] Probability for the comparison of fexofenadine versus combination from an ANCOVA model including treatment and baseline value

[f] Probability for the comparison of pseudoephedrine versus combination from an ANCOVA model including treatment and baseline value

Supporting Data: Appendix L1.8

APPENDIX III: Outlier Laboratory Values

[S9-V1-p. 139-141]

Table 52

Number of Patients with Laboratory Post Baseline Outlier Values
(Safety Population)

Analyte	*Treatment*	*N*	*Low n(%)*	*High n(%)*
LIVER				
AST (SGOT) (U/L)	Pseudoephedrine	190	-	1 (0.53)
ALT (SGPT) (U/L)	Fexofenadine	209	-	1 (0.48)
	Pseudoephedrine	190	-	2 (1.05)
TOTAL BILIRUBIN (mg/dL)	Pseudoephedrine	190	-	1 (0.53)
	Combination	207	-	1 (0.48)
HEMATOLOGY				
HEMOGLOBIN (g/dL)	Combination	207	3 (1.45)	0 (0.00)
WBC (x10³/mL)	Combination	207	0 (0.00)	1 (0.48)
NEUTROPHILS (COUNT) (x10³/mL)	Fexofenadine	209	3 (1.44)	0 (0.00)
	Combination	207	0 (0.00)	2 (0.97)
LYMPHOCYTES (COUNT) (x10³/mL)	Combination	207	1 (0.48)	0 (0.00)
MONOCYTES (COUNT) (x10³/µL)	Pseudoephedrine	189	-	1 (0.53)
EOSINOPHILS (COUNT) (x10³/mL)	Fexofenadine	209	-	1 (0.48)
	Pseudoephedrine	189	-	3 (1.59)
	Combination	207	-	5 (2.42)
BANDS (COUNT) (x10³/mL)	Combination	207	-	1 (2.42)
ELECTROLYTES				
MAGNESIUM (mEq/L)	Combination	208	0 (0.00)	1 (0.48)
MISCELLANEOUS CHEMISTRY				
LDH (µ/L)	Fexofenadine	209	-	1 (0.48)

Supporting Data: Appendix M

Table 51. Laboratory Outlier Criteria		
Parameter	*Low Outlier*	*High Outlier*
LIVER FUNCTION		
SGOT (AST) (U/L)	---	)2xULN and ↑ ≥20
SGPT (ALT) (U/L)	---	)2xULN and ↑ ≥20
Alkaline Phosphatase (U/L)	---	)1.4xULN and ↑ ≥25
Total Protein (g/dL)	(0.9xLLN and ↓ ≥0.5	)1.15xULN and ↑ ≥1
Albumin (g/dL)	(0.9xLLN and ↓ ≥0.20	)1.1xULN and ↑ ≥0.5
Total Bilirubin (mg/dL)	---	)1.5xULN and ↑ ≥0.3
RENAL FUNCTION		
Creatinine (mg/dL)	---	)1.25xULN and ↑ ≥0.2
BUN (mg/dL)	---	)1.25xULN and ↑ ≥5
HEMATOLOGY		
RBC (x 10^6/µL)	(0.75xLLN and ↓ ≥0.20	)1.2xULN and ↑ ≥0.20
Hematocrit (%)	(0.95xLLN and ↓ ≥1	)1xULN and ↑ ≥1
Hemoglobin (g/dL)	(0.85xLLN and ↓ ≥0.1	)1.05xULN and ↑ ≥0.1
WBC (x 10^3/µL)	(0.85xLLN and ↓ ≥0.20	)1.25xULN and ↑ ≥0.20
Neutrophils (x 10^3/µL)	(0.75xLLN and ↓ ≥0.2	)1.1xULN and ↑ ≥0.5
Eosinophils (x 10^3/µL)	---	)1xULN and ↑ ≥0.4
Bands (x 10^3/µL)	---	)1xULN and ↑ ≥0.02
Monocytes (x 10^3/µL)	---	)1xULN and ↑ ≥0.1
Basophils (x 10^3/µL)	---	)1xULN and ↑ ≥0.1
Lymphocytes (x 10^3/µL)	(0.90xLLN and ↓ ≥0.25	)1.2xULN and ↑ ≥0.25
Platelets (x 10^3/µL)	(0.90xLLN and ↓ ≥20	)1.1xULN and ↑ ≥50
ELECTROLYTES		
Calcium (mg/dL)	(0.90xLLN and ↓ ≥0.25	)1.1xULN and ↑ ≥0.25
Sodium (mEq/L)	(0.95xLLN and ↓ ≥5	)1.05xULN and ↑ ≥5
Potassium (mEq/L)	(0.95xLLN and ↓ ≥0.2	)1.05xULN and ↑ ≥0.2
Chloride (mEq/L)	(0.9xLLN and ↓ ≥5	)1.0xULN and ↑ ≥5
Bicarbonate (mEq/L)	(0.85xLLN and ↓ ≥1.0	)1.15xULN and ↑ ≥1.0
Magnesium (mEq/L)	(0.85xLLN and ↓ ≥0.2	)1.05xULN and ↑ ≥0.2
MISCELLANEOUS CHEMISTRY		
Glucose (mg/dL)	(0.85xLLN and ↓ ≥10	)1.5xULN and ↑ ≥20
Triglycerides (mg/dL)	---	)2xULN and ↑ ≥50
Globulin (g/dL)	(0.90xLLN and ↓ ≥0.2	)1xULN and ↑ ≥0.2
A/G Ratio	(0.85xLLN and ↓ ≥0.1	)1.05xULN and ↑ ≥0.1
LDH (µ/L)	---	)1.4xULN and ↑ ≥15
LLN = Lower limit of normal ULN = Upper limit of normal		

