patients per study site [V1.83:38]. However, because an insufficient number of patients were recruited into the study due to an unusually rainy hay fever season in spring and summer, the study was extended to include 15 centers in South Africa and 1 center in Australia [V1.83:38]. A table of study procedures is provided in Appendix 1 [V1.83:87].

Importantly, and slightly different from the inclusion criteria noted in study 3081, for patients to enroll in study PJPR0032, at visit 1 (=screening visit) the patient's reflective total symptom score (TSS=sum of sneezing, rhinorrhea, itchy nose, palate and/or throat, and itchy, watery, or red eyes, rated on the same 0-4 scale as in pivotal SAR trial 3081 [V1.83:48]) for the previous 24 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' [V1.83:41].

At visit 2 (=baseline/randomization visit), the total symptom score (TSS) must have been ≥ 5 for at least 2, 24 hour reflective assessments, with 2 or more symptoms with a score of "2" or "3", and no symptom, including nasal congestion was to be rated as 'very severe' at any a.m. or p.m. reflective assessment [V1.83:41]. To ensure similar baseline reflective TSS across double-blind treatment groups, a stratified randomization was used, based on the average baseline 24-hour reflective TSS. Qualifying patients were placed into 1 of 2 categories based upon the average baseline 24-hour reflective TSS: (1) low average baseline 24-hour reflective TSS: ≥ 5 and < 8, and (2) high average baseline 24-hour reflective TSS: ≥ 8 and ≤ 12 [V1.83:47].

Reviewer's Note: As previously noted in the pivotal SAR trial, 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.

At Visit 1, patients were instructed to take the initial dose of single-blind study medication, then at 8:00 a.m. (± 1 hour) the morning after, and then daily at 8:00 a.m. (± 1 hour) [V1.83:45]. At Visit 2, upon randomization, patients were assigned to 1 of the following 4 treatment groups:

Double Blind Treatment Groups:	
STUDY GROUPS	**DOSING**
(1) **Fexofenadine HCl 120 mg po qd**	**2, 60 mg capsules (fexofenadine HCl 120 mg) + 1 placebo capsule (placebo**; identical in appearance to the fexofenadine HCl 60 mg capsule) **q a.m. (8 a.m.)**
(2) **Fexofenadine HCl 180 mg po qd**	**3, 60 mg capsules (fexofenadine HCl 180mg) q a.m.**
(3) **Cetirizine 10 mg po qd**	**1. 10 mg cetirizine capsule + 2 placebo capsules q a.m.**
(4) **Placebo qd**	**3, placebo capsules q a.m.**

Patients were instructed to take double-blind medication (in which placebo and cetirizine capsules were identical in appearance to fexofenadine HCl 60 mg capsules) during the double-blind period daily at 8:00 a.m. (± 1 hour).

Reviewer's Note: Importantly, fexofenadine capsules and not 'to-be-marketed' tablets were evaluated in this study.

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.

The primary efficacy variable was defined as: the change from baseline in the average 24 hour reflective TSS (average of daily 24 hour reflective TSS during the double-blind treatment period) from average baseline 24 hour reflective TSS (average of daily 24 hour reflective TSS during the placebo lead-in period) [V1.83:30]. 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 [V1.83:62, 63].

Reviewer's Note: The above primary efficacy variable was different from that recommended by the Agency and utilized in pivotal SAR trial 3081: the change from baseline in the average 8:00 a.m. instantaneous TSS over the 2 week double-blind treatment period (which would ensure measurement of the end-of-dosing interval).

Secondary efficacy variables consisted of the following [V1.83:63]:
(1) Change from baseline in the average trough 8:00 a.m. instantaneous TSS (over the 2 week double-blind treatment period)-used to assess the 'end-of-dosing interval',
(2) Change from baseline in the average 8:00 a.m. reflective TSS (over the 2 week double-blind treatment period),
(3) Change from baseline in the average daily 8:00 p.m. reflective TSS (over the 2 week double-blind treatment period),
(4) Change from baseline in the average 24 hour reflective individual 24-hour reflective symptom scores (over the 2 week double-blind treatment period),
(5) Patient assessment of overall study drug effectiveness, and
(6) Physician assessment of overall study drug effectiveness.

Reviewer's Note: Although the sponsor included the change in average somnolence score from the average baseline somnolence score as a secondary efficacy endpoint, this was deemed to be more appropriate as a safety

assessment and was evaluated in the 'Safety Analysis' section of the medical review for study PJPR0032.

All primary and secondary efficacy endpoints were analyzed using the 'intent-to-treat population', defined as 'patients who received at least 1 dose of double-blind treatment, with at least 1, 24 hour reflective TSS and 1, 24 hour reflective post-baseline TSS' [V1.83:61], along with the evaluation of the primary efficacy endpoint using 'protocol correct' patients (= 'intent-to-treat' patients with no major protocol violations) [V1.83:61].

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

Statistical analysis consisted of a calculation of the sample size of 200 patients per treatment arm to yield 83% power and detect a difference of 0.7 units in 24 hour reflective TSS between active dose and placebo, based on results from previous fexofenadine clinical studies [V1.83:61]. The estimated average difference in the change in 24 hour reflective TSS between fexofenadine 60 mg bid and placebo ranged in these studies from 0.4-1.0, with a standard deviation of 2.4.

The primary efficacy endpoint was analyzed using an ANCOVA model with investigative site, treatment, and average baseline TSS included as independent variables [V1.83:63] and with plan to include these variables in the final model if significant at the α=0.10 level. Baseline symptom scores were included as a continuous covariate. Pairwise comparison of the fexofenadine group vs. placebo was performed using a step-down procedure, with no adjustment for multiple comparisons [V1.83:63]. The primary efficacy variable was also assessed by subgroups consisting of: age, gender, investigative site, race, and country [V1.83:64].

The same statistical model used in the primary endpoint analysis was used for secondary efficacy variables, with minor exceptions for the endpoints of: (1) improvement in 24 hour reflective TSS (analyzed by Mantel-Haenzel method), (2) the physician overall assessment of effectiveness (analyzed by Mantel-Haenzel method, stratifying for investigative site), and patient assessment of overall study drug effectiveness (analyzed using a rank ANOVA model) [V1.83:64].

Safety assessment consisted of the usual planned analyses: lab tests (Visit 1 and 4), vital signs, abnormal physical findings, and patient adverse event reports.

8.6.3. Results

Evaluation of patient enrollment in study PJPR0032 indicated that of 843 patients randomized to receive study medication, 3 patients discontinued the study

following randomization but prior to receiving double-blind study medication. A total of 864 patients were randomized into the study, with all randomized patients exposed to double-blind study medication. The remaining 839 patients comprised the 'safety population' and a further 18 patients were excluded, as they had no 24 hour reflective baseline of post-baseline TSS, leaving 821 patients in the ITT population. Seven hundred and twenty two (722) patients completed the study. [V1.83:67]. A total of 117 patients (14% of total) discontinued the study prior to completion (36 patients or 17% in the placebo group, 29 patients or 14% in the fexofenadine 120 mg po qd group, 32 patients or 15% in the fexofenadine 180 mg po qd group, and 20 patients or 10% in the cetirizine group) [V1.83:94]. The most common reason for early patient withdrawal was 'lack of effect', followed by 'lost to follow-up'. Overall the rate of patient withdrawal was comparable amongst the 4 treatment groups, with a somewhat lower % noted in the cetirizine group.

