1. Known lack of a positive response to antihistamines for symptoms of SAR.
2. Upper respiratory tract infection within 30 days prior to visit 1.
3. Evidence of sinusitis or otitis media within 30 days prior to visit 1.
4. Vasomotor rhinitis.
5. Deviated nasal septum or obstructive nasal polyposis.
6. Presence of any disease state or surgery known to affect the gastrointestinal absorption of drugs.
7. 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.
8. Clinically significant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease which would make interpretation of the protocol results difficult.
9. Patients on immunotherapy, except those on stable maintenance immunotherapy for at least 6 months prior to visit 1.
10. 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.
11. Use of any investigational new drug within 30 days prior to visit 1.
12. Hypersensitivity to terfenadine, fexofenadine HCl, or the tablet ingredients (e.g. cellulose, lactose, cornstarch, magnesium stearate, croscarmellose sodium) in either of these medications.
13. At visit 2, patients who had been < 100% compliant with the single-blind medication during the placebo lead-in period (Amendment 1).
14. Females who are pregnant, lactating, or not using a medically acceptable form of birth control.
15. Urine drug screen positive for recreational drugs identified as cocaine, phencyclidine hydrochloride, or cannabinoids.

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 [V1.64:51-52, 170-172]: The following medications were to be discontinued within the indicated time periods prior to visit 1, and were not allowed between Visit 1 and 2 (Amendment 2):

	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.	Nedocromil or cromolyn sodium	≥ 14 days
6.	Fexofenadine HCl	≥ 72 hours
7.	Astemizole	≥ 60 days
8.	Loratadine	≥ 7 days
9.	Terfenadine	≥ 72 hours
10.	Cetirizine	≥ 72 hours
11.	Hydroxyzine	≥ 72 hours
12.	Other H_1 antagonists	≥ 24 hours
13.	H_2 antagonists	≥ 24 hours
14.	Antihistamine, NSAID, or α-adrenergic eye drops	≥ 48 hours
15.	Oral decongestants, decongestant nasal sprays or drops, including all OTC preparations	≥ 24 hours
15.	α-adrenergics (e.g. decongestants or drugs which produce adrenergic activity)	≥ 48 hours
16.	Anticholinergic agents, sedatives, or hypnotics	≥ 3 days
17.	Antidepressant medications (serotonin-noradrenaline reuptake inhibitors and tricyclics)	≥ 21 days
18.	Phenothiazines, benzodiazepines	≥ 21 days
19.	Oral and parenteral macrolide antibiotics (e.g. erythromycin, troleandomycin, azithromycin, clarithromycin)	≥ 30 days
20.	Oral and parenteral ketoconazole, fluconazole, or itraconazole.	≥ 90 days
21.	Diet aids (e.g. OTC: Dexatrim, Rx: REDUX, phentermine and/or fenfluramine)	≥ 48 hours ≥ 21 days

8.1.3.1.b. Procedure

(I) Screening Visit (Visit 1) [V1.64:33-34, 43-56, 59-60, 174, 177-181]:

Patients were instructed to fast ≥ 10 hours prior to Visit 1. A complete medical history, physical examination (including vital signs), laboratory evaluation, assessment of adverse events, and confirmation of the patient's allergen hypersensitivity with autumnal allergens indigenous to the study site with skin prick testing (if not performed within the past 15 months) was performed at the screening visit. The study was conducted during the autumn season. A 12-lead ECG was not performed at any study visit for this trial.

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, excluding nasal congestion) for the previous 12 hours had to be ≥ 6, 2 or more SAR symptoms (excluding nasal congestion) were to be rated as 'moderate' or 'severe', and no SAR symptom (including nasal congestion) 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 5-7 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 tablet identical in appearance to the 'to-be-marketed' fexofenadine 120 mg tablet and 1 placebo tablet identical in appearance to the 'to-be-marketed' fexofenadine HCl 180 mg tablet were both to be taken once daily in the morning (8:00 a.m. ± 1 hour) by patients. Patients were instructed to take the initial dose of single-blind study medication at 8:00 a.m. (± 1 hour) in the morning of the day following Visit 1. Patients were asked to score their allergy symptoms daily at 8:00 a.m. (± 1 hour) immediately prior to taking the study medication. Subsequent doses of study medication were taken at 8:00 a.m. (± 1 hour) daily after completing the assessments and diary entries.

SAR symptoms were assessed 'reflectively' (over the previous 12 hour period), 'instantaneously' (over the previous 1 hour period immediately prior to taking study medication). Additionally, patients assessed their SAR symptoms reflectively at 8:00 p.m. (± 1 hour) daily. 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, mouth, throat and/or ears
(5) itchy, watery, red eyes

Each SAR symptom was rated on a 0-4 (5 point) 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, 5-7 days after Visit 1) [V1.64:44, 60-61, 175, 182-184, 224-227]:

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 compliance with study medication was not 100% for the single-blind lead in period were discontinued from the study [V1.64:44, 226]. Furthermore, patients were required to have completed at least 5, 8:00 a.m. symptom assessments [V1.64:44, Amendment 1]. In order to qualify for randomization, patients were required to have fulfilled the same inclusion criteria as specified for Visit 1 [V1.64:44, 224-225, Amendment 1].

Patients whose baseline allergy symptoms were sufficiently severe to qualify for randomization to double-blind medication (refer to 'Inclusion Criteria' section above) 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 number of 8:00 a.m. instantaneous assessments of total symptom scores (TSS) during the placebo lead-in period having a TSS ≥ 5 and placed patients into one of 2 categories of symptom severity:

a 'low' category: the number of 8:00 a.m. instantaneous TSS ≥ 5 ranged from 4-5 depending on the number of symptom assessments completed (5-7) and
a 'high' category: the number of 8:00 a.m. instantaneous TSS ≥ 5 ranged from 5-7 depending on the number of symptom assessments completed (5-7) [V1.64:218, 227, 286-287, Amendments 1 and 3].

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 [V1.64:53-54, 173-174]:

Double Blind Treatment Groups:	
STUDY GROUPS	**DOSING**
(1) **Fexofenadine HCl 120 mg po qd**	**1 tablet (fexofenadine HCl 120 mg) +** **1 tablet (placebo**; identical in appearance to the fexofenadine HCl 180 mg tablet) **q a.m. (8 a.m.)**
(2) **Fexofenadine HCl 180 mg po qd**	**1 tablet (fexofenadine HCl 180mg) +** **1 tablet (placebo;** identical in appearance to the fexofenadine HCl 120 mg tablet) **q a.m.**
(3) **Placebo qd**	**1 tablet (placebo**; identical in appearance to fexofenadine HCl 120 mg tablet) + **1 tablet (placebo;** identical in appearance to fexofenadine HCl 180 mg tablet) **q a.m.**

Patients were instructed to take their initial dose of double-blind study medication at 8:00 a.m. (± 1 hour) in the morning of the day following Visit 2 and subsequent doses at 8:00 a.m. (± 1 hour) daily after completing their instantaneous and reflective symptom assessments and diary entries.

Patients were furthermore reminded to record the 8:00 a.m. symptom assessment and take the 8:00 a.m. medication prior to visit 3.

(III) Visit 3 (Week 3, 5-9 days after Visit 2) [V1.64:62-63, 184-185, 2[illegible], 295]:

During visit 3 of the study, SAR symptoms were assessed by the investigator via review of patient diaries and concomitant medications were recorded. Again, study medication was to be taken at 8:00 a.m. (± 1 hour) in the morning of the day following Visit 3, with subsequent doses taken at 8:00 a.m. (± 1 hour) daily after completing the symptom diary entries. Patients were scheduled to return in 8 (± 2 days) (at least 5 days of dosing) for Visit 4 (the final

study visit) at 8:00 a.m. (± 1 hour) before the patient recorded his/her 8:00 a.m. symptom assessment in the week 3 diary. Patients were not to take the 8:00 a.m. dose of study medication on the day of Visit 4.

Blood samples to evaluate the plasma concentration of fexofenadine HCl were collected at a random/variable time during this visit at all study sites [V1.64:47, 260-261, 273-276, 295, Amendments 2 and 3]. The time of the blood sample collection and the time of the last dose of study medication were recorded.

(IV) Visit 4 (Week 4, 6-10 days after Visit 3) [V1.64:44, 63, 185, 257-258, 260-263, 270-271, 296-297]:

During visit 4 of the study, patients underwent repeat physical examination, along with a review of SAR symptoms and concomitant medications by the investigator. Patients were not to have taken the 8:00 a.m. dose of study medication. Trough blood samples for fexofenadine HCl concentration were taken at 8:00 a.m. (± 1 hour), prior to that day's symptom assessments. Again, the date and time of blood sample collection and date and time of the last dose of study medication were recorded. At several sites, complete laboratory analysis was performed.

(V) Collection of ragweed pollen counts [V1.64:57-58, 228]:

Pollen counts for ragweed, tree, grass, or other indigenous allergens (to the study site area) were collected on a daily basis on the sponsor-provided pollen count form for at least 5 days a week [V1.64:57-58, 228]. Pollen counts were to be recorded beginning 2 weeks prior to the day the 1st patient qualified at Visit 1 and was to continue until the last patient enrolled completed Visit 4.

Reviewer's Note: No mention of who (investigator, sponsor, 3rd party) would be recording the pollen counts is provided in either the study protocol or study report. Neither is provided a quantitative measure (e.g. # grains/m^3) of what would constitute a 'low' vs. 'high' pollen count for any given allergen.

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, excluding nasal congestion).

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

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

Primary Efficacy Variables [V1.64:44, 72, 192, 222, 245-246]:

(1) The change from baseline in the average 8:00 a.m. instantaneous TSS over the 2 week double-blind treatment period [V1.64:44, 222, Protocol Amendment 1].

Change from baseline was computed by subtracting the average 8:00 a.m. instantaneous TSS during the placebo lead-in period from the average 8:00 a.m. instantaneous TSS during the double-blind dosing period. Missing symptom scores were handled such that if any of the individual symptoms used in calculating the TSS were missing, then the average of the non-missing data was computed [V1.64:47, 290, Protocol Amendment 3].

Reviewer's Note: The above primary efficacy variable was recommended by the Agency and was changed from the original primary efficacy variable of: average 24-hour reflective TSS (the average of 2, 12 hour reflective TSSs following each dosing) over the 2 week double-blind treatment period [V1.64:44, Protocol Amendment 1].