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #:	20-786	APPLICATION TYPE:	NDA
SPONSOR:	Hoechst Marion Roussel, Inc.	PRODUCT/PROPRIETARY NAME:	Allegra-D
		USAN / Established Name:	Fexofenadine HCL, 60 mg/ pseudoephedrine HCL, 120 mg
CATEGORY OF DRUG:	Antihistamine plus nasal decongestant	ROUTE OF ADMINISTRATION:	Oral
MEDICAL REVIEWER:	Alexandra S. Worobec, M.D.	REVIEW DATE:	December 20, 1996

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
December 20, 1996	December 20, 1996	NDA	45-Day Clinical Review

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: This is a 45 Day NDA Clinical Review of NDA 20-786. With the exception of the outstanding issues listed below, the NDA submission appears adequate from a clinical standpoint.

Outstanding Issues: (1) Request for single dose bioequivalence study for the to-be marketed drug product.
(2) Followup of 12 month CMC stability data.
(3) Request for data from the Canadian SAR trial for possible review.

Recommended Regulatory Action: Review may proceed. | **N drive location:**

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: _____ Approvable _____ Not Approvable

Signed: **Medical Reviewer:** Alexandra S Worobec MD **Date:** 02/06/97

Medical Team Leader: [signature] **Date:** 3/18/97

45 Day Clinical Review:

I. NDA Filing:

As discussed in the 21-day filing meeting for NDA 20-782, dated 01/16/97, this NDA is deemed complete and can be filed from a clinical standpoint. While not a filing issue, our division has requested in a teleconferance with the sponsor (HMR) dated 01/22/97, that the sponsor provide a single dose bioequivalence study for the to-be-marketed formulation as this important information was not provided in the NDA submission. This point is discussed in further detail in Sections IV.1 and IV.2.

II. Foreign Marketing and Regulatory History:

As of December 1, 1996 the combination product fexofenadine HCL/pseudoephedrine HCL (Allegra-D) has not been approved in any country [1.1:55]. There have not been any commercial marketing experiences or foreign marketing regulatory actions with this combination product.