Review of patient demographics indicates that no statistically significant differences with respect to gender, age, race, weight, height, or duration of SAR were noted amongst the 4 treatment arms [V1.83:94].

Furthermore, no statistically significant differences were noted across the treatment groups for any of the efficacy endpoints at baseline (for combined scores and individual symptoms, reflective and instantaneous), including the primary efficacy endpoint [V1.83:96-99].

Use of a disallowed concomitant medication prior to or throughout the study duration was noted in 8 placebo group patients (4%), 6 fexofenadine 120 mg qd group patients (3%), 5 fexofenadine 180 mg qd group patients (2%), and 1 (< 1%) cetirizine 10 mg qd group patient [V1.83:69]. The most frequently used disallowed medications consisted of oral corticosteroids and other H_1 antagonists such as loratadine [V1.83:102].

The mean duration of exposure was approximately 13 days for all 4 treatment groups (12.9-13.4 ± 0.2 days), and ranged from 1-18 days (duration of exposure calculated from summing the # of days since the last visit, as recorded in the CRF) [V1.83:68, 100]. Compliance with study medication (determined by the total # of doses dispensed minus the total # of doses returned) was noted to be adequate, with an average compliance rate of 99% seen [V1.83:69, 101].

With respect to pollen counts, the sponsor noted that in the U.K., the hay fever season was shorter than usual, with lower pollen counts than usual (< 200 grains/mm^3/24 hours (compared to > 300 grains/mm^3/24 hours noted in 1994) [V1.83:78]. Similar findings were seen in France and Germay at 11 centers in each country, with 1 center in France having 14 days in May with a pollen count of 0 [V1.83:78].

8.6.4. Efficacy Endpoint Outcomes

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=211 for fexofenadine HCl 120 mg group, n=202 for fexofenadine HCl 180 mg group, n=207 for the cetirizine 10 mg group, and n=201 for placebo)

for the primary efficacy variable or the change from baseline in the average 24 hour reflective TSS for the 2 week double-blind period; where the primary comparison of interest was the response of the 2 fexofenadine doses vs. placebo. This primary efficacy endpoint did not provide information about the end-of-dosing interval efficacy (or duration of drug effect).

Reviewer's Note: It was noted during review of study 0032 that the sponsor stated that many transcription errors for symptom scores were made and a reanalysis requested by the Agency was performed by the sponsor [Response to FDA Request, 05/24/99, NDA 20-872, Wayne F. Vallee, Drug Regulatory Affairs, Quintiles, Inc.].

Results of the sponsor's initial primary efficacy analysis are summarized in Table I. below and show that for both the fexofenadine HCl 120 mg (p=.0001) and 180 mg (p=0.0001) po qd doses (as well as the cetirizine group (p=0.0001), a statistically significant difference in the change in the 24 hour reflective 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 [V1.83:103]. Numerically, the change from baseline in the 24 hour reflective TSS over the 2-week double-blind treatment period was comparable amongst the 3 active treatment groups. Evaluation of the 'protocol correct' population yielded similar results with regard to the primary efficacy endpoint [V1.83:104]. Subgroup analysis for the primary efficacy endpoint revealed that there were no interactions either by baseline characteristics (race, gender, age), investigative site, or country [V1.83:103, 116-118].

Nonetheless, 1 of the study sites (#21 in the U.K) enrolled an extraordinarily large # of patients (n=165) compared to other study sites (general range of patients enrolled=10-30), followed in number by a French/Belgian site (#991) which enrolled 55 patients [V1.83:90, 113]. Importantly, both these study sites displayed a very small placebo response (-0.1 ± 0.4 units for TSS in study site #21 and 0.0 ± 0.6 units for TSS in study site #991) in comparison to the other study sites evaluated (range of: -0.5—3.5 units ± 0.7-2.3) [V1.83:113-114]. In addition, the same investigator who enrolled 165 patients in study 0032 (Dr. Martin Stern, Midland Asthma and Allergy Reseach Association) also enrolled 206 patients into nonpivotal adult SAR study 0061 [Statistics Review, Biometrics II, NDA 20-872, 06/18/99, Barbara Elashoff, p. 7]. A total of 100 patients were enrolled into both SAR trials.

Hence, it is quite possible that the large # of patients enrolled at these 2 study sites (220 patients for both study sites out of a total 821 ITT patients) and imbalance in the patient numbers across study sites may have influenced the findings of the primary efficacy endpoint, in terms of accentuating patient response in the active treatment groups. Comparison of the treatment effect seen at these 2 sites with that of the other study sites in terms of % change indicated that the overall numerical differences from baseline at the 2 larger sites were

greater for active treatment vs. placebo. These findings do not invalidate the clinical findings in this study as the overall numerical trends display greater efficacy for the active treatment groups than for placebo treatment.

However, re-analysis of the primary efficacy endpoint using the 'corrected' data and excluding site #21, while slightly different numerically from the sponsor's initial analysis, also revealed a statistically significant improvement in the 24 hour reflective TSS over the 2-week double-blind treatment period (mean change in TSS for the fexofenadine 120 mg group=-2.76 units ($p=0.0001$ compared with placebo), for the fexofenadine 180 mg group=-3.01 units ($p<0.0001$ compared with placebo), for the cetirizine group=-2.93 units ($p<0.0001$ compared with placebo), and for the placebo group=-1.74 units [Response to FDA Request, 05/24/99, NDA 20-872, Wayne F. Vallee, Drug Regulatory Affairs, Quintiles, Inc.].

Reviewer's Note: The fexofenadine 180 mg po qd dose demonstrated only a slightly greater numerical decrease (-0.3 units) in the primary efficacy endpoint and both doses of fexofenadine were shown to be statistically significantly more efficacious than placebo for the 2 week double-blind treatment period.

Table I.
Efficacy of Fexofenadine HCl 120 mg qd, Fexofenadine HCl 180 mg qd, vs. Cetirizine 10 mg qd, and vs. Placebo
Primary Efficacy Variable: Intent-to-Treat (ITT) Population [V1.83:83, 103]

	TREATMENT GROUP						
Primary Efficacy Variable	**(A) Fexo 120 mg qd**	**(B) Fexo 180 mg qd**	**(C) Cetirizine 10 mg qd**	**(D) Placebo**	**P-value**		
					A-D	**B-D**	**C-D**
24 Hour Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)							
	(n=211)	**(n=202)**	**(n=202)**	**(n=201)**			
Baseline TSS	7.2 ± 0.1	7.4 ± 0.1	7.3 ± 0.1	7.3 ± 0.1			
Double-blind Treatment Period TSS	4.7 ± 0.2	4.5 ± 0.2	4.4 ± 0.2	5.8 ± 0.2			
Change from baseline in average 24 hour reflective TSS	-3.0 ± 0.2	-3.3 ± 0.2	-3.3 ± 0.2	-1.9 ± 0.2	0.0001	0.0001	0.0001
Mean Difference ± SE					-1.1±.2	-1.4± 2	-1.4±.2

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

A summary of analysis of the secondary efficacy variables for the ITT population is provided in Table II. below and indicates that for all of the secondary efficacy endpoints, a statistically significant difference in symptom scores was seen for both of the fexofenadine doses compared to placebo. The numerical difference in decreasing the respective secondary efficacy endpoint for the fexofenadine 180 mg po qd group was generally only slightly greater (~ -0.1-0.3 units) than that of the fexofenadine 120 mg po qd group [V1.83:105-108, 110-111].