Secondary Efficacy Variables [V1.64:72-73, 192-193, 222, 247]:

(1) Change from baseline in the average 24-hour reflective TSS (over the 2 week double-blind treatment period).
(2) Change from baseline in the average 8:00 a.m. 12-hour reflective TSS (over the 2 week double-blind treatment period).
(3) Change from baseline in the average daily 8:00 p.m. 12-hour reflective TSS (over the 2 week double-blind treatment period).
(4) Change from baseline in the average individual 24-hour reflective symptom scores (over the 2 week double-blind treatment period).
(5) Change from baseline in the average individual 8:00 a.m. instantaneous symptom scores (over the 2 week double-blind treatment period).
(6) Change from baseline week 1 average 24 hour reflective TSS.
(7) Change from baseline week 2 average 24 hour reflective TSS.
(8) Change from baseline week 1 average 8:00 a.m. instantaneous TSS.
(9) Change from baseline week 2 average 8:00 a.m. instantaneous TSS.

All primary and secondary efficacy endpoints were analyzed using the 'intent-to-treat population', defined as 'patients with baseline and post-baseline 8:00 a.m. instantaneous TSS' [V1.64:44, 248-249, Protocol Amendment 1], along with the evaluation of the primary efficacy endpoint using 'protocol correct' patients (= 'intent-to-treat' patients with no major protocol violations) [V1.64:193, 194].

Reviewer's Note: The secondary efficacy endpoints were deemed acceptable from the FDA standpoint.

8.1.3.3. Statistical Analysis [V1.64:73, 194-196, 250]

Originally, the sample size of 200 patients per treatment arm was calculated based on the original primary efficacy endpoint of change in 24-hour reflective TSS from baseline between placebo and a treatment (of note: which was subsequently changed to an instantaneous total symptom score (TSS), see below for discussion of powering) to detect a treatment difference of at least 0.65 units in the average change of the 24-hour reflective TSS symptom score from baseline between placebo and treatment given a standard deviation of no larger than 2.0 with 90% power, given a 2-sided test with type I α error=0.05. This sample size would also provide 80% power to detect a true difference of 0.62 units in average change of the 24- hour 'trough' instantaneous TSS from baseline between placebo and a treatment given the standard deviation of no larger than 2.2. Using the original primary efficacy endpoint: 'the average 24-hour reflective TSS (the average of 2, 12 hour reflective TSSs following each dosing) over the 2 week double-blind treatment period', these power calculations were based on previous SAR trials of fexofenadine HCl conducted by the sponsor in adult patients (studies PJPR0023, Report K-95-0005-CDS, PJPR0024, Report K-95-0007-CDS, and PJPR0032, Report K-96-0284-C) [V1.64:194].

When the original primary efficacy endpoint was changed to the final primary efficacy endpoint or 'the change from baseline in the average 8:00 a.m. instantaneous TSS over the 2 week double-blind treatment period' [V1.64:44, Protocol Amendment 1], the sample size per treatment group was changed from 200 to 250 (or a total of 750 patients from a previous total sample size of 600 patients for the entire study), and the number of randomized patients required changed from 630 to 800 [V1.64:45, 221, 223, 250, Protocol Amendment 1]. This new sample size was calculated using the 8:00 a.m. instantaneous TSS in which the observed standard deviation ranged from 2.1-2.4, and the observed difference in reduction from baseline between 120 mg qd or 60 mg po bid of fexofenadine HCl and placebo ranged from 0.6-1.05 units in studies PJPR0023, PJPR0024, and PJPR0032 [V1.64:194].

ANCOVA was used to compare the effects of fexofenadine HCl 120 mg po qd and fexofenadine HCl 180 mg po qd and placebo. The primary efficacy variable, was included as the dependent variable. In addition, the ANCOVA model contained terms for investigative sites, treatment groups, and the primary efficacy variable as predictor variables. The baseline 8:00 a.m. instantaneous TSS was included as a continuous variable.

Pairwise dose comparisons to placebo were made based on a step-down procedure so as to protect the overall type I error rate (Hochberg Y and Tamhane AC, Multiple Comparisons Procedures, 1st Ed, New York, NY, John Wiley & Sonce, Inc., 1987) [V1.64:195]. In particular, the following comparisons were made sequentially: fexofenadine HCl 180 mg po qd vs. placebo, and fexofenadine HCl 120 mg po qd vs. placebo. If the p-value for the comparison of the fexofenadine HCl 180 mg po qd with placebo was < 0.05, then the comparison between fexofenadine HCl 120 mg po qd and placebo was also performed. If the p-value for the comparison of the fexofenadine HCl 180 mg po qd with placebo

was > 0.05, then the comparison between fexofenadine HCl 120 mg po qd and placebo was performed only for exploratory purposes. In addition, a test for overall treatment difference and comparison of the average effect of fexofenadine HCl (average of the 120 mg and 180 mg responses) vs. placebo was also performed.

Additional supportive analyses of the primary efficacy variable were performed using the rank transformed primary efficacy variable. Treatment comparsions were performed using an ANCOVA model for these rank transformed variables.

Treatment effect was characterized in subgroups of patients defined by investigative site, age, gender, weight, and race. Age was categorized as < 16, 16 to ≤ 40, ≥ 40 years old. Race was categorized as Caucasian and other. Weight was categorized as < 60 kg, 60 kg to < 90 kg, and ≥ 90 kg.

No interim analysis was performed for this study.

Evaluation of safety parameters were performed by tabulating the frequency of adverse events (AEs) for each double-blind treatment period. No statistical comparisons were made.

Change from baseline to end-of-study in vital signs were compared across treatment groups using an ANOVA model adjusting for treatment group. In addition, potentially clinically significant outliers were identified.

8.1.3.4. Pharmacokinetic Analysis [V1.63:298-301, V1.64:197]

Plasma fexofenadine concentrations were fitted to the appropriate population pharmacokinetic model by nonlinear mixed effects modeling (NONMEM) and investigated with regard to patient demographics, medical history, concomitant medications, etc. The NONMEM model building was based on examining the goodness of fit of the model as well as statistical significance of covariates, e.g. weighted residual vs. covariate groups, observed vs. predicted plasma concentration plot, and the objective function value.

8.1.3.5. Adult Health Outcomes Studies
(Quality of Life (QOL) Questionnaire Evaluation, SF-36, and WPAI Evaluation)

A number of different health outcomes surveys were conducted in adult SAR patients enrolled in study 3081 using: (1) the Juniper 'Rhinoconjunctivitis Quality of Life' questionnaire (RQLQ), (2) the general health survey, SF-36, and (3) the Work Productivity and Activity Impairment questionnaire (WPAI) which calculated the effect of general health and symptom severity on work/classroom productivity and daily activities [V1.161:10].

The primary objective of the Juniper 'Rhinoconjunctivitis Quality of Life' survey—the QOL measure deemed most important from the sponsor's perspective with regard to SAR, was to assess the impact of treatment on adult patients with SAR measured by the overall score of the RQLQ (note the survey

was completed at each of the 4 study visits and the average change from baseline (Visit 2) was calculated using the average of all 'post-baseline' visits (visits 3 and 4). Hence, the primary outcome measure was the change from baseline in the overall QOL score generated by the RQLQ over the 2-week double-blind treatment period. A secondary objective was to assess the effect of treatment on each of the 7 domains of the RQLQ: (1) nose symptoms, (2) eye symptoms, (3) practical problems, (4) miscellaneous symptoms, (5) activities, (6) sleep, and (7) emotions [V1.161:17]. Domains were calculated as the average of items pertaining to the domain; the overall score was the average of all items [V1.161:22]. Numerous publications have been published regarding the Juniper QOL instrument which was developed to assess the impact on QOL in patients with pollen-induced rhinoconjunctivitis. This instrument has been shown to be reproducible, valid, and responsive [V1.161:153-169, 172-178]. Secondary endpoints were defined as the average change from baseline in each of the 7 RQLQ domains. With regard to the QOL analysis, no amendments were made to protocols 3081. A sample case report form for the RQLQ questionnaire is presented on pages 116-146 of Volume 161 of NDA 20-872.

Importantly, the QOL instrument utilized in this study was the Juniper Rhinoconjunctivitis Questionnaire, with evaluative use of the instrument assessed by checking the responsiveness and longitudinal construct validity. Both were determined to be acceptable—the questionnaire picked up changes in quality of life in children whose rhinoconjunctivitis changed, and it was able to detect a difference between children who remained stable and those who changed. The PRQLQ also was shown to be reliable as children who were stable between consecutive visits showed stable quality of life [V1.255:18]. The QOL assessments were intended to evaluate the patient's perception of their state of health and how it impacted their life style and were not intended to generate data or information on either the efficacy or safety profiles of fexofenadine HCl in this study. Furthermore, this information was to be used by the sponsor to support additional marketing claims and/or indications after the dose selection of fexofenadine was made.

A full discussion of statistical approaches in evaluation of the RQLQ is presented on pages 19-25 of Volume 161, however in summary, sample size for this QOL study was dependent on the sample size SAR study 3081 for ITT patients, at a 2-sided α level of 0.05 (with all patients randomized to 3081 eligible for participation in the health outcomes study). Demographic variables and baseline (Visit 2) disease severity was assessed for comparability amongst the 3 treatment groups using the Fisher's exact test for categorical characteristics and the ANOVA for continuous characteristics [V1.161:23].

ANCOVA was used for the average changes from baseline over the 2-week double-blind treatment period (with terms for treatment, investigative site, and baseline overall QOL score as predictor variables). Each dose level was compared to placebo with no adjustment for multiple comparisons. The last

observation carried forward was used for any missing post-baseline observations of the RQLQ variables.

For the WPAI questionnaire, work, productivity, and resource utilization were generally rated on a scale of 1-10 [V1.161:22]. Within the WPAI, the change from baseline to combined week 1 and week 2 (the double-blind period) was calculated for: % of work time missed, % of work impairment, overall work impairment, % of class time missed, % of classroom impairment, overall classroom impairment, and % of regular activity impairment [V1.161:24]. The effect of time in % of work time missed and % of work impairment was investigated by calculating the change from baseline to week 1 and from baseline to week 2. In these computations, the higher the score, the greater the impairment of quality of life.

The SF-36, a disease non-specific QOL questionnaire was comprised of 3 domains: (1) general health perceptions, (2) change in health domain, and (3) role-physical functioning. Scoring was performed differently for each domain, but for all domains higher scoring indicated 'a better health state' [V1.161:23]. For this instrument, the change from baseline in week 1 and 2 in the general health perception and role-physical functioning domains were investigated taking into account the effect of time [V1.161:24-25].