III. Preliminary Label Review:

As per the Allegra-D label, the combination product fexofenadine HCL, 60 mg/pseudoephedrine, 120 mg. will be administered orally in tablet form, twice a day (bid) to subjects, age 12 and older, for the treatment of symptoms of seasonal allergic rhinitis (SAR). Proposed SAR symptoms treated effectively with the combination product include: rhinorrhea, sneezing, itchy nose/palate/throat, itchy/watery/red eyes, and temporary relief of nasal congestion. The indications are based on the clinical efficacy findings of the separate NDAs for the single ingredient products of fexofenadine HCL and pseudoephedrine HCL.

Tablets will contain magnesium stearate as an inactive ingredient; an inactive ingredient which is known to influence the extent of drug release. The amount of magnesium stearate in the to-be-marketed product has been changed by the sponsor, with the final to-be-marketed formulation delivering approximately 75% less magnesium stearate and therefore a substantially lower dose of pseudoephedrine (Refer to Sections IV. and VII.). Potentially problematic for labeling purposes, this change in formulation will require an additional pharmacokinetic study for the purpose of demonstrating bioequivalence of the combination product with the two separate single ingredients. The single dose data available in the screening study of five potential Allegra-D formulations do not support the to-be-marketed formulation and therefore, the current label does not reflect the pharmacokinetics of the to-be-marketed formulation. The pharmacokinetics section of the label will need to be modified pending the results of the single dose bioequivalence study for the to-be-marketed formulation of Allegra-D.

Aside from the pharmacokinetics section discussed above, the majority of the product label is taken directly from the label for Allegra (fexofenadine HCL, 60 mg) with additional information provided about pseudoephedrine (from the Sudafed label) and overall appears acceptable. Dosing of Allegra-D in renally impaired subjects in the Allegra-D label is based on plasma fexofenadine levels in subjects with renal insufficiency as per findings in the Allegra NDA and as discussed in the Allegra label.

IV. Pharmacokinetic Trials:

A total of five pharmacokinetic studies were conducted by the sponsor. These are the following:

(1) Protocol PJR0038

A pharmacokinetic and bioavailability study of the 5 prototype fexofenadine HCL/ pseudoephedrine HCL combinations compared to the immediate release fexofenadine HCL 60 mg. tablet formulation and Sudafed 12 hour, extended release pseudoephedrine HCL 120 mg.

caplet. The study was an open-label, 4-period, 6-treatment, incomplete crossover single-dose design. A total of 30 healthy male volunteers, between 18-43 years of age were enrolled to receive fexofenadine HCL, 60 mg (treatment A or reference treatment) and 3 of the 5 prototype treatments [1.1:101]. Randomization procedures are not discussed in the submission. All treatments were separated by a washout period of 6 days and serial plasma levels were obtained for 36 hours following drug administration. A review of the study design indicates that Protocol PJR0038 is of reasonable design as a study whose goal it is to characterize different formulations of the combination product.

Based on bioavailability results obtained in Protocol PJR0038, prototype B (RG9549) was chosen for further drug development [1.1:80], however the sponsor changed to a different formulation for the final drug product (RC9614)[1.1:81], a formulation in which a single dose bioavailability study was either not performed or results not submitted by the sponsor. Theerefore, the single dose data available in this screening study do not support the to-be-marketed formulation. In either case, the division considers the single dose study of critical importance for a combination product that may be used on an 'as needed' basis such as Allegra-D, in order to assure single dose efficacy and safety and since the multiple dose study is not as sensitive in detecting true differences in the formulations. Based on a review of the PK and bioavailability studies and conclusions reached during an internal pulmonary division meeting, a teleconferance was conducted with the sponsor, Hoechst Marion Roussel, on January 22, 1997 and the sponsor has been asked to submit a single dose bioequivalence study with the to-be-marketed formulation of Allegra-D.

(2) Protocol DDPR0001

This study comprised the sponsor's 'pivotal' bioequivalence study of the fexofenadine HCL 60 mg/pseudoephedrine HCL 120 mg combination product as compared to the reference products fexofenadine HCL, 60 mg tablet and Sudafed 12 hour 120 mg. caplet. Multiple dose pharmacokinetics of fexofenadine and pseudoephedrine were characterized for the to-be-marketed combination tablet (RC9614) which is the drug formulation representative of full scale manufacturing.