Specifically with regard to analysis of the end-of dosing interval (the 8 a.m. instantaneous trough TSS), both fexofenadine treatment groups displayed statistically significantly greater decrease in TSS compared to placebo treatment, with a slightly greater numerical decrease afforded by the fexofenadine 180 mg po qd group (-0.1 greater decrease in TSS over the fexofenadine 120 mg po qd group) [V1.83:107]. Results for the end-of-dosing interval for the cetirizine treatment group were comparable to that of the 2 fexofenadine treatments. A treatment by investigative site interaction was present (p=0.0158), however no uniform pattern was noted in the site differences [V1.83: 83, 107]. When the re-analysis of the end-of-dosing interval data which excluded site #21 was performed, the numerical degree of change for all 4 treatment groups (including placebo) was slightly lower than in the original analysis (a 0.3-0.4 unit difference), however statistical significance was maintained for both fexofenadine treatment groups (p=0.0021 for the 120 mg group and p=0.0003 for the 180 mg group) and the cetirizine group (p=0.0004) [Response to FDA Request, 05/24/99, NDA 20-872, Wayne F. Vallee, Drug Regulatory Affairs, Quintiles, Inc.].

Reviewer's Note: The fexofenadine 180 mg po qd dose demonstrated only a slightly greater numerical decrease (-0.3 units) in the primary efficacy endpoint and both doses of fexofenadine were shown to be statistically significantly more efficacious than placebo for the 2 week double-blind treatment period.

Onset of action in this study was to be evaluated via the time on the 1st day of medication that the patient felt improvement of SAR (as recorded on the diary card at week 2, day 2 (p.m. score) [V1.83:30], however after review of these data, the sponsor determined that these were not well collected to undertake an analysis of this measure [V1.83:79]. Per the sponsor's explanation, this inability to analyze the data was primarily due to the CRF's design being inadequate in allowing patients to record if no improvement was seen [V1.83:79]. Similarly, duration of action was not analyzed for the same reason, per the sponsor [V1.83:79-80]. Week 1 vs. week 2 analyses of the primary efficacy endpoint or change in average 8:00 a.m. instantaneous total symptom scores were not performed by the sponsor in this study.

Reviewer's Note: Analysis of the secondary efficacy endpoints revealed a numerically minimal and statistically insignificant numerical difference betweeen the fexofenadine 180 mg and 120 mg treatment groups. For all secondary efficacy endpoints examined, both fexofenadine groups (as well as the cetirizine active comparator) demonstrated statistically signficiantly greater improvement in the respective parameter than did placebo treatment.

Based on these data, either the fexofenadine 120 mg po qd or 180 po qd dose would appear to be reasonable doses for the treatment of SAR symptoms in patients 12-65 years of age.

Table II: Secondary Efficacy Variables for the ITT Population and Treatment with Fexofenadine HCl 120 mg qd, Fexofenadine HCl 180 mg qd, and Placebo [V1.83:105-108, 110-111]

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No	
	Fexofenadine 180 mg qd	Fexofenadine 120 mg qd
Secondary Efficacy Variables		
1. Change from baseline in the average trough 8:00 a.m. instantaneous TSS	*Yes* (p=0.0443)	*Yes* (p=0.0238)
2. Change from baseline in the average 8:00 a.m. reflective TSS	*Yes* (p=0.0001)	*Yes* (p=0.0001)
3. Change from baseline in the average daily 8:00 p.m. reflective TSS	*Yes* (p=0.0001)	*Yes* (p=0.0001)
4. 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=0.0421)	*Yes* (p=0.0484)
–Itchy nose, mouth, throat and/or ears	*Yes* (p=0.0001)	*Yes* (p=0.0001)
–Itchy, watery, red eyes.	*Yes* (p=0.0001)	*Yes* (p=0.0001)
–Nasal congestion	*Yes* (p=0.0001)	*Yes* (p=0.0001)
5. Patient assessment of overall study drug effectiveness (0-100 Visual analog scale)	*Yes* (p=0.0031)	*Yes* (p=0.0149)
6. Physician assessment of overall study drug effectiveness (1-5 scoring system: complete relief=1, marked relief=2, moderate relief=3, slight relief=4, no relief/worse=5)	*Yes* (p=0.001)	*Yes* (p=0.001)

Δ=Change, TSS=Total symptom score

8.6.5. Safety Analysis

Safety analysis for protocol PJPR0032 consisted of an evaluation of adverse events, standard laboratory tests, and vital signs pre-and post-treatment in patients randomized into the study and 'exposed' to study medication (the safety evaluable population). 12-lead ECGs were not performed in this study. Eight hundred and thirty nine (839) patients comprised the total safety population, which consisted of 213 fexofenadine HCl 120 mg and 208 fexofenadine HCl 180 mg safety evaluable patients, 209 cetirizine 10 mg safety evaluable patients, and 209 placebo group [V1.83:120]. In this trial, the safety evaluable population was almost the same as

the ITT population with exception of the 18 patients that were excluded due to insufficient post-baseline TSS scores.

Demographics of the exposed population was almost the same as the ITT population that was previously presented. All 4 treatment groups were similar in baseline characteristics

The overall incidence of all 'treatment emergent' adverse events (i.e. those AE's occurring during treatment) were generally similar for the 4 treatment groups (including placebo) and ranged from 33-44% for all AEs combined [V1.83:120]. The most frequent adverse event for all 3 treatment groups consisted of headache (with an incidence of 13% in the fexofenadine HCl 120 mg group, an incidence of 12% in the fexofenadine HCl 180 mg group, an incidence of 14% in the cetirizine group, and an incidence of 12 % in the placebo group), followed by drowsiness (an incidence of 4% in the fexofenadine HCl 120 mg group, an incidence of 5% in the fexofenadine HCl 180 mg group, an incidence of 7% in the cetirizine group, and an incidence of 5% in the placebo group) [V1.83:120]. The frequency of all other AEs in this study was low and ≤ 3%. No dose response for AE frequency was noted across treatment groups for the 2 fexofenadine doses.

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 PJPR0032 is presented in Table 35 in the study report for PJPR0032 [V1.83:120-123].

Incidence of somnolence in study PJPR0032 was also evaluated separately (in addition to the AE database) using a visual analogue somnolence score in which patients scored the degree of somnolence experienced over the previous daytime (awake hours over the previous 24 hour period) in a diary prior to bedtime. The visual analogue score consisted of a line at which the patient marked the degree of drowsiness which could range from 'no drowsiness' to 'very severe drowsiness' [V1.83:314]. An ordinal scale was not assigned to the line, making interpretation of the patient's degree of drowsiness highly subjective. Neither the protocol nor study report discussed who or how patients' marks were translated into numerical values, and this feature makes interpretation of results of this endpoint problematic. The sponsor states that the change in the average p.m. reflective assessment (average of daily scores during the double-blind treatment period) from baseline p.m. reflective assessment of somnolence were to be calculated. The sponsor's analysis of these data indicate that both fexofenadine doses, as well as the cetirizine group failed to be statistically significantly difference than placebo, with the implication that both doses were similarly 'sedating' [V1.83:112]. Nonetheless, the cetirizine group of patients trended toward greater statistical significance (p=0.0810) [V1.83:112]. No statistically significant difference was noted amongst the 3 active treatment groups.