For none of these 3 QOL instruments was an a priori treatment effect size and determination of sample size performed. The number of patients enrolled was simply based upon the numbers of patients randomized into study 3081 who were willing to participate in the QOL health outcomes survey.

Reviewer's Note: Of the 3 QOL instruments utilized by the sponsor for assessment of adult SAR patient health outcomes, only the Juniper Rhinoconjunctivitis Questionnaire is disease-specific for the clinical indication under study and has demonstrated validity, reliability (consistency and reproduciblity), and responsiveness for the SAR indication. Importantly however, no pre-specified clinically meaningful change in domain scores (a priori determination of the expected effect size) was provided for 3081 which is a critical part of the study design and which thus limits interpretability of results from study 3081. Furthermore, no adjustment for multiple comparisons was proposed [V1.161:23], and this might tend to increase the probability of making a false conclusion that a treatment difference exists when one indeed does not (increase the probability of a type I error).

8.1.4. Results

8.1.4.1. Patient Demographics [V1.64:76-81, V1.71:55-70]

(A) A total of 864 patients were randomized into the study, with all randomized patients exposed to double-blind study medication. One patient was randomized to double-blind medication at 2 different study sites (patient #983-019, fexofenadine HCl 120 mg group and patient #962-031,

fexofenadine HCl 180 mg group) [V1.64:76] This was discovered by the sponsor during a check of patients who had participated in previous protocols. As a result of this survey, this patient was hence classified as 'not protocol correct' at both sites and each of the 2 patient numbers to which this patient was assigned were treated as a separate patients and thus this patient appears twice in all of the analyses and patient counts. Thirty-nine exposed patients (4.5%) discontinued the study and 825 (95.5%) completed the entire study.

Eight hundred and sixty three (863) patients of the 864 patients were identified as safety evaluable (=exposed to double-blind medication with a post-baseline adverse event (AE) assessment) and were used in the safety analysis. Patient #972-024 was identified as not 'safety evaluable' because there was no post-baseline AE assessment. Eight hundred and sixty one (861) patients were identified as 'intent-to-treat' patients (=exposed patients with baseline and post-baseline 8:00 a.m. instantaneous symptom assessments) and were used in the 'intent-to-treat' analysis. Patients #972-024, #974-016, and #974-021 were excluded from the ITT analyses because they had no post-baseline 8:00 a.m. instantaneous symptom assessments. Of the 861 ITT patients, 775 had no major protocol violations and were classified as 'protocol correct' [V1.71:55-70]. A distribution of the patient population is summarized in Table II. below:

Table II. Patient Disposition [V1.64:79]

	Fexofenadine 120 mg	Fexofenadine 180 mg	Placebo	TOTAL
Randomized	288	283	293	864
Intent-to-Treat	287	282	292	861
Safety Evaluable	287	283	293	863
Protocol Correct	255	263	257	775

(B) A total of 39 patients exposed to double-blind medication discontinued the study prior to scheduled completion [v1.71:119-121]. The most common reason for early discontinuation consisted of treatment failure (11 total patients or 1.3% of patients in all 3 treatment groups) or an adverse event (10 total patients or 1.2% of patients in all 3 treatment groups).

This data is summarized in Table III. [V1.64:81].

Table III. Number and Percentage (%) of Randomized Patients Who Discontinued the Study with Reasons for Discontinuation, ITT Population [V1.64:81]:

	TREATMENT GROUP			
	Fexofenadine 120 mg (n=288)[1]	Fexofenadine 180 mg (n=283)	Placebo (n=293)	TOTAL (n=864)
Number (%) Completed	277 (96.2%)	270 (95.4%)	278 (94.9%)	825 (95.5%)
Reason for Discontinuation				
Adverse event	0 (0.0%)	7 (2.5%)	3 (1.0%)	10 (1.2%)
Elected to discontinue	2 (0.7%)	0 (0.0%)	4 (1.4%)	6 (0.7%)
Treatment Failure	5 (1.7%)	2 (0.7%)	4 (1.4%)	11 (1.3%)
Lost to follow-up	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Use of prohibited medication	0 (0.0%)	1 (0.4%)	4 (1.4%)	5 (0.6%)
Other	3 (1.0%)	3 (1.1%)	0 (0.0%)	6 (0.7%)
ALL REASONS	11 (3.8%)	13 (4.6%)	15 (5.1%)	39 (4.5%)

[1]n=number of randomized patients at the time of study initiation.

Reviewer's Note: For all 3 treatment groups, the total % of patient discontinuation was less than 10% of the total number of patients randomized in the study. The overall discontinuation rate for all 3 treatment arms ranged from approximately 4-5% which represents an acceptable rate of premature patient discontinuation. The reasons for early patient discontinuation were deemed acceptable by the medical reviewer.

(C) Pooled demographic data with regard to patient characteristics in the intent-to-treat population are summarized in Table IV. Below:

Table IV: Patient Demographics for the ITT Population [V1.64:82]:

Variable	Fexofenadine 120 mg (n=287)	Fexofenadine 180 mg (n=282)	Placebo (n=292)	P-Value
Gender: (n, (%))				
Male	105 (37%)	98 (35%)	101 (35%)	
Female	182 (63%)	184 (65%)	191 (65%)	.8567[1]
Race: (n, (%))				
Caucasian	248 (86%)	257 (91%)	256 (88%)	
Black	26 (9%)	13 (5%)	25 (9%)	
Asian	6 (2%)	5 (2%)	5 (2%)	
Multiracial	7 (2%)	7 (2%)	6 (2%)	.5190
Age: (yrs)				
Mean ± SD	32 ± 12 yrs.	33 ± 12 yrs.	32 ± 12 yrs.	
Range	12-64 yrs.	12-65 yrs.	12-65 yrs.	.8922
Weight: (kg)				
Mean ± SD	72 ± 18 kg.	73 ± 18 kg	72 ± 20 kg	
Range	31-139 kg	39-143 kg	34-167 kg	.5125
Height: (cm)				
Mean ± SD	168 ± 10 cm	168 ± 10 cm	167 ± 10 cm	
Range	139-193 cm	135-193 cm	144-201 cm	.2216
Years since first episode of SAR occurred:				
Mean ± SD	17 ± 11 yrs.	17 ± 11 yrs.	17 ± 11 yrs.	
Range	2-60 yrs.	2-52 yrs.	2-48 yrs.	.8974

[1]P-value comparing the 3 treatment groups from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors.

Reviewer's Note: It was noted that patient demographics were similar amongst the 3 treatment groups, with the majority of patients Caucasian and an approximately 2:1 ratio of female:male patients. No statistically significant differences or trends were noted between the treatment groups with regard to demographic factors.

(D) Patient distribution by disease severity at baseline in the ITT population was provided by the sponsor and no statistically significant difference was noted between the 3 ITT treatment groups for the 8:00 a.m. instantaneous symptom assessments: the 8:00 a.m. instantaneous TSS (excluding nasal congestion, p-value=0.6527), and the 8:00 a.m. instantaneous individual SAR symptom scores (nasal congestion, sneezing, rhinorrhea, itchy nose, mouth, throat and/or ears, and itchy, watery, red eyes) [V1.64:83]. The range in 8:00 a.m. instantaneous TSS for the ITT population ranged from 7.6-7.7 with a standard deviation ranging from 1.7-1.8 [V1.64:83]. Neither were statistically significant differences noted between the 3 ITT treatment groups for the baseline 8:00 a.m. reflective symptom assessments (TSS and individual SAR symptom scores, $p>0.50$ for all assessments), the baseline 8:00 p.m. reflective symptom assessments (TSS and individual SAR symptom scores, $p>0.69$ for all assessments), or the baseline 24-hour reflective SAR symptom assessments (TSS and individual SAR symptom scores, $p>0.78$ for all assessments) [V1.64:84-86].

(E) Patient Validity [V1.64:79-80, 89]

Eighty nine patients (or 10% of all exposed patients) (33 treated with fexofenadine HCl 120 mg, 20 treated with fexofenadine HCl 180 mg, and 36 treated with placebo) valid for efficacy had a 'major' protocol violation. The most common 'major' protocol violations consisted of the following: use of prohibited medications (5% of total patients), followed by failure to meet entrance criteria (3% of total patients). The % of patients with a violation of: 'failure to meet entrance criteria' was comparable among the 3 treatment groups. The fexofenadine HCl 180 mg group had the lowest frequency (3%) of prohibited medication use prior to or during the study, whereas the placebo group and fexofenadine HCl 120 mg group each had a frequency of 6% [V1.64:89]. A summary of invalidated patients and the reasons for invalidation are summarized in Table 7 of the NDA [V1.64:80].

Reviewer's Note: Criteria for invalidation of patient data were comparable to those seen in other SAR trials and thus deemed reasonable by the medical reviewer. In addition, the overall degree of patient invalidation was slightly lower for the fexofenadine HCl 180 mg arm but comparable in terms of % amongst the 3 treatment arms.

(F) Duration of Study Medication Exposure [V1.64:87, V1.71:123-140]

The mean duration of double-blind exposure to study treatment for the safety population was 13 days (± 2 days) for all 3 treatment groups. The range of duration of exposure was 2-19 days for the placebo group (n=292 patients), 4-19 days for the fexofenadine HCl 120 mg group (n=287), and 1-18 days for the fexofenadine HCl 180 mg group (n=283). Duration of exposure was calculated using the first and last dosing day of the double-blind treatment.

(G) Patient Compliance [V1.64:87-88, V1.71:142-159]

Assessment of patient compliance with double-blind medication was evaluated by the sponsor by dividing the total # of tablets taken during the double-blind dosing period (i.e. the total # of tablets dispensed – the total # of tablets returned) by the total # of tablets that should have been taken based on the # of days the patients participated in the double-blind period. Average compliance was found to be 100% for the placebo group, 101% both the fexofenadine HCl 120 mg and 180 mg groups. An average compliance > 100% for the 2 fexofenadine groups resulted from the numerous patients who took their last dose of study medication of the day of Visit 4, rather than on the day before the visit as stated in Amendment 3. Based on these measurements, compliance was noted to be acceptable according to the sponsor's original protocol and protocol amendments.