This study was conducted using an open label, randomized, complete, 2-period crossover, multiple dose design in male subjects, 18-44 years of age. A total of 50 subjects were enrolled in the study, but a total of 5 subjects discontinued the study (4 for personal reasons and 1 due to a protocol violation), resulting in a significant subject drop-out rate of 10%. The 2 study periods consisted of: (A) multiple oral doses of fexofenadine HCL 60 mg. and pseudoephedrine HCL 120 mg. for 11 doses and (B) multiple oral doses of the to-be-marketed combination product fexofenadine HCL 60 mg./pseudoephedrine HCL 120 mg. (RC9614) for 11 doses. Serial plasma levels were obtained for 12 hours following drug administration on day 6 of the study and trough plasma levels were obtained prior to the morning dose on days 4, 5, and 6 of the study.

Several problems were noted on preliminary review of Protocol DDPR0001. The pseudoephedrine point estimates for this study (0.90) suggest that the two formulations (combination product Allegra-D vs. reference pseudoephedrine) are different and by overpowering the study with 45 subjects (a signficantly larger number of subjects for a study of this type, and particularly for a product with CVs ≤ 28% (for pseudoephedrine) and 48% (for fexofenadine)), the sponsor was able to show bioequivalence in the multiple-dose study by narrowing and possiby shifting the confidence interval for C_{max}. Even with overpowering, a review of the muliple dose study indicates that the Allegra-D formulation barely passes

bioequivalence for pseudoephedrine, with plasma levels being on the low side. These findings once again support the need for a single dose bioequivalence study using the to-be-marketed formulation of Allegra-D for drug approval, with possible requirement of a clinical program to show clinical efficacy if bioequivalence is not demonstrated.

(3) Protocol DDPR0002

This study examined the effect of food on the pharmacokinetics (rate and extent of absorption) of the individual components of the fexofenadine HCL/pseudoephedrine combination product. The study was an open label, 2-period, randomized, crossover single dose design, where serial plasma levels for fexofenadine and pseudoephedrine were obtained for 48 hours following drug administration of the fexofenadine combination product (RC9614) during either a fasting state or after a high fat breakfast in male subjects who were between 19-43 years of age. Preliminary review of the AUC (0-∞) and C_{max} values for fed and fasting subjects indicates that there appears to be a significant food effect on fexafenadine absorption from the combination tablet but not on pseudoephedrine absorption. These findings are appropriately referenced by the sponsor in the label.

(4) Protocol DDPR0003

The objective of this study was to determine the relative bioavailiablity of two prototype fexofenadine HCL/pseudoephedrine HCL formulations (RF9625-fast release formulation and FR9623-slow release formulation) as compared to the to-be-marketed combination fexofenadine HCL/pseudoephedrine product (RC9614).

This study was an open label, randomized, 3-period complete crossover, single dose design where serial plasma pseudoephedrine concentrations were measured for 36 hours following drug administration in healthy male subjects between 19 and 42 years of age. A total of 15 subjects were enrolled in the study. A preliminary review of the ratios of the mean pseudoephedrine AUC (0-∞) and Cmax values for the fast releasing and slow releasing pseudoephedrine formulations indicated that both formulations are bioavailable to the reference (RC9614).

(5) Protocol PJPR0043

The objective of this study was to determine the effect of pseudoephedrine on the pharmacokinetics of fexofenadine and the effect of fexofenadine on the pharmacokinetics of psuedoephedrine.

This study was an open label, randomized, complete 3-period crossover, multiple dose design. The 3 periods of the study consisted of: (A) fexofenadine HCL 60 mg. po bid for 9 doses, (B) pseudoephedrine HCL 120 mg. po bid for 9 doses, and (C) fexofenadine HCL 60 mg. tablet and pseudoephedrine HCL 120. mg caplet bid for 9 doses. These treatments were given to male subjects between 18-43 years of age. Serial plasma levels were obtained for 72 hours following drug administration on day 5. Trough plasma levels were obtained prior to the morning dose on days 3, 4, and 5. A total of 22 subjects were enrolled in the study.