Cardiovascular adverse events in the study PJPR0032 (for patients ≥ 12 years of age) safety database were only specifically recorded under the 'cardiovascular' category for the clinical endpoint of palpitation (0% incidence

for all 4 treatment groups [V1.83:120]; 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 4 treatment groups.

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 4 treatment groups [V1.83:127].

Although adverse event stratification by duration of treatment was not performed by the sponsor, given the study's entire duration of 2 weeks, as discussed previously, 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.

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

In terms of patient discontinuation due to AEs, a total of 15 AEs, or 4 patients in the placebo group, 4 patients in the fexofenadine 120 mg group, 6 patients in the fexofenadine 120 mg group, and 1 patient in the cetirizine 10 mg group led to premature discontinuation of treatment due to adverse events [V1.83:128-129]. The majority of reasons noted for patient withdrawal were due to bronchitis, followed less frequently by bronchospasm or dizziness, and were unlikely to be related to study medication. The one cetirizine patient (#21-060) discontinued treatment, amongst other reasons (abdominal pain and constipation) because of drowsiness, but no similar cases were seen in the 2 fexofenadine groups [V1.83:129

No deaths or [6]serious treatment emergent adverse events were reported during this SAR trial for any of the 4 treatment groups.

Assessment of laboratory tests performed during visit 1 (pre-randomization) and visit 4 (completion of treatment) 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 using shift tables, outlier analyses, or evaluation of the average baseline, end of study, and change from baseline laboratory values [V1.83:130-140]. Similarly, analysis of patient vital signs via evaluation of the average baseline, end of study, and change from baseline vital signs and review of outliers failed to reveal any worrisome trends or significant differences amongst the 4 treatment groups.

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[6] 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.

8.6.6. 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 qd dose for the treatment of symptoms of SAR (excluding nasal congestion) in adults and adolescents age 12-65 years of age, however a more informative analysis would have been possible—especially with respect to efficacy of the 120 mg fexofenadine dose, if the sponsor had provided a completely correct study report. Minimal numerical differences were noted between the fexofenadine 180 mg and 120 mg doses across all efficacy endpoints, including the primary efficacy endpoint. Nasal congestion was not evaluated in this study, hence no comment can be made with regard to fexofenadine's efficacy or lack thereof with respect to this endpoint. Both doses of QD ALLEGRA demonstrated an adequate duration of effect with respect to SAR symptoms, as per analysis of the end-of-dosing interval for the TSS endpoint (the 8:00 a.m. instantaneous trough TSS score for the 2 week double-blind treatment period) compared to placebo treatment.

Many study design flaws were noted in PJPR0032 which make it less persuasive in terms of efficacy review, including use of the fexofenadine capsule, rather than the 'to-be-marketed' tablet, imbalance of patient enrollment across study centers, inconsistent or low pollen counts at some study centers, and choice of the primary efficacy endpoint as the change from baseline in the 24 hour reflective TSS rather than the change from baseline in the end-of-dosing interval, 8:00 a.m. instantaneous (or trough) TSS. Nonetheless, efficacy findings in this study were found to generally support those seen in the pivotal SAR study 3081.

Overall, ALLEGRA was safe and well-tolerated given once a day, at a dose of 120 mg or 180 mg in 839 patients. No serious related adverse events occurred in patients treated with ALLEGRA, nor were any deaths reported. Similar to placebo treatment, headache was the most common adverse event. 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. No abnormal trends or worrisome laboratory findings were noted in study PJPR0032. No significant changes in vital signs were noted at the final study visit in safety evaluable patients.

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 adolescents 12-65 years of age.

APPENDIX I: Study Procedure for PJPR0032

Table 4. Table of Study Procedures

Study Procedure	Visit				
	1 (Screen)	2	3	4	Early Discontinuation
Informed consent	x				
Demographics	x				
Medical history	x				
Skin test	x				
Single-blind unit does card dispensed	x				
Entrance criteria	x	x			
Physical examination	x			x	x
Clinical labs	x			x	x
Medication history	x				
Serum pregnancy test	x			x	x
Patient qualifying SAR assessment for single-blind placebo lead-in	x				
Patient qualifying SAR assessment for double-blind medication		x			
Daily symptom diary issued	x	x	x		
Adverse event diary issued	x	x	x		
Daily somnolence diary issued	x	x	x		
Investigator assessment of overall study drug effectiveness				x	x*
Patient assessment of overall study drug effectiveness					x*
Double-blind unit does card dispensed		x	x		
Assess use of concomitant medications		x	x	x	x
Collect unit does card and diaries		x	x	x	x
Determine study drug compliance		x	x	x	x
Adverse event assessment		x	x	x	x

* Not required if patient has not received double-blind study medication.

SEASONAL ALLERGIC RHINITIS IN ADULTS (QD Dosing, Non-Pivotal Trial):

8.7. Protocol PJPR0061: A multi-center, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 2 dosage strengths of fexofenadine HCl (80 mg and 120 mg qd) in the treatment of seasonal allergic rhinitis (SAR).

Principal Investigator: None, multi-center study.

Participating Centers: 126 European centers.

8.7.1. Objective

The primary objective of this study was to investigate the safety and efficacy of fexofenadine HCl 80 mg po qd and fexofenadine HCl 120 mg po qd compared to placebo treatment in patients age 12-65 years for the treatment of symptoms of grass pollen-induced (indigenous to the region) seasonal allergic rhinitis (SAR) using a different formulation (the 40 mg capsule) than those previously evaluated in the SAR trials in this NDA.

Secondary objectives of the study were to determine onset of action and duration of action of fexofenadine over 24 hours.

8.7.2. Study Design

The study was a phase 3, multi-center, randomized, double-blind, parallel group, with a 3 day single-blind placebo lead-in, safety and efficacy study of the treatment of fexofenadine HCl 80 mg po qd, vs. fexofenadine HCl 120 mg po qd, and vs. placebo in 1415 intent-to-treat (ITT) grass pollen sensitive seasonal allergic patients, between the ages of 12 and 65 (excluding German sites, where enrollable patients had to be at least 18 years of age-65 years of age) [V1.136:51, 52]. The overall study design was essentially the same as that utilized in the pivotal adult SAR trial 3081 and in the non-pivotal SAR trial 0031 and will only be briefly discussed here (for complete details of study design, refer to SAR Study 3081 and PJPR0031).

Unlike the previous 2 SAR trials, this study consisted of only 2 subject visits: 1 screening/baseline visits (visits 1; week 1), and 1 treatment visits (visit 2; week 2) such that patients received double-blind study medication for only approximately 7-10 days [V1.136:40]. The inclusion/ exclusion criteria and disallowed medications for study enrollment were essentially the same as those noted in studies 3081 and PJPR0031 [V1.136:52-55]. The usual safety monitoring procedures (AE reporting, physical exam, but excluding lab testing) and assessment of compliance were performed throughout the trial [V1.136:61-62].

A total of approximately 1415 patients were to be randomized to the 3 treatment groups. A table of study procedures is provided in Appendix 1 [V1.83:87].

In terms of the qualifying severity of symptom scores for inclusion, study PJPR0061 had similar criteria as the other ALLEGRA SAR clinical trials evaluated [V1.136:41] .