8.1.4.2. Efficacy Endpoint Outcomes

(I) Primary Efficacy Variables:

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=287 for fexofenadine HCl 120 mg group, n=282 for fexofenadine HCl 180 mg group, and n=292 for placebo) for the primary efficacy variable the change from baseline in the average 8:00 a.m. instantaneous TSS; where the primary comparison of interest was the response of the 2 fexofenadine doses vs. placebo. This primary efficacy endpoint was important in that it provided information about the end-of-dosing interval efficacy (or duration of drug effect).

Results of the primary efficacy analysis are summarized in Table V. below and show that for both the fexofenadine HCl 120 mg (p=.0505) and 180 mg (p=0.0016) doses, a statistically significant difference in the change in 8:00 a.m. instantaneous TSS over the 2 week double-blind treatment period was noted compared to placebo treatment, though the change was marginally statistically significant for the fexofenadine 120 mg dose. Numerically, the fexofenadine 180 mg group showed the largest numerical difference in decreasing the 8:00 a.m. instantaneous TSS. Similar results were seen with analysis of the 'protocol correct' group, although there was a slight increase in response in the placebo group (from –0.87 to –0.90) and a slight decrease in response in the fexofenadine HCl 120 mg group (from –1.17 to –1.15) which caused a loss of statistical significance for the comparison of 120 mg to placebo.

Using the step-down procedure in pairwise comparison of active doses vs. placebo (in order to control the overall type I α error), the overall results of the change from baseline in the 8:00 a.m. instantaneous TSS reveal a positive dose-response relationship (-0.87 for placebo, -1.17 for fexofenadine HCl 120 mg, and –1.36 for fexofenadine HCl 180 mg).

Importantly, the test for the covariate of the baseline 8:00 a.m. instantaneous TSS was statistically significant (p=0.0001), indicating that patients with higher baseline TSS were more likely to show a larger decrease in the TSS regardless of treatment [V1.64:91].

Reviewer's Note: The fexofenadine 180 mg po qd dose demonstrated a greater numerical decrease in the primary efficacy endpoint, though both doses of fexofenadine were shown to be statistically significantly more efficacious than placebo for the 2 week double-blind treatment period.

Table V.
Efficacy of Fexofenadine HCl 120 mg vs. Fexofenadine HCl 180 mg, vs. Placebo
Primary Efficacy Variable-Intent-to-Treat (ITT) Population [V1.64:91]

Primary Efficacy Variable	TREATMENT GROUP (A) Fexofenadine 120 mg qd (n=287)	(B) Fexofenadine 180 mg qd (n=282)	(C) Placebo (n=292)	P-value A-C	B-C	A-B
(1) 8 a.m. instantaneous Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)						
Baseline TSS	7.72 ± 0.10	7.69 ± 0.11	7.61 ± 0.10			
Double-blind Treatment Period TSS-NCS	6.54 ± 0.14	6.34 ± 0.14	6.78 ± 0.13			
Change from baseline in average 8 a.m. instantaneous TSS	**-1.17 ± 0.11**	**-1.36 ± 0.11**	**-0.87 ± 0.11**	**0.0505**	**0.0016**	0.2227
Mean Difference ± SE				-.30±.15	-.49±.16	.19±.16

P-values, means and associated standard errors from an ANCOVA model containing adjustment for site, treatment, and baseline symptom severity

Daily Analysis of the Primary Efficacy Variable ('Onset of Action')

Analysis of the primary efficacy variable or daily change from baseline change from baseline in the 8:00 a.m. instantaneous total symptom score for the double-blind treatment period for the intent-to-treat population was performed by the sponsor and illustrated a statistically significant decrease for the fexofenadine HCl 120 mg and 180 mg groups compared to placebo for the 1st 3 days of treatment, however, this decrease was not sustained thereafter. Results are summarized in Table VI. below. For the fexofenadine HCl 180 mg dose, a statistically significant decrease in the primary efficacy variable was again noted from day 5-day 9 and again for day 11 but was not consistently sustained thereafter for the remainder of the 2 week double-blind treatment period.

Reviewer's Note: Analysis of the onset of action for the 2 fexofenadine doses (120 and 180 mg) failed to show a consistent sustained statistically significant decrease in the primary efficacy endpoint on a daily basis for the 2 week double-blind treatment period.

Subgroup Analysis of the Primary Efficacy Variable:

A subgroup analysis of the primary efficacy variables to examine treatment interactions was performed by the sponsor on the basis of age [V1.64:112], gender [V1.64:113], race [V1.64:115], weight [V1.64:114], study site [V1.64:108-111], and baseline symptom severity (as determined by the average 8:00 a.m. instantaneous TSS during the placebo lead-in period [V1.64:116].

With regard to baseline symptom scores, patients were categorized into 'low' or 'high' baseline symptom groups based on whether their baseline 8:00 a.m. instantaneous TSS was ≤ to the median baseline 8:00 a.m. instantaneous TSS of the ITT population.

No statistical significance was noted for the study site by treatment interaction (p=.2914), the gender by treatment (p=0.5519), weight by treatment (p=0.4146), and race by treatment interactions (p=0.2113). In other words, the effect of the 3 treatment groups was not statistically significantly different among subgroups of patients defined by these factors.

Evaluation of age by treatment interaction revealed a marginally statistically insignificant difference (p=0.0581), indicating a trend for different treatment effects based on age. This result was primarily driven by the observed low treatment effect of fexofenadine 180 mg in young patients (< 16 years). The age 16 to < 40 year age group had the greatest treatment effect and the < 16 year age group the lowest treatment effect for the 2 fexofenadine doses.

Evaluation of the level of baseline symptoms by treatment interaction revealed a statistically significant effect (p=0.0256), indicating that treatment effect varies with the level of baseline symptoms. A larger treatment effect for patients receiving placebo (-0.28 and –1.50 for 'low' and 'high' symptom score groups, respectively) than the 2 fexofenadine groups. Furthermore, 'high' baseline patients had larger reductions than the 'low' baseline patients for all 3 treatment groups.

Table VI.
Efficacy of Fexofenadine HCl 120 mg, vs. Fexofenadine HCl 180 mg, vs. Placebo
DAILY CHANGE FROM BASELINE IN THE 8:00 a.m. INSTANTANEOUS TOTAL SYMPTOM SCORE FOR THE DOUBLE-BLIND TREATMENT PERIOD, ITT Population [V1.64:98-99]

Efficacy Variable	TREATMENT GROUP (A) Fexofenadine 120 mg qd	(B) Fexofenadine 180 mg qd	(C) Placebo	[1]P-value A-C	B-C
Change from Baseline in 8 a.m. instantaneous Total Symptom Score: (N, Mean ± Standard Error)					
DAY 1	286 -0.87 ± 0.13	282 -0.88 ± 0.13	292 -0.29 ± 0.13	0.0016	0.0014
DAY 2	285 -0.87 ± 0.14	281 -1.06 ± 0.14	290 -0.32 ± 0.14	0.0039	0.0001
DAY 3	285 -0.95 ± 0.14	279 -1.01 ± 0.15	289 -0.41 ± 0.14	0.0067	0.0023
DAY 4	285 -1.06 ± 0.14	280 -1.00 ± 0.14	288 -0.69 ± 0.14	0.0574	0.1150
DAY 5	284 -1.00 ± 0.15	280 -1.30 ± 0.15	287 -0.78 ± 0.15	0.2914	0.0103
DAY 6	281 -1.12 ±0.15	279 -1.45 ± 0.15	287 -0.90 ± 0.15	0.2850	0.0074
DAY 7	278 -1.25 ± 0.15	272 -1.46 ± 0.15	283 -1.01 ± 0.15	0.2486	0.0293
DAY 8	275 -1.22 ± 0.15	268 -1.49 ± 0.16	278 -0.99 ± 0.15	0.2821	0.0193
DAY 9	274 -1.30 ± 0.15	265 -1.58 ± 0.15	274 -1.06 ± 0.15	0.2465	0.0148
DAY 10	274 -1.43 ± 0.16	265 -1.64 ± 0.16	276 -1.25 ± 0.16	0.3911	0.0747
DAY 11	274 -1.48 ± 0.16	263 -1.59 ± 0.16	275 -1.13 ± 0.16	0.1076	0.0388
DAY 12	268 -1.41 ± 0.16	256 -1.49 ± 0.17	269 -1.26 ± 0.16	0.5062	0.3114
DAY 13	235 -1.38 ± 0.17	224 -1.74 ± 0.17	245 -1.39 ± 0.17	0.9445	0.1425
DAY 14	99 -1.31 ± 0.31	110 -1.64 ± 0.29	110 -1.11 ± 0.29	0.6135	0.1647

[1]P-values for comparison of fexofenadine HCl doses to placebo, means, and associated standard errors from an ANCOVA model containing investigative site, treatment, and baseline.

(II). Secondary Efficacy Variables:

A summary of analysis of the secondary efficacy variables for the ITT population is provided in Table VIII. below and indicates that for the majority of secondary efficacy endpoints, a statistically significant difference in symptom scores was seen for both of the fexofenadine doses compared to placebo.

Specifically with regard to analysis of the week 1 vs. week 2 change in average 8:00 a.m. instantaneous total symptom scores, both fexofenadine treatment groups showed a statistically significantly greater decrease compared to placebo treatment for week 1 of treatment ($p=0.0121$ for the 120 mg group and $p=0.0004$ for the 180 mg group), though the numerical difference was greater for the fexofenadine 180 mg group. Again, the numerical difference was greater for the fexofenadine 180 mg group at week 2 of treatment than for the 120 mg group, and the latter did not show a statistically significant difference compared to placebo ($p=0.2849$) with respect to decreasing the 8:00 a.m. instantaneous total symptom score at week 2. These results are illustrated in Table VII. below.

With regard to the other secondary efficacy endpoints, a statistically significant difference between the 2 fexofenadine groups and placebo was seen for all reflective TSS (average 24 hour, week 1 average 24 hour, week 2 average 24 hour, 8:00 a.m. 12 hour reflective, and 8:00 p.m. 12 hour reflective) with a slight numerical advantage for the fexofenadine 180 mg group in decreasing these reflective symptoms over the 120 mg group.

Analysis of the average individual 24 hour reflective symptom scores over the 2 week double-blind period also revealed a statistically significant improvement for all individual symptom scores in both of the fexofenadine treatment groups compared to placebo with the exception of a marginally statistically insignificant improvement for the nasal congestion score in the fexofenadine 120 mg group. Efficacy results for the individual 8:00 a.m. instantaneous symptom scores over the 2 week double-blind period were less consistent, with a greater number of statistically significant differences between active drug and placebo (for the sneezing, rhinorrhea, itchy nose, mouth, throat and/or ears and itchy, watery, red eyes) seen for the fexofenadine 180 mg dose. For the fexofenadine 120 mg dose, only the sneezing symptom score was shown to be statistically significantly better than placebo. In general, the numerical difference in effect for all the individual symptom scores was greater for the fexofenadine 180 mg dose than the 120 mg dose.