A preliminary review of the pharmacokinetics data in this study indicates that there was no pharmacokinetic drug interaction between fexofenadine and pseudoephedrine when the two were dosed together. A potential study design flaw which may influence the conclusions made from this study is the lack of a study period of the to-be-marketed drug formulation--the combination fexofenadine HCL 60 mg/pseudoephedrine HCL 120 mg product.

V. Clinical Trials:

Two adequate and well-controlled efficacy and safety phase III clinical trials were not required by the Pulmonary Drug Product Division of the FDA as a basis for approval of this application. Based on the 1992 FDA Guidance 'Statistical Procedures for Bioequivalence Studies Using the Standard Two-Treatment Crossover Design', the sponsor has elected to follow the bioequivalence approach as the basis for approval of this combination product.

While not included with this NDA submission, the sponsor conducted an uncontrolled, single comparative two week study (Protocol 016455PR0035) of the efficacy and safety of fexofenadine HCL 60 mg./pseudoephedrine HCL 120 mg. po bid vs. the single components alone (fexofenadine 60 mg. po bid and pseudoephedrine 120 mg. sustained release po bid) in the treatment of seasonal allergic rhinitis (ragweed allergy) during the 1996 fall season. As of December 1, 1996 data collection and processing were ongoing for this study. This study may be reviewed in this NDA submission pending results of the single dose bioequivalence study for the to-be-marketed drug formulation.

VI. Safety Concerns:

A total of 136 male subjects were treated with the combination product fexofenadine HCL/pseudoephedrine HCL. Despite the absence of a placebo control group, a brief overview of the pre- and post-treatment laboratory tests, vital signs and EKGs does not reveal any clinically significant adverse events or abnormalities. Overall, the combination product appears to be well tolerated. Based on the safety profile of fexofenadine, as demonstrated in the NDA and post-marketing reports for Allegra, the safety findings of fexofenadine HCL/pseudoephedrine HCL combination (Allegra-D) in these five pharmacokinetic studies are similar to those seen with fexofenadine HCL alone (Allegra).

VII. Other Relevant Review Issues:

(A) Biopharmaceutics

As discussed in Section IV.1. and IV.2., while the sponsor has provided multiple dose bioavailability data for the to-be-marketed fexofenadine combination product, data from a pivotal single dose bioavailability study for the to-be-marketed fexofenadine combination product is not provided. This information will be critical for the approval process and thus we are requesting from the sponsor inclusion of a single dose bioequivalence study for the to-be-marketed drug product.

(B) CMC Stability Data:

The NDA submission contains 6 months accelerated and 6 months regular stability data on the primary stability batches. There are some supporting stability data for up to 12 months, but they are not for the to-be-marketed formulation and/or to-be-marketed packaging. As per the ICH Stability Guidelines, current recommendations are for provision by the sponsor of at least 12 month stability data at the time of the submission of the NDA, however, a lack of this data would not constitute grounds for a refusal-to-file as per a "gentleman's agreement" that will officially become center-wide policy on January 1, 1998.

Since the 6/6 month stability data submitted by the sponsor only became available in November, 1996, the earliest the 12 month data could become available to the agency would be June, 1997. Based on this timeline, it will not be practical to approve the application prior to review of the 12 month data since the expiration dating that the 6 month data would support would be too short for the sponsor to distribute and market the product.

VIII. NDA Completion Time Line:

Based on this preliminary review of NDA 20-786, and assuming that the sponsor will provide the necessary information pertaining to a single dose study of the combination product and assuming this information is acceptable to the Division, the division will not request additional clinical studies to support efficacy of Allegra-D. This NDA review should then be completed from a clinical standpoint in approximately one month's time. Assuming initiation of the review by early March, the clinical review should be complete by early April, 1997.

Alexandra S. Worobec, M.D 02/06/97

Alexandra S. Worobec, M.D.
Medical Officer HFD-570

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc: Division file
cc: Martin Himmel
cc: John Jenkins
cc: Gretchen Trout
cc: Cathie Schumaker