At Visit 1, patients were instructed to take the initial dose of single-blind study medication, then in the same time in the a.m. (± 1 hour) at least 30 minutes after getting up daily, record the same SAR symptoms as used in other SAR trials in this NDA, on a 0-4 symptom severity scale [V1.136:40-41]. This consisted of a reflective TSS for the previous 24 hours and a trough instantaneous TSS for the previous 30 minutes. Symptom scores were also recorded in the p.m. [V1.136:58]. Patients were stratified by symptom score (high or low TAN) prior to randomization, similar to previous SAR trials [V1.136:56]. Single-blind medication (placebo) was taken, for 3 days (starting on the a.m. after Visit 1 (Day 2)) and this was subsequently followed by 7-10 days of double-blind medication, in which patients were assigned to 1 of the following 3 treatment groups [V1.136:55]:

Double Blind Treatment Groups:	
STUDY GROUPS	**DOSING**
(1) **Fexofenadine HCl 80 mg po qd**	**2, 40 mg capsules (fexofenadine HCl 120 mg) + 1 placebo capsule (placebo**: identical in appearance to the fexofenadine HCl 40 mg capsule) **q a.m. (8 a.m.)**
(2) **Fexofenadine HCl 120 mg po qd**	**3, 40 mg capsules (fexofenadine HCl 180mg) q a.m.**
(4) **Placebo qd**	**3, placebo capsules q a.m.**

The final dose of double-blind study medication was taken on the morning of Visit 2 (day 11-14) [V1.136:55]. Patients were not restricted from taking food before or after study medication. The study made an attempt to define the onset of action of the 2 fexofenadine doses (relative to placebo) by asking patients to record whether they noticed an improvement in < 20 minutes, < 40 minutes, or < 1 hour [V1.136:58]. If the time to improvement was ≥ 1 hour, patients were asked to note the time of improvement. Likewise, patients were permitted to note that no improvement had occurred.

Reviewer's Note: Importantly, 40 mg fexofenadine capsules and not 'to-be-marketed' tablets were evaluated in this study.

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: Same as the other SAR trials reviewed, given a symptom score range of 0-4 for any individual SAR symptom, patients could achieve a TSS ranging from 0-16.

The primary efficacy variable was defined as: the change from baseline in the average 24 hour reflective TSS (average of daily 24 hour reflective TSS during the double-blind treatment period) from average baseline 24 hour reflective TSS (average of daily 24 hour reflective TSS during the placebo lead-in period) [V1.136:41].

Reviewer's Note: The above primary efficacy variable was different from that recommended by the Agency and utilized in pivotal SAR trial 3081: the change from baseline in the average trough instantaneous TSS over double-blind treatment period (which would ensure measurement of the end-of-dosing interval) and was identical to that utilized in the non-pivotal SAR trial PJPR0031.

Secondary efficacy variables consisted of the following [V1.136:41]:
(1) Change from baseline in the average trough 30 minute instantaneous TSS (over the double-blind treatment period)-used to assess the 'end-of-dosing interval,
(2) Change from baseline in the average trough 30 minute instantaneous individual symptom scores (over the double-blind treatment period),
(3) Change from baseline in the average 24 hour reflective individual 24-hour reflective symptom scores (over the 2 week double-blind treatment period),
(4) Patient assessment of overall study drug effectiveness,
(5) Patient improvement based on average 24 hour reflective TSS
(6) Physician assessment of overall study drug effectiveness, and
(7) Time from dosing to improvement on the day of 1st double-blind medication

All primary and secondary efficacy endpoints were analyzed using the 'intent-to-treat population', defined as 'patients who received at least 1 dose of double-blind treatment, with at least 1, 24 hour reflective TSS in the placebo run-in and double-blind treatment period [V1.136:66], along with the evaluation of the primary efficacy endpoint using 'protocol correct' patients (= 'intent-to-treat' patients with no major protocol violations) [V1.136:66].

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

Statistical analysis consisted of a calculation of the sample size of 279 patients per treatment arm to yield 90% power and detect a difference of 0.55 units in 24 hour reflective TSS between active dose and placebo, based on results from previous fexofenadine clinical studies [V1.136:65-66]. The estimated

average difference in the change in 24 hour reflective TSS between fexofenadine 60 mg bid and placebo ranged in these studies from 0.4-1.0, with a standard deviation of 2.0.

Reviewer's Note: Reliance by the sponsor on an average difference of 0.55 units in the change of the 24 hour reflective TSS between fexofenadine and placebo for the purpose of powering of this study is somewhat lower than that chosen in other SAR trials reviewed in this NDA and a weakness of this study's design (and at the lower end of the treatment difference between active drug and placebo noted in NDA 20-625, ALLEGRA 60 mg capsules bid).

Centers containing small numbers of patients were pooled together prior to unblinding (based on region) to form 'pooled centers' with at least 9 ITT patients [V1.136:68-69].

The primary efficacy endpoint was analyzed using an ANCOVA model with pooled center and treatment as independent variables, and the average baseline 24 hour TSS included as a continuous covariate [V1.136:69]. These variables were included in the final model if significant at the α=0.10 level. Pairwise comparison of the fexofenadine group vs. placebo was performed using a step-down procedure, with no adjustment for multiple comparisons [V1.136:69]. The primary efficacy variable was also assessed by subgroups consisting of: age, gender, investigative site, race, type of center (general practive vs. allergy clinic), and country [V1.136:69].

The same statistical model used in the primary endpoint analysis was used for secondary efficacy variables, with minor exceptions for the endpoints of: (1) improvement from baseline in the 24 hour reflective TSS (analyzed by Mantel-Haenzel method), (2) the physician overall assessment of effectiveness (analyzed by Mantel-Haenzel method, stratifying for pooled center), (3) patient assessment of overall study drug effectiveness (analyzed by Mantel-Haenzel method, stratifying for pooled center), and (4) time from dosing to improvement on day of the 1st dose of double-blind medication [V1.136:70].

Safety assessment consisted of the usual planned analyses: vital signs, abnormal physical findings, and patient adverse event reports but excluded performance of lab tests [V1.136:70-71].

8.7.3. Results

Evaluation of patient enrollment in study PJPR 0061 indicates that of 1415 patients randomized to receive study medication, 49 patients discontinued the study following randomization but prior to receiving double-blind study medication. A total of 864 patients were randomized into the study, with all randomized patients exposed to double-blind study medication. The remaining 1366 comprised the 'safety population' and a further 70 patients were excluded.

as they had no 24 hour reflective baseline of post-baseline TSS, leaving 1296 patients in the ITT population. Seven hundred and twenty two (722) patients completed the study. [V1.136:72]. A total of 205 patients (15% of total) discontinued the study prior to completion [V1.136:73]. The most common reason for early patient withdrawal were 'patient decision to discontinue (12% of total), 'other' (6% of total), and adverse events (4%) [V1.136:73]. A somewhat higher % of placebo group patients withdrew from the study (19%) than patients from either of the 2 fexofenadine groups (12-14% range) [V1.136:99].

Review of patient demographics indicates that no statistically significant differences with respect to gender, age, race, weight, height, duration of SAR, home environment, work/school environment, family history of atopy or smoking status were noted amongst the 3 treatment arms [V1.136:100-101].

Furthermore, no statistically significant differences were noted across the treatment groups for any of the efficacy endpoints at baseline (for combined scores and individual symptoms, reflective and instantaneous), with the exception of the average baseline trough instantaneous nasal congestion score which was highest in the fexofenadine 80 mg group ($p=0.0487$) [V1.136:106]. Overall, however, the trough symptom scores tended to be lower numerically than the 24 hour reflective scores [V1.136:105-106].