Reviewer's Note: Analysis of the secondary efficacy endpoints revealed a numerically greater and a more consistent decrease in symptom scores for the fexofenadine 180 mg po qd group over the 120 mg po qd group, though in general, for both of these active treatment groups, the majority of secondary efficacy endpoints were statistically significantly more efficacious than placebo treatment.

Table VII.
Efficacy of Fexofenadine HCl 120 mg, Fexofenadine HCl 180 mg, vs. Placebo
Secondary Efficacy Variable: TSS; ITT Population-
WEEK 1 vs. WEEK 2 of Treatment
[V1.64:96]

	TREATMENT GROUP				
Secondary Efficacy Variable	**(A) Fexofenadine 120 mg qd**	**(B) Fexofenadine 180 mg qd**	**(C) Placebo**	**P-value**	
				A-C	**B-C**
(1) 8 a.m. Instantaneous Total Symptom Score excluding the Nasal Congestion Score: WEEK 1 (Mean ± Standard Error)					
WEEK 1	n=286	n=282	n=292		
Baseline Mean ± SE	7.72 ± 0.10	7.69 ± 0.11	7.61 ± 0.10		
Treatment Mean ± SE	6.71 ± 0.14	6.53 ± 0.14	7.03 ± 0.13	**0.0121**	**0.0004**
Mean Change ± SE	**-1.00 ± 0.11**	**-1.17 ± 0.11**	**-0.61 ± 0.11**		
WEEK 2	n=277	n=270	n=278		
Baseline Mean ± SE	7.71 ± 0.10	7.65 ± 0.11	7.60 ± 0.11		
Treatment Mean ± SE	6.30 ± 0.16	6.07 ± 0.16	6.45 ± 0.15	0.2849	**0.0313**
Mean Change ± SE	**-1.41 ± 0.13**	**-1.62 ± 0.13**	**-1.22 ± 0.13**		

[1]P-value obtained from an ANCOVA model containing adjustment for site, treatment, and baseline symptom severity score and for comparison of fexofenadine HCl doses to placebo.

Table VIII: Secondary Efficacy Variables for the ITT Population and Treatment with Fexofenadine HCl 120 mg, Fexofenadine HCl 180 mg, and Placebo.

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No	
	Fexofenadine 120 mg qd	Fexofenadine 180 mg qd
Secondary Efficacy Variables		
1. Δ from baseline week 1 average 8:00 a.m. instantaneous TSS	*Yes* (p=0.0121)	*Yes* (p=0.0004)
2. Δ from baseline week 2 average 8:00 a.m. instantaneous TSS	No (p=0.2849)	*Yes* (p=0.0313)
3. Δ from baseline in average 24-hr reflective TSS (over the 2 week double-blind period)	*Yes* (p=0.0001)	*Yes* (p=0.0001)
4. Δ from baseline in average 8:00 a.m. 12-hr reflective TSS (over the 2 week double-blind treatment period).	*Yes* (p=0.0012)	*Yes* (p=0.0001)
5. Δ from baseline in average 8:00 p.m. 12-hr reflective TSS (over the 2 week double-blind treatment period).	*Yes* (p=0.0001)	*Yes* (p=0.0001)
6. Δ from baseline in average individual 24-hr reflective symptom scores (over the 2 week double-blind period):		
--Sneezing	*Yes* (p=0.0001)	*Yes* (p=0.0001)
--Rhinorrhea	*Yes* (p=0.0013)	*Yes* (p=0.0012)
--Itchy nose, mouth, throat and/or ears	*Yes* (p=0.0034)	*Yes* (p=0.0001)
--Itchy, watery, red eyes.	*Yes* (p=0.0036)	*Yes* (p=0.0005)
--Nasal congestion	*Yes* (p=0.0475)	No (p=0.0604)
7. Δ from baseline in average individual 8:00 a.m. instantaneous symptom scores (over the 2 week double-blind period):		
--Sneezing	*Yes* (p=0.0008)	*Yes* (p=0.0117)
--Rhinorrhea	*Yes* (p=0.0333)	No (p=0.1351)
--Itchy nose, mouth, throat and/or ears	*Yes* (p=0.0106)	No (p=0.3217)
--Itchy, watery, red eyes.	*Yes* (p=0.0194)	No (p=0.2188)
--Nasal congestion	No (p=0.7915)	No (p=0.9762)
8. Δ from baseline week 1 average 24 hr.reflective TSS	*Yes* (p=0.0001)	*Yes* (p=0.0001)
9. Δ from baseline week 2 average 24 hr.reflective TSS	*Yes* (p=0.0017)	*Yes* (p=0.0165)

Δ=Change, TSS=Total symptom score

8.1.4.2.1. Adult Health Outcomes Studies (Quality of Life (QOL) Questionnaire Evaluation, SF-36, and WPAI Evaluation)

A total of 864 patients were enrolled in the health outcomes study, of which 861 met ITT criteria [V1.161:27]. Patients' demographic characteristics were similar amongst the 3 treatment groups (with overall more women than men enrolled in the trial across treatment arms). The overall RQLQ score ranged from 2.67-2.74 with a std. error range of 0.96-1.02 [V1.161:45]. These scores were somewhat low on a scale of 0-6 and indicated a mild-moderate degree of 'health impairment'. The individual domain scores were likewise comparable amongst the 3 treatment arms [V1.161:46] and of mild-moderate severity.

The sponsor's evaluation of the health outcome parameters in adult SAR study 3081 indicated that on average, both fexofenadine treatment groups reported a statistically significantly greater improvement in health-related quality of life (QOL) in the Juniper RQLQ, as measured by average change from baseline in overall DLQI score compared to placebo treatment for combined weeks 1 and 2

($p < 0.0059$). Results of this primary analysis and the individual domains is presented below in Table IX. The difference (treatment effect) between the fexofenadine 180 mg and 120 mg doses for the overall RQLQ score was –0.07 units—a numerically minimal difference [V1.161:29]. When results for change from baseline for week 2 alone were analyzed, only the fexofenadine 180 mg group demonstrated a statistically significantly greater decrease in overall RQLQ domain over placebo ($p=0.0021$) [V1.161:36], although this finding may in part, be attributed to the greater placebo response noted in week 2.

For the 7 individual domains however, only the fexofenadine 180 mg group demonstrated a statistically significantly greater decrease in score compared to placebo across all domains ($p \leq 0.01$) [V1.161:31]. The numerical difference in scores between the 2 fexofenadine treatments for the individual domains ranged from 0.01-0.09 units. The fexofenadine treatment group demonstrated a statistically significant improvement in individual domain scores over placebo for 3 out of the 7 individual domains. When results for change from baseline for week 2 alone were analyzed, only the fexofenadine 1890 mg group demonstrated a statistically significantly greater decrease in scores for all 7 domains over placebo ($p=0.0021$), with the fexofenadine 120 mg group demonstrating a statistically significant improvement only for nasal symptoms and emotions, as compared to placebo [V1.161:36].

Treatment by site and treatment by baseline interactions for the overall RQLQ was assessed by the sponsor and revealed no significant baseline-by-treatment interaction, but did reveal a significant treatment-by-site interaction ($p=0.0484$) [V1.161:31]. When baseline-by-treatment interaction was excluded from the model, a significant treatment-by-site interaction remained ($p=0.0395$). As a further test for significance of treatment in the presence of the significant treatment-by-site interaction, a multiple partial F-test was performed and this likewise showed a significant interaction ($p=0.0055$) [V1.161:31]. The sponsor did not examine the source of the interaction, stating that 'it was of o concern because the treatment effect was statistically significant in the present of the interaction'. In the opinion of the statistical reviewer, the true treatment effect could not be estimated in the presence of an interaction and hence the different study sites should be analyzed together, and an overall treatment effect should not be calculated under such circumstances [Statistical Review, Biometrics II, NDA 20-872, 06/18/99, Barbara Elashoff, p. 15].

Analyses of changes in the 6 individual DLQI domains (symptoms/feelings, daily activities, leisure, work/school, personal relations, and treatment) were performed to explore the extent of the differences observed in the overall DLQI score and showed improvement in approximately half (3 out of 6) domains, (excluding the leisure, treatment, and personal relations domain) for all 4 fexofenadine groups compared to placebo, with the exception of the fexofenadine 20 mg bid group ($p \leq 0.0169$ for the symptoms/feelings domain, $p \leq 0.0096$ for the daily activities domain, and $p \leq 0.0099$ for the work/school domain [V1.221:120]. Aside from the fexofenadine 60 mg group, there were no

statistically significant differences among treatments with respect to the treatment domain. The fexofenadine 60 mg and 120 mg bid groups had significantly greater improvement than placebo in the personal relations domain ($p \leq 0.0046$). The domain which appeared to contribute the most to the determination of the overall DLQI score (the primary endpoint) for each of the 4 fexofenadine treatment groups consisted of the symptoms/feelings domain. These results are summarized in Table 8 of Volume 221 of NDA 20-872 [V1.221:46] and are presented below in Table VII.

With respect to the change from baseline in the Work Productivity and Activity Impairment (WPAI) assessment for combined weeks 1 and 2, both fexofenadine doses were statistically significantly superior to placebo with respect to average change from baseline in percent work productivity ($p \leq 0.0006$), with a slightly greater numerical decrease (~1.5 unit decrease from a baseline value of ~ 40 units) afforded by the fexofenadine 180 mg group [V1.161:32]. These results are summarized in Table 4 of Volume 161 of NDA 20-872 [V1.161:32]. For the endpoint of change from baseline in % work time missed, there were no statistically significant differences among treatments with respect to average change from baseline in % work time missed as compared to placebo [V1.161:33, 53]. For the endpoint of change from baseline in % impairment at work and % overall work impairment, both fexofenadine treatment groups demonstrated a statistically significantly greater improvement than placebo treatment ($p \leq 0.002$) [V1.161:33, 53].

For the classroom productivity domain, both fexofenadine treatment groups failed to report a statistically significant increase in classroom productivity compared to baseline, based the WPAI endpoints of: (1) % work time missed as compared to placebo, % impairment in the classroom, and overall % classroom impairment, even though small numerical differences were noted [V.161:54]. Since each treatment arm had 76-79 patients, it is possible that the study may have been underpowered, however no a priori treatment effect differences were specified by the sponsor.

And finally, with respect to average change from baseline in regular activity, both fexofenadine groups reported an increase in regular activity that was statistically significantly superior to placebo ($p \leq 0.0048$) [V1.161:33]. These results are presented in Table 8 of Volume 161 of NDA 20-872 [V1.161:53].

Results of the SF-36 showed a more consistent statistically significant improvement in the fexofenadine 120 mg group patients when compared to placebo for combined weeks 1 and 2 (than did the fexofenadine 180 mg group) [V1.161:35, 56].

In summary, results of the Juniper Rhiniconjunctivitis Questionnaire, the WPAI questionnaire, and the SF-36 indicate that fexofenadine at doses of 120 mg and 180 mg qd appeared to improve most domains of health-related quality of life, productivity, and regular activity significantly more than placebo in adult SAR patients. Because of inherent problems regarding lack of an a priori definition of a clinically significant effect for all of these domains and choice of 2

instruments which are not disease specific for SAR, the conclusions that can be reached from these studies are limited. Also somewhat problematic is the lack of a statistically significant effect at week 2 for the fexofenadine 120 mg dose seen for most domains in the Juniper Rhiniconjunctivitis Questionnaire, although this finding may in part, be attributed to the greater placebo response noted in week 2.

Table IX: RQLQ SUMMARY: [1]Average Change from Baseline [V1.161:29, 31]

DOMAINS	Treatment Comparison, Mean ± Std. Error (Change from baseline, as compared with placebo)	
	Fexo 120 mg qd	Fexo 180 mg qd
1. Overall DLQI Score (Planned Primary Analysis)	-0.57 ± .05 **(p=0.0059)**	-0.64 ± .05 **(p=0.0002)**
2. Miscellaneous Symptoms Domain	-0.12 ± .07 (p=0.0768)	-0.18 ± .07 **(p=0.0112)**
3. Activities Domain	-0.14 ± .09 (p=.1307)	-0.25 ± .09 **(p=0.0069)**
4. Sleep Domain	-0.12 ± .08 (p=0.1372)	-0.24 ± .08 **(p=0.0026)**
5. Practical Problems Domain	-0.25 ± .09 **(p=0.0037)**	-0.31 ± .09 **(p=0.0003)**
6. Emotions Domain	-0.21 ± .07 **(p=0.0048)**	-0.22 ± .07 **(p=0.0028)**
7. Eye Symptoms Domain	-0.17 ± .08 **(p=0.0378)**	-0.26 ± .08 **(p=0.0015)**
8. Nasal Symptom Domain	-0.26 ± .08 **(p=0.0012)**	-0.35 ± .08 **(p=0.0028)**

[1]Average of the data from Visit 2 and the final/early termination visit. Adjusted means (least square means), adjusted standard errors, and p-values from an ANCOVA containing site, treatment, baseline, and their interactions (if significant).

8.1.4.3. Safety Analysis

Safety analysis for protocol 3081 consisted of an evaluation of adverse events, standard laboratory tests (note: not analyzed post-treatment for all patients, but rather at select study sites), and vital signs pre-and post-treatment in patients randomized into the study and 'exposed' to study medication (the safety evaluable population). Two hundred and eighty seven (287) and 283 patients comprised the fexofenadine HCl 120 mg and fexofenadine HCl 180 mg safety evaluable populations, respectively; and 293 patients comprised the placebo treatment safety evaluable population [V1.64:117]. In this trial, the safety evaluable population was almost the same as the ITT population with the addition of 1 patient to the fexofenadine 180 mg group and 1 patient to the placebo group.

8.1.4.3.1. Demographics of the Exposed Population

Demographics of the exposed population is almost the same as the ITT population that was presented in section 8.1.4.1 ('Patient Demographics') of the medical officer review of NDA 20-872 and is re-summarized in Table X below. All 3 treatment groups were similar in baseline characteristics.

Table X. Patient Demographics for the ITT Population [V1.64:82]:

Variable	Fexofenadine 120 mg (n=287)	Fexofenadine 180 mg (n=282)	Placebo (n=292)	P-Value
Gender: (n, (%))				
Male	105 (37%)	98 (35%)	101 (35%)	
Female	182 (63%)	184 (65%)	191 (65%)	.8567[1]
Race: (n, (%))				
Caucasian	248 (86%)	257 (91%)	256 (88%)	
Black	26 (9%)	13 (5%)	25 (9%)	
Asian	6 (2%)	5 (2%)	5 (2%)	
Multiracial	7 (2%)	7 (2%)	6 (2%)	.5190
Age: (yrs)				
Mean ± SD	32 ± 12 yrs.	33 ± 12 yrs.	32 ± 12 yrs.	
Range	12-64 yrs.	12-65 yrs.	12-65 yrs.	.8922
Weight: (kg)				
Mean ± SD	72 ± 18 kg.	73 ± 18 kg	72 ± 20 kg	
Range	31-139 kg	39-143 kg	34-167 kg	.5125
Height: (cm)				
Mean ± SD	168 ± 10 cm	168 ± 10 cm	167 ± 10 cm	
Range	139-193 cm	135-193 cm	144-201 cm	.2216
Years since first episode of SAR occurred:				
Mean ± SD	17 ± 11 yrs.	17 ± 11 yrs.	17 ± 11 yrs.	
Range	2-60 yrs.	2-52 yrs.	2-48 yrs.	.8974

[1]P-value comparing the 3 treatment groups from Kruskal-Wallis test for continuous factors and chi-square test for categorical factors.

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 13 days (± 2 days) for all 3 treatment groups. The range of duration of exposure was 2-19 days for the placebo group (n=292 patients), 4-19 days for the fexofenadine HCl 120 mg group (n=287), and 1-18 days for the fexofenadine HCl 180 mg group (n=283).

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 3 treatment groups (including placebo) and was ~ 30% for all AEs combined [V1.64:118-121, V1.80:2-9]. The most frequent adverse event for all 3 treatment groups consisted of headache (with an incidence of 7.3% in the fexofenadine HCl 120 mg group, an incidence of 10.6% in the fexofenadine HCl 180 mg group, and an incidence of 7.5% in the placebo group), followed by upper respiratory tract infection (an incidence of 2.1% in the fexofenadine HCl 120 mg group, an incidence of 3.2% in the fexofenadine HCl 180 mg group, and an incidence of 3.1% in the placebo group) [V1.64:118-121]. No dose response for AE frequency was noted across treatment groups with the minor exception of a slightly higher incidence of

epistaxis in the fexofenadine 180 mg group, compared to an incidence of 0.7% in both the fexofenadine 120 mg and placebo groups.

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 3081 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 previous teleconferences with the sponsor, HMR, the medical officer 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 and most recently the current NDA #20-872. For this NDA, investigators used the MMDWHO AE Dictionary and were advised to capture a syndrome or diagnosis if available, rather than listing all associated symptoms.

With regard to somnolence, the frequency of reports for this AE ranged from 0-0.4% across all 3 treatment groups [V1.64:118].

A summary of all reported adverse events ('treatment emergent') for placebo treatment, as compared to the fexofenadine HCl 120 mg and fexofenadine HCl 180 mg treatments in study 3081, is presented in Table XI.

Table XI. Adverse Event (AE) Frequency:
AE's ≥ 1% for ALLEGRA (Fexofenadine 120 mg, Fexofenadine 180 mg, vs. Placebo), by Organ System and Preferred Term; Safety Evaluable Population [V1.64:118-121]

BODY SYSTEM	Preferred Term	Fexofenadine HCl 120 mg (n=287) n (%)	Fexofenadine HCl 180 mg (n=283) n (%)	Placebo (n=293) n (%)
All Systems	Any AE	86 (30.0%)	86 (30.4%)	88 (30.0%)
Neurologic	**Headache**	**21 (7.3%)**	**30 (10.6%)**	**22 (7.5%)**
Respiratory	Upper respiratory tract infection	6 (2.1%)	9 (3.2%)	9 (3.1%)
	Pharyngitis	8 (2.8%)	6 (2.1%)	9 (3.1%)
	Epistaxis	2 (0.7%)	5 (1.8%)	2 (0.7%)
	Upper respiratory congestion	3 (1.0%)	3 (1.1%)	0 (0.0%)
	Sinusitis	1 (0.3%)	4 (1.4%)	4 (1.4%)
	Coughing	3 (1.0%)	1 (0.4%)	3 (1.0%)
	Rhinitis	4 (1.4%)	0 (0.0%)	1 (0.3%)
	Wheezing	0 (0.0%)	3 (1.1%)	2 (0.7%)
Body as a Whole-General	Back Pain	8 (2.8%)	8 (2.8%)	4 (1.4%)
	Pain	7 (2.4%)	5 (1.8%)	10 (3.4%)
	Abdominal Pain	2 (0.7%)	3 (1.1%)	2 (0.7%)
Gastrointestinal	Dyspepsia	3 (1.0%)	3 (1.1%)	3 (1.0%)
Musculoskeletal	Myalgia	3 (1.0%)	8 (2.8%)	9 (3.1%)
Infectious Disease	Influenza	3 (1.0%)	3 (1.1%)	2 (0.7%)
Hematologic	Lymphadenopathy	3 (1.0%)	0 (0.0%)	0 (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 QD SAR (for patients ≥ 12 years of age) safety database were only specifically recorded under the 'cardiovascular'

category for the clinical endpoint of tachycardia; however the additional adverse events of: dizziness and chest pain were added to the list of cardiovascular adverse events by the medical reviewer even though AE frequencies for these 2 categories were < 1% for across all 3 treatment groups. In fact, the incidence of chest pain and tachycardia were slightly higher in the placebo treatment group over the 2 fexofenadine groups. 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, and ECGs pre- and post-treatment with the 3 study medications were not evaluated as a separate safety endpoint.

Adverse event stratification by severity assessment (rated subjectively as either mild, moderate, or severe in nature) by the patient and/or investigator indicated that the majority of AEs reported by patients were of mild-moderate intensity, and comparable in frequency between the 3 treatment groups [V1.64:121, V1.80:11-24, 26-41].

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 an H_1 antihistamine whose onset of action is well within 12 hours. Many of the adverse events described in the safety database for study 3081 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 or due to an idiosyncratic (unpredictable) reaction(s).