Use of a disallowed concomitant medication prior to or throughout the study duration was noted in 39 placebo group patients (9%), 40 fexofenadine 80 mg qd group patients (9%), and 27 fexofenadine 120 mg qd group patients (6%), [V1.136:109]. The most used disallowed medications comprised oral loratadine/cetirizine, and other H_1 antagonists [V1.136:109].

The mean duration of exposure was approximately 11 days for all 3 treatment groups (± 2 days), and ranged from 1-15 days (duration of exposure calculated from summing the # of days since the last visit, as recorded in the CRF) [V1.136:74, 108]. Compliance with study medication (determined by the total # of doses dispensed minus the total # of doses returned) was noted to be adequate, with an average compliance rate of 100% noted [V1.136:75, 108].

Quantitation of pollen counts was not discussed in either the study protocol or study report for 0031.

8.7.4. Efficacy Endpoint Outcomes

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=438 for fexofenadine HCl 80 mg group, n=436 for fexofenadine HCl 120 mg group, and n=422 for placebo) for the primary efficacy variable the change from baseline in the average 24 hour reflective TSS for the double-blind period; where the primary comparison of interest was the response of the 2 fexofenadine doses vs. placebo. This primary efficacy endpoint did not provide information about the end-of-dosing interval efficacy (or duration of drug effect). Like adult SAR study 0032, this study was flawed by having 68 patients enrolled from 1 study site (Dr. Peter Howarth, Southhampton General Hospital), along with having the same 100 patients enrolled in study 0061 as in study 0032. Of

note, the protocol for study 0061 did not specify in the exclusion criteria that patients should not have participated in study C032 or other previous SAR trials.

Results of the primary efficacy analysis are summarized in Table I. below and show that for both the fexofenadine HCl 80 mg (p=.0001) and 120 mg (p=0.0001) po qd doses, a statistically significant difference in the change in the 24 hour reflective TSS over the double-blind treatment period was noted compared to placebo treatment [V1.83:136:76]. Numerically, the change from baseline in the 24 hour reflective TSS over the double-blind treatment period was very similar between the 2 active treatment groups but was somewhat lower numerically compared to treatment effects seen in prior SAR trials reviewed (e.g. refer to study 0031). The 2 fexofenadine groups were not significantly different from one another. Evaluation of the 'protocol correct' population yielded similar results with regard to the primary efficacy endpoint [V1.136:111]. Subgroup analysis for the primary efficacy endpoint revealed that there were no interactions either by baseline characteristics (race, gender, age), center, type of center (allergy clinic vs. general practice) or country [V1.136:127-136].

Reviewer's Note: Based on this study both the fexofenadine 80 mg and the 120 po qd doses demonstrated a statistically significant decrease in 24 hour reflective TSS over the double-blind period, however the actual numerical difference was ~ half of that noted in prior SAR trials reviewed in this submission. This difference can only be partially attributed to the slightly lower entry (baseline) TSS in 0061, since the difference in baseline scores was only 1-2 units lower than that seen in other SAR trials of similar design.

Table I.
Efficacy of Fexofenadine HCl 80 mg qd, Fexofenadine HCl 120 mg qd, and vs. Placebo
Primary Efficacy Variable: Intent-to-Treat (ITT) Population [V1.136:76]

	TREATMENT GROUP					
Primary Efficacy Variable	**(A) Fexo 80 mg qd**	**(B) Fexo 120 mg qd**	**(C) Placebo**	**[1]P-value**		
				A-C	**B-C**	**A-B**
24 Hour Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)						
	(n438)	**(n=436)**	**(n=422)**			
Baseline TSS	6.8 ± 0.1	6.7 ± 0.1	6.8 ± 0.1			
Double-blind Treatment Period TSS	5.2 ± 0.1	5.2 ± 0.2	6.1 ± 0.2			
Change from baseline in average 24 hour reflective TSS	-1.7 ± 0.1	-1.7 ± 0.1	-0.7 ± 0.2	**0.0001**	**0.0001**	0.9766
Mean Difference ± SE				-1.1±.2	-1.1 ±.2	0.0 ±.2

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

A summary of analysis of the secondary efficacy variables for the ITT population is provided in Table III. 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. The numerical difference in decreasing the respective secondary efficacy endpoint for the fexofenadine 120 mg po qd group was generally only slightly greater (~ -0.1-0.4 units) than that of the fexofenadine 120 mg po qd group and a similar degree of treatment difference was seen between the higher and lower fexofenadine dose in study 0031[V1.136:112-126].

Specifically with regard to analysis of the end-of dosing interval (the 30 minute instantaneous trough TSS), only the fexofenadine 120 mg qd treatment group displayed a statistically significantly greater decrease in trough TSS compared to placebo treatment, with a slightly greater numerical decrease afforded by the fexofenadine 120 mg po qd group over the fexofenadine 80 mg group (-0.3 greater decrease in trough TSS over the fexofenadine 80 mg po qd group) [V1.136:112]. These data are presented in Table II. below. When trough individual symptom scores were evaluated, however, only the trough sneezing score for the fexofenadine 120 mg group demonstrated a statistically significant difference compared to placebo treatment over the double-blind treatment period [V1.136:119]. A treatment by center interaction was present (p=0.0047), with test for baseline by treatment interaction also showing evidence of inconsistency in treatment effect with baseline TSS [V1.136:77-80].

Table II.
Efficacy of Fexofenadine HCl 80 mg qd, Fexofenadine HCl 120 mg qd, and vs. Placebo
Secondary Efficacy Variable: Average Trough 30 Minute Instantaneous TSS
Intent-to-Treat (ITT) Population [V1.136:112]

	TREATMENT GROUP					
Primary Efficacy Variable	**(A) Fexo 80 mg qd**	**(B) Fexo 120 mg qd**	**(C) Placebo**	**[1]P-value**		
				A-C	**B-C**	**A-B**
Average Trough 30 Minute Instantaneous Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)						
	(n=437)	**(n=430)**	**(n=417)**			
Baseline TSS	5.8 ± 0.1	5.7 ± 0.1	5.5 ± 0.1			
Double-blind Treatment Period TSS	5.1 ± 0.1	4.9 ± 0.2	5.0 ± 0.1			
Change from baseline in average trough 30 minute instantaneous TSS	-0.6 ± 0.1	-0.9 ± 0.1	-0.6 ± 0.1	0.2133	0.0379	0.3955
Mean Difference ± SE				-0.2±.1	-0.3 ±.1	0.1 ± 1

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

Onset of action in this study was to be evaluated via the time on the 1st day of double-blind medication that the patient felt improvement of SAR symptoms, however time to improvement was quantified in the following manner: time to improvement < 20 minutes, 20 to < 40 minutes, 40 to < 60 minutes, ≥ 60 minutes, or no improvement [V1.136:126]. Because of the design of the analysis and statistical test employed, exact quantitation of time (in minutes) to onset of action was not possible in this study. Rather, the purpose was to determine if fexofenadine treated patients had a faster onset of action than the placebo group. Based on this categorical analysis, both fexofenadine 80 mg and 120 mg treated patients demonstrated a statistically significantly greater onset of action than did placebo patients, however ~ 1/3 of fexofenadine patients did not demonstrate any improvement after dosing (compared with 49% of placebo patients) [V1.136:126].