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 7 patients treated with either of the 2 doses of fexofenadine HCl (1.2%) and 4 patients treated with placebo (1.4%) discontinued treatment prematurely due to adverse events [V1.64:, V1.80:77-78]. On review of the adverse event summaries by the medical reviewer, only 2 patients (0.4%), (both receiving fexofenadine HCl 180 mg, patients #967-023 and #972-007), experienced an AE that appeared to be related to study medication which resulted in discontinuation of treatment [V1.64:127-128, V1.80:84]. The reasons for discontinuation were upper respiratory tract infection in the 1 patient and somnolence, respectively, in the other [V1.80:84]. In both cases, the AE resolved without sequelae. There were no patients in the 120 mg group who discontinued study medication due to an adverse event.

8.1.4.8. Serious Adverse Events and Death

No deaths were reported during this SAR trial for any of the 3 treatment groups. The sponsor's definition of 'serious treatment emergent adverse events was modified somewhat in this study to include, in addition to the standard regulatory criteria for a 'serious' adverse event (listed in the footnote below), additional criteria of: (1) an adverse event which resulted in withdrawal from the study, (2) temporary interruption of study medication, or (3) treatment with a counteractive medication [V1.64:125].

Reviewer's Note: The addition of the latter 3 criteria to the definition of AEs, especially the 'treatment with a counteractive medication' criteria increased the number of serious AEs, though the majority of these cases occurred in patients treated with a counteractive medication. When the 'treated with counteractive medication' cases were removed as serious AE criteria, the frequency of patients experiencing a treatment-related serious AE decreased to 0% (0/293) for placebo treated patients and 0.5% (3/570) for fexofenadine HCl patients [V1.64:125, V1.80:46-75]. In addition to the 2 fexofenadine patients discussed above who withdrew from the study due to a URI and somnolence, respectively; the 3rd patient—a 35 year old female with a history of SAR but no prior history of asthma (who did not withdraw from the study) with a serious treatment-related AE (#970-017) experienced a medically important AE 36 hours after completing the study on fexofenadine 120 mg. The patient went to the ER with 'shortness of breath', was treated for allergic bronchospasm with Proventil and Medrol Dose Pack and was released with no subsequent sequelae [V1.64:126, V1.80:83].

8.1.4.9. Laboratory Test Results

Laboratory tests performed during visit 1 (pre-randomization) and visit 4 (completion of treatment) of the study at several sites (complete laboratory analysis was not required at visit 4) and which consisted of a complete blood count with differential count, blood chemistries (to include cholesterol, triglycerides, total globulin and albumin:globulin ratio), liver function tests (SGOT(AST), SGPT(ALT), alkaline phosphatase, total protein, albumin, and total bilirubin, and LDH), urinalysis (to include screening for drugs of abuse), and serum pregnancy test (for all women) did not reveal any unexpected abnormalities in fexofenadine HCl or placebo treated patients. The effects of the 3 treatments on laboratory parameters were analyzed (with the exception of serum pregnancy tests) using a tabulation of outlier values for individual patients in order to identify potentially clinically important changes [V1.64:130]. 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 [V1.64:132-133.

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[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.

V1.80:88-91]. Summary statistics for each laboratory value was not computed using an ANOVA model with adjustment for site as had been done in previous NDA submissions (e.g. ALLEGRA-D, NDA 20-786) [V1.64:130]. Neither were shift tables performed in this study as a mean of presenting laboratory data [V1.64:131].

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 [V1.80:88-91]) for each laboratory test showed no obvious difference in the number of patients with outliers between the 3 treatment groups, nor any obvious dose-related trends for laboratory outlier trends; although interpretation of these data are limited since serial laboratory tests (i.e. Visit 4 tests) were not obtained on all study patients (n=55 to 64 patients total per treatment group for outlier laboratory tests) [V1.64:134]. These data are summarized in Table 41 of the study report of trial 3081 [V1.64:134].

'High' outlier values were reported in 5 fexofenadine HCl 120 mg treatment patients (3 patients had 'high' outlier bilirubin levels (patients #964-019: total bilirubin=2.4 mg/dL, #964-027: total bilirubin=3.00, #967-032: total bilirubin=2.2 mg/dL), 1 had 'high' outlier glucose levels (patient #964-021, serum glucose=151 mg/dL), and 1 had a 'high' triglyceride levels (patient #980-009, serum triglyceride=584 mg/dL [V1.64:134, V1.80:94]. No patients in the fexofenadine 180 mg group had 'high' outlier values. 'Low' outlier values were seen in 3 placebo patients (for WBC (2 patients, #964-005:WBC=2.46 x 10^9 L, #987-001:WBC=3.16 x 10^9 L), and neutrophil count on the differential (1 patient, #964-005, WBC=1.36 x 10^9 L), 2 fexofenadine HCl 120 mg group patients (for WBC, patients #963-028: WBC=3.68 x 10^9 L, #966-018, WBC=3.33 x 10^9 L), and 1 fexofenadine HCl 180 mg group patient (for WBC, patient, #963-007, WBC=2.46 x 10^9 L with decrease in neutrophil differential count to 0.98 x 10^9 L) [V1.80:94].

8.1.4.10. Vital Signs and Weight

Vital signs (blood pressure (systolic and diastolic), and heart rate 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 between the 3 treatment groups [V1.64:135]. These data are summarized in Table 42 of the study report for trial 3081[V1.64:135].

8.1.4.11. Pharmacokinetic Studies

Population pharmacokinetic studies of fexofenadine HCl in patients with SAR was performed in order to characterize this population PK and to determine the impact of covariates on PK parameter estimates for fexofenadine HCl. Re-iterating the study design, patients had blood samples collected on Visit 3 (week 3) and Visit 4 (week 4). Plasma fexofenadine levels were analyzed for

fexofenadine (MDL 16,455) using with an assay sensitivity of ng/mL [V1.63:299].

A total of 1088 fexofenadine plasma samples were collected from 563 patients (from the 2 fexofenadine treatment groups) and 971 plasma sample concentrations from 548 patients were ultimately included in the population PK analysis. Reasons for which some patients samples were discarded from analysis comprised the following: plasma concentrations=0, patients assigned to placebo treatment, possible incorrectly recorded dosing event, or possible missing dosing event. Demographic data for all participating fexofenadine patients were analyzed (Table 8-49, [V1.63:299] and revealed very similar patient demographics for the data set used in the NON-MEM (nonlinear mixed-effects modeling) population PK analysis as compared to the full data set. Two covariates, sex and height, were evaluated sequentially in NONMEM by comparing the full model with the covariate included to the reduced model with covariated deleted (for more information, refer to [V1.63:300]. The population PK model best describing the data was a 2-compartment oral model with proportional residual error structure [V1.63:301].

Results of this analysis agreed with previous PK studies performed with fexofenadine and showed:

1.	an apparent clearance (L/h) of:	55.2 (95% CI: 49.4, 61.0)
2.	an apparent volume of distribution (L) of:	364 (95% CI: 356, 373)
3.	an inter-compartmental clearance (L/h) of:	16.6 (95% CI: 10.0, 23.2)
4.	a peripheral compartment model (L) of:	3380 (95% CI: 1692, 5068)
5.	an absorption rate constant (per hour) of:	1.67 (95% CI: 0.70, 2.64)
6.	an inter-subject variance (ω^2) of:	0.382 (CV=68%)
7.	a residual variance (σ^2) of:	0.723 (CV=103%)

In summary, the PK of fexofenadine in patients with SAR appeared not to be affected by patient demographics and base model population parameter estimates were found to agree with previous PK studies performed with fexofenadine.

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

The results of this study support the safety of once daily ALLEGRA at either the fexofenadine HCl 120 mg or 180 mg dose for the treatment of symptoms of SAR (excluding nasal congestion) in adults and children 12 years of age and older. The more effective dose was noted to be the 180 mg dose which demonstrated a greater numerical and more consistent improvement in the various efficacy parameters evaluating SAR symptoms and demonstrated improvement in a greater number of these parameters than did the 120 mg dose. The 120 mg dose was seen to be marginally effective at the end-of-dosing interval. A consistent onset of

action was not seen in this study, though a statistically significant decrease in the primary efficacy endpoint of the 8:00 a.m. instantaneous TSS was seen by week 1 of treatment with both doses of qd fexofenadine HCl. Both doses of QD ALLEGRA failed to provide an adequate duration of decongestant effect, as per analysis of the end-of-dosing interval for the nasal congestion endpoint (the 8:00 a.m. instantaneous nasal congestion score for the 2 week double-blind treatment period) compared to placebo treatment.

QOL studies performed consisted of the Juniper Rhinoconjunctivitis Questionnaire, the WPAI questionnaire, and the SF-36 survey. Of these 3 instruments, only the Juniper Rhinoconjunctivitis Questionnaire was disease specific and deemed appropriate as a QOL instrument, however several study design flaws (no pre-specified clinically significant effect size and hence no powering of the study, no adjustment for multiple comparisons) limit strict interpretations of the results. Nonetheless, the data obtained would appear to indicate that at least for the fexofenadine 180 mg dose, greater improvement in QOL measures were seen both for the 2 week double-blind period and at week 2.

Overall, ALLEGRA tablets were safe and well-tolerated given once a day, at a dose of 120 mg or 180 mg in 570 patients. No serious related adverse events occurred in patients treated with ALLEGRA tablets, nor were any deaths reported. Similar to placebo treatment, headache was the most common adverse event, followed by upper respiratory tract infection, pharyngitis, and back pain. Virtually no cardiac adverse events were reported, although this may be a virtue of the limited adverse event reporting classification categories employed in this study and due to a lack of performing serial ECGs throughout the study. Interpretation of laboratory testing was limited due to the fact that serial labs were not obtained at all study sites but only several at the final study visit. Nonetheless, based on these data no abnormal trends or worrisome laboratory findings were noted in study 3081. No significant changes in vital signs were noted at the final study visit in safety evaluable patients. In addition, population PK studies performed in fexofenadine treated patients were consistent with findings seen in previous fexofenadine PK studies and failed to show a demographic influence on population PK.

Summary:

Based on the results of this SAR trial, ALLEGRA tablets 120 mg qd and 180 mg qd demonstrated adequate evidence of efficacy and safety compared with placebo, for the once daily treatment of SAR symptoms in adults and children 12 years of age and older.

APPENDIX I: STUDY 3081: ALLEGRA QD

f. Table of Study Procedures

Study Procedure	Visit			
	1 (Entry)	2 (Randomization)	3 (Interim)	4 (Final or Early Discontinuation)
Informed Consent	X			
Demographics	X			
Medical History	X			
Skin Test	X			
Single-Blind Medication Unit Dose Card Dispensed	X			
Entrance Criteria	X	X		
Physical Exam (including vital signs)	X			X
Urine Sample for Drugs of Abuse	X			
Urine Pregnancy Test	X			X
Clinical Labs	X			X*
Medication History	X			
Qualifying SAR Assessment for Single-blind Placebo Lead-in	X			
Qualifying SAR Assessment for Double-Blind Medication		X		
Daily Symptom Diary Issued	X	X	X	
Adverse Event and Concomitant Medication Diary Issued	X	X	X	
Double-Blind Medication Unit Dose Card Dispensed		X	X	
Assess Use of Concomitant Medications		X	X	X
Collect Unit Dose Card and Diaries		X	X	X
Determine Study Drug Compliance		X	X	X
Plasma Sample for Fexofenadine Level			X	X†
Adverse Event Assessment		X‡	X	X§

* Not required if patient has not received double-blind study medication. Was to be obtained for follow-up of patients discontinued due to a treatment-emergent adverse event, or if deemed necessary by investigator due to safety concerns.

† Sample taken at Early Discontinuation only if last dose of study medication was ≤ 48 hours before this visit, the patient had been exposed to double-blind study medication, and the patient had documented the date and time of the last dose in his/her diary.

‡ Prior to randomization only serious adverse events were reported and documented in the patient's casefile.

§ Adverse events were to be reported if experienced within 72 hours after last dose of study medication.

SEASONAL ALLERGIC RHINITIS IN PEDIATRIC PATIENTS (BID Dosing, Pivotal Trials (0066/0077):

8.2. Protocols No. PJPR0066/0077 Combined (and as Separate Studies): A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 3 dosage strengths of fexofenadine HCl 15 mg, 30 mg, and 60 mg bid in pediatric patients (ages 6-11 years) in the treatment of seasonal allergic rhinitis.

Principal Investigator: None, multi-center study.

Participating Centers: 58 U.S. centers (for combined studies 0066 and 0077)

8.2.1. Objective

The primary objective of this study was to investigate the safety and efficacy of fexofenadine HCl at 15 mg po bid, 30 mg po bid, 60 mg po bid, compared to placebo treatment in patients age 6-11 years for the treatment of symptoms of seasonal allergic rhinitis (SAR).

A secondary objective of the study was to characterize the population pharmacokinetics of fexofenadine bid in pediatric SAR patients.

8.2.2. Study Design

The basic study design for studies PJPR0066 and PJPR0077 (which were both identical in study design but conducted separately) was almost identical to that of the adult SAR QD trial 3081 with minor exceptions (delineated below). Studies 0066 and 0077 were both phase III, multi-center, randomized, double-blind, parallel group, with a 5-7 day single-blind placebo lead-in, safety and efficacy study of the treatment of fexofenadine HCl 15 mg po bid, 30 mg po bid, 60 mg po bid, vs. placebo in 875 pediatric seasonal 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 approximately 2 weeks. Patients participated in the study for a total of 18-25 days [V1.225:25, 310, 311, 325, Amendment 2]. A total of approximately 1200 patients were to be randomized to the 4 treatment groups for the 2 studies (or 600 patients/study), with approximately 30 study sites/study and approximately 20 patients per study site [V1.225:26, 317]. A table of study procedures is provided in Appendix 1 [V1.225:47, 188].

8.2.3. Protocol

8.2.3.1.a. Population: Male or female pediatric patients, 6-11 years of age, with a history of SAR for at least 1 fall season documented by a positive skin test to at least 1 fall allergen indigenous to the study site at Visit 1 or

during the previous 12 month period [V1.225:27, 150, 163].

(I) Inclusion Criteria [V1.225:27, 163-164]:
Patients had to have essentially the same inclusion criteria as denoted for study 3081 with the following criteria emphasized:

1. 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 (excluding nasal congestion), 2 or more additional SAR symptoms (excluding nasal congestion) were to be rated as 'moderate' or 'severe', and no SAR symptom was to be rated as 'very severe'.
2. At visit 2 (=baseline/randomization visit), the 7 p.m. reflective allergy symptom assessment (excluding nasal congestion) had to meet the following criteria in order to be randomized to double-blind medication: (1) for 4, 7 p.m. reflective assessments completed, at least 4 assessments must have had: a total symptom score (TSS) ≥ 5, and 2 or more symptoms with a minimum score of "2" (moderate severity), (2) for 5, 7 p.m. reflective assessments completed, at least 3 assessments must have had: a total symptom score (TSS) ≥ 5, and 2 or more symptoms with a score of "2", (3) for 6, 7 p.m. reflective assessments completed, at least 4 assessments must have had: a total symptom score (TSS) ≥ 5, and 2 or more symptoms with a score of "2", and (4) for 7, 7 p.m. reflective assessment completed, at least 5 assessments must have had: a total symptom score (TSS) ≥ 5, and 2 or more symptoms with a score of "2". No symptom, including nasal congestion was to be rated as 'very severe' at any a.m. or p.m. assessment.
3. Patient had to demonstrate (at Visit 1) an ability to swallow a tablet.

(II) Exclusion Criteria [V1.225:28-30, 165-167]:
Exclusion criteria for studies 0066/0077 were essentially the same as that for adult study 3081 and will not be re-iterated here (refer to section 8.1.3.) with the exception of these specific ECG exclusion criteria:

1. Patients having any of the following at Visit 2 (randomization visit) were excluded from the study:
   -rhythm disturbance (other than sinus arrhythmia)
   -heart rate ≤ 50 beats/minute on ECG or physical exam
   -PR interval < 120 msec or > 200 msec.
   -QRS interval > 120 msec.
   -QT interval > 450 msec.

Reviewer's Note: Similar to study 3081, 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 [V1.225:29-30, 166-168]: The list of medications to be discontinued within the indicated time periods prior to visit 1, and not allowed between Visit 1 and 2 were the same as those discussed in the adult SAR QD trial 3081 and will not be re-iterated here with the exception of delineating differences in discontinuation times or noting medications that had not been previously included on the discontinuation list:

	Medication	Time Discontinued Prior to Visit 1
1.	H_2 antagonists	≥ 72 days
2.	Cough/cold preparations	≥ 48 hours
3.	Sleep aids	≥ 48 hours
4.	Antacids	≥ 8 hours
5.	Saline eye drops	≥ 4 hours
6.	Antihistamine, NSAID, or α-adrenergic eye drops	≥ 24 hours

8.2.3.1.b. Procedure

(II) Screening Visit (Visit 1) [V1.225:41-43, 151, 179-181]:

The procedure for Visit 1 (along with other study visits) was similar to those performed in the Adult SAR QD study 3081, with a complete medical history, physical examination (including vital signs), laboratory evaluation, assessment of adverse events, and confirmation of the patient's allergen hypersensitivity with autumnal allergens indigenous to the study site with skin prick testing (if not performed within the past 12 months) performed at the screening visit. In studies 0066/0077 (unlike study 3081), patients were not required to fast ≥ 10 hours prior to Visit 1. The 2 studies were conducted during the autumn season.

Similar the study 3081, it was determined during Visit 1 whether the 12 hour reflective allergy symptom scores (see Tables I and II, study 3081) 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, excluding nasal congestion) for the previous 12 hours had to be ≥ 6, 2 or more SAR symptoms (excluding nasal congestion) were to be rated as 'moderate' or 'severe', and no SAR symptom

(including nasal congestion) was to be rated as 'very severe', see symptom scoring below).

Patients who fulfilled the SAR symptom score criteria based on this 12 hour reflective assessment then entered into a 5-7 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— a placebo tablet identical in appearance to the 'to-be-marketed' fexofenadine HCl 60 mg tablet which were both to be taken twice daily (in the morning at 7:00 a.m. ± 1 hour and in the evening at 7:00 p.m. ± 1 hour) by patients. Patients were instructed to take the initial dose (2 tablets) of single-blind study medication (2 placebo tablets) at 7:00 p.m. (± 1 hour) on the evening of Visit 1 [V1.225:32]. Patients and their caregivers were asked to jointly score the patient's allergy symptoms daily at 7:00 p.m. (± 1 hour) immediately prior to taking the study medication and scores were recorded in the symptom diary by the caregiver. Subsequent doses of study medication were taken at 7:00 a.m. (± 1 hour) daily and 7:00 p.m. (± 1 hour) daily after completing the assessments and diary entries. It was recommended that the one and same caregiver act as primary supervisor to the patient's daily study participation and administer the daily symptom assessments throughout the entire study duration [V1.225:34].

SAR symptoms were assessed 'reflectively' (over the previous 12 hour period), 'instantaneously' at both 7:00 a.m. (± 1 hour, over the previous 1 hour period immediately prior to taking study medication) and at 7:00 p.m. (± 1 hour) daily). 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, mouth, throat and/or ears
(5) itchy, watery, red eyes

Each SAR symptom was rated on a 0-4 (5 point) 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 annoying and bothersome and interfered with normal daily activity or sleep)
4	**Very Severe** (symptom prevented normal daily activity or sleep)

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.

Beginning with Visit 1, patients were administered the pediatric rhinoconjunctivitis quality of life questionnaire (QOL assessment) which evaluated patient quality of life in terms of nasal symptoms, eye symptoms, and activities of daily living [V1.225:41]. This questionnaire was re-administered at each subsequent (Visits 2-4) visit.

(III) Visit 2 (Week 2, 4-7 days after Visit 1) [V1.225:43-44, 181-183]:

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. A 12-lead ECG was performed at Visit 2 which was reviewed by the investigator and if he/she had further questions as to the interpretation, a copy of the ECG was faxed to the medical monitor at the contract research organization, PAREXEL, Inc. where the ECG would be reviewed and it would be determined if the patient was suitable for further participation in the study [V1.225:43].

Patients whose compliance with study medication was not between 90-110% for the single-blind lead in period were further questioned for possible discontinuation from the study [V1.225:44]. Furthermore, patients were required to have completed at least 5, 8:00 a.m. symptom assessments [V1.64:44, Amendment 1]. In order to qualify for randomization, patients were required to have fulfilled the same inclusion criteria as specified for Visit 1 [V1.64:44, 224-225, Amendment 1].

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 number of 7:00 p.m. reflective