Reviewer's Note: Analysis of the secondary efficacy endpoints revealed a greater numerical difference for the fexofenadine 120 mg qd dose, which is consistent with prior PK studies conducted with different doses of fexofenadine. While all reflective symptom scores showed a statistically significant difference between active treatment and placebo, most of the trough measurements did not. Thus, based on these data, the fexofenadine 120 mg po qd dose is the more appropriate dose to consider for treatment of SAR symptoms in patients 12-65 years of age, especially with regard to maintenance of effect at the end-of-dosing interval. Nonetheless, for the majority of individual SAR symptoms even the 120 mg dose was not able to show a statistically significant efficacy at the end-of-dosing interval, although the numerical trend in individual trough symptom scores indicated that fexofenadine 120 mg qd appeared to be more effective than placebo treatment.

Table III: Secondary Efficacy Variables for the ITT Population and Treatment with Fexofenadine HCl 80 mg qd, Fexofenadine HCl 120 mg qd, and Placebo [V1.136:77, 112-126]

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No	
	Fexofenadine 80 mg qd	Fexofenadine 120 mg qd
Secondary Efficacy Variables		
1. Change from baseline in the average trough 30 minute instantaneous TSS	No (p=0.2133)	Yes (p=0.0379)
2. Patient improvement based on average 24 hour reflective TSS	Yes (p=0.0001)	Yes (p=0.0008)
3. Δ from baseline in average trough 30 minute instantaneous individual symptom scores (over the double-blind period):		
–Sneezing	No (p=0.1559)	Yes (p=0.0421)
–Rhinorrhea	No (p=0.9508)	No (p=0.3256)
–Itchy nose, mouth, throat and/or ears	No (p=0.6404)	No (p=0.1275)
–Itchy, watery, red eyes.	No (p=0.2149)	No (p=0.0814)
–Nasal congestion	No (p=0.9938)	No (p=0.8133)
4. Δ from baseline in average individual 24-hr reflective symptom scores (over the double-blind period):		
–Sneezing	Yes (p=0.0001)	Yes (p=0.0001)
–Rhinorrhea	Yes (p=0.0001)	Yes (p=0.0001)
–Itchy nose, mouth, throat and/or ears	Yes (p=0.0001)	Yes (p=0.0001)
–Itchy, watery, red eyes.	Yes (p=0.0001)	Yes (p=0.0001)
–Nasal congestion	Yes (p=0.0088)	Yes (p=0.0067)
5. Patient assessment of overall study drug effectiveness (1-5 scoring system: complete relief=1, marked relief=2, moderate relief=3, slight relief=4, no relief/worse=5)	Yes (p=0.0004)	Yes (p=0.0011)
6. Physician assessment of overall study drug effectiveness (1-5 scoring system: complete relief=1, marked relief=2, moderate relief=3, slight relief=4, no relief/worse=5)	Yes (p=0.0001)	Yes (p=0.0008)
7. *Time from dosing to improvement after 1st double-blind treatment dose	Yes (p<0.0001)	Yes (p=0.0007)

Δ=Change, TSS=Total symptom score

*P-value for onset of action calculated from Mantel-Haenszel analysis (correlation statistic) of treatment differences, stratifying by center.

8.7.5. Safety Analysis

Safety analysis for protocol PJPR0061 consisted of an evaluation of adverse events, and vital signs pre-and post-treatment in patients randomized into the study and 'exposed' to study medication (the safety evaluable population). 12-lead ECGs were not performed in this study. One thousand three hundred and sixty six (1366) patients comprised the total safety population, which consisted of 457 fexofenadine HCl 80 mg, 461 fexofenadine HCl 120 mg safety evaluable patients, and 448 placebo group patients [V1.136:137].

Demographics of the exposed population is almost the same as the ITT population that was previously presented. All 3 treatment groups were similar in baseline characteristics

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 ranged from 31-34% for all AEs combined [V1.136:137]. The most frequent adverse event for all 3 treatment groups

consisted of headache (with an incidence of 11% in the fexofenadine HCl 80 mg and 120 mg groups and an incidence of 14% in the placebo group), followed by drowsiness and nausea (an incidence of 3% in the fexofenadine HCl 80 mg group, an incidence of 2% in the fexofenadine HCl 120 mg group, and an incidence of 2% in the placebo group for both AEs, respectively) [V1.136:137]. The frequency of all other AEs for the fexofenadine treatment arms in this study was low and ≤ 2%, including cardiovascular AEs of palpitations, chest pain. No dose response for AE frequency was noted across treatment groups for the 2 fexofenadine doses.

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 [V1.136:143]. Adverse event stratification by demographics was not performed in this study.

In terms of patient discontinuation due to AEs, 50 total, or 23 patients in the placebo group, 5 patients in the fexofenadine 80 mg group, and 22 patients in the fexofenadine 120 mg group discontinued treatment prematurely due to adverse events [V1.136:99]. The majority of reasons noted for patient withdrawal were due to rhinitis, followed less frequently by headache or dizziness, and were unlikely to be related to study medication.

No deaths and only 2 [7]serious treatment emergent adverse events were reported during this SAR trial for 1 placebo (ovarian cyst) and 1 fexofendadine 80 mg (hiatus hernia) group patient [V1.136:83].

Assessment of laboratory tests was not performed in this study. Analysis of patient vital signs via evaluation of the average baseline, end of study, and change from baseline vital signs and review of outliers failed to reveal any worrisome trends or significant differences amongst the 3 treatment groups [V1.136:147-148]

8.7.6. 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 dose for the treatment of symptoms of SAR (excluding nasal congestion) in adults and adolescents age 12-65 years of age. For trough symptom measurements, the fexofenadine HCl 80 mg dose did not demonstrate a statistically significant improvement over placebo, indicating that duration of effect was < 24 hours.

Similar to study PJPR0061, several study design flaws were noted in PJPR0032 which make it less persuasive in terms of efficacy review, including use of the fexofenadine capsule, rather than the 'to-be-marketed' tablet, and more

[7] 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.

importantly, choice of the primary efficacy endpoint as the change from baseline in the 24 hour reflective TSS rather than the change from baseline in the end-of-dosing interval, 8:00 a.m. instantaneous (or trough) TSS. Nonetheless, efficacy findings in this study were found to generally support those seen in the pivotal SAR study 3081.

Overall, ALLEGRA was safe and well-tolerated given once a day, at a dose of 80 mg or 120 mg in 1366 safety evaluable patients. No serious related adverse events occurred in patients treated with ALLEGRA, nor were any deaths reported. Similar to placebo treatment, headache was the most common adverse event. Virtually no cardiac adverse events were reported, although again, 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. No significant changes in vital signs were noted at the final study visit in safety evaluable patients.

Summary:

Based on the results of this SAR trial, ALLEGRA capsules 120 mg qd demonstrated adequate evidence of efficacy and safety compared with placebo, for the once daily treatment of SAR symptoms in adults and adolescents 12-65 years of age.

APPENDIX I: Study Procedure for Study PJPR0061

Table 2. Table of study procedures

Study Procedure	Day			
	1 (visit 1)	2-11 (doses 1-10)	12-14 (doses 11-13 if required)	11–14 (visit 2 on last dose day)
Informed Consent	X			
Demographics	X			
Medical History	X			
Urine Pregnancy Test	X			X
Skin Prick Test	X			
Inclusion/Exclusion	X			
Physical Examination	X			X
Diary/Drug Dispensed	X			
Medication Intake		X	X	X
TSS Completed	Xi	X	X	X
Collect Diary/Drug				X
Assess Compliance				X
Assess Effectiveness				X
Document AE's		Xp	Xp	X

Xl = screening assessment used to determine inclusion and stratification

Xp = adverse events documented by the patient in the diary cards

Controlled Long-term Safety Study, Non-Pivotal Trial (0027):

8.8. Protocol No. PJPR0027: A 12 month safety/tolerance study of 240 mg MDL 16,455 qd and placebo in normal healthy subjects.

Principal Investigator: None, multi-center study.

Participating Centers: 14 U.S. centers

8.8.1. Objective

The primary objective of this study was to investigate the safety of fexofenadine HCl 240 mg qd given as 4, 60 mg capsules qd, compared to placebo treatment given qd in normal, healthy subjects ≥ 12 and ≤ 65 years of age over a period of 1 year. The primary safety parameter of interest was the QTc interval on 12 lead ECG. The qd dose of 240 mg of fexofenadine was chosen to support the ongoing development program of fexofenadine in CIU. A secondary objective was to assess population PK of fexofenadine HCl.

8.8.2. Study Design

The study design of 0027 was that of a placebo-controlled, double-blind, randomized, parallel group, safety/tolerance study in ~ 400 normal, healthy subjects. In addition to the usual inclusion/exclusion criteria seen previously in studies reviewed throughout this ALLEGRA NDA submission, subjects were: (1) required to have fasted for ≥ 10 hours prior to the Screening Visit, (2) to have serum electrolyte levels within pre-specified normal limits, (3) not to have any of the following ECG findings at the Screening Visit: rhythm disturbance, other than sinus arrhythmia, heart rate < 50 beats/minute on ECG or physical examination, PR interval < 120 msec or > 200 msec, QRS interval > 120 msec, and QT interval > 450 msec [V1.259:24-26]. The list of disallowed medications included other H_1 antihistamines, antidepressant medications, oral and parenteral macrolide antibiotics, and oral, parenteral, and topical azole antifungals [V1.259:25].

The study consisted of a total of 14 visits (1 screening visit, followed ≤ 14 days later by 13 study visits, each visit separated by 30 ± 2 days). After qualification for study enrollment at Visit 1, patients were assigned a TAN and randomized to receive either: (1) placebo (4 capsules qd) or (2) fexofenadine HCl 60 mg, 4 capsules qd (total dose 240 mg qd) which were identical in appearance [V1.259:34]. Subjects took their 1st dose of study medication in the next morning (a.m.) after Visit 1. Subjects were given compliance diaries, AE cards, and concomitant medication cards and instructed in their completion. Because the study also assessed PK, at Visits 2, 3, 4, 7, and 10, subjects were required to fast for ≥ 10 hours prior to these study visits and 12-lead ECGs were also performed 1-3 hours after blood tests for plasma fexofenadine levels were obtained [V1.259:35]. ECGs were to be recorded in 4 channels (to include a 10 second

rhythm strip in lead II) and were to include interval values (heart rate, PR, QRS, and QT interval) [V1.259:33]. The ECGs were reviewed by a central reviewer for ECGs changes and any significant morphology changes (e.g. prominent U waves or T wave changes). Blinded copies of the ECGs were sent to Dr. Joel Morganroth, an independent consultant cardiologist, who selected the PR, QRS, QT, and RR intervals to be measured/digitized. ECG intervals (in msec) were then measured by a blinded technician using a SIGMASCAN digitizer [V1.259:33]. The cycle length was to be measured for 3 consecutive PR, QRS, QT, and RR intervals in lead II. QT_c was calculated using Bazett's formula for each of the 3 consecutive beat intervals [V1.259:33]. If lead II was inadequate for quality measurements, a chest lead was to be used and noted in the database.

A schedule of study procedures is provided in Appendix I of review of study 0027 [V1.259:36].

8.8.3. Results

A total of 477 subjects were randomized into the trial and exposed to study medication (237 subjects in the placebo group and 240 subjects in the fexofenadine 240 mg group) [V1.259:43, 52]. A total of 469 subjects comprised the safety evaluable population and 332 subjects completed the study [V1.259:44]. A total of 145 subjects exposed to double-blind study medication discontinued prior to completion of the study, with the most common reason for early discontinuation being 'elected to discontinue' (16.4% of total), followed by 'other reason' (8.2% of total), and adverse event (6.5% of total).

Subject demographics were similar between the 2 treatment groups, with no statistically significant differences noted with respect to age, gender, race, weight, or height [V1.259:46-47].

The mean duration of subject exposure was 285.9 days (range: 0.5-378.5 days) for the placebo group and 271.2 days (range: 1.5-722.5 days) for the fexofenadine group [V1.259:48].

Subject compliance with study medication (calculated by dividing the total # of doses taken during the double-blind treatment period by the total # of doses that should have been taken, based on the # of days that the subject was exposed to double-blind medication: i.e. the total # of doses dispensed minus the total # of doses returned) was 96.4% in the placebo group and 97.3% in the fexofenadine group [V1.259:49].

With respect to use of concomitant medications during the study, 84 subjects (35.4%) in the placebo group and 73 subjects (30.4%) in the fexofenadine group used at least 1 additional medication. Other H_1 antagonists were the most frequently prescribed medication, taken by 60 (25.3%) of subjects in the placebo group and 54 subjects (22.5%) in the fexofenadine group [V1.259:49]. These results are summarized in Table 12 of the study report for PJPR0027 [V1.259:50].

Results of ECG analysis are presented in Tables I. and II. below and indicate that no statistically significant change in QTc, QT, QRS PR, or HR from

baseline to the last visit was seen in exposed fexofenadine subjects compared to exposed placebo subjects.

Table I: Average Baseline, Endstudy and Change from Baseline ECG Parameter Values for Fexofenadine 240 mg po qd vs. Placebo [V1.259:89]

ECG Parameter	Treatment (qd)	n	Mean ± Standard Error			*P-value
			Baseline mean ± SE	Endstudy mean ± SE	Change from Baseline mean ± SE	
QTc (msec)	Placebo	233	396.9 ± 1.47	402.5 ± 1.42	5.6 ± 1.49	0.1876
	Fexofenadine 240 mg	231	398.4 ± 1.44	401.4 ± 1.50	3.0 ± 1.32	
QT (msec)	Placebo	233	387.4 ± 1.54	388.2 ± 1.69	0.8 ± 1.42	0.7614
	Fexofenadine 240 mg	231	388.7 ± 1.73	390.1 ± 1.77	1.4 ± 1.39	
QRS (msec)	Placebo	233	81.5 ± 0.44	84.3 ± 0.52	2.7 ± 0.47	0.3150
	Fexofenadine 240 mg	231	80.8 ± 0.44	82.9 ± 0.43	2.1 ± 0.41	
PR (msec)	Placebo	233	149.3 ± 1.33	151.5 ± 1.26	2.3 ± 0.90	0.2931
	Fexofenadine 240 mg	231	147.8 ± 1.18	151.4 ± 1.23	3.6 ± 0.90	
HR (bpm)	Placebo	233	63.6 ± 0.60	65.3 ± 0.67	1.7 ± 0.64	0.1860
	Fexofenadine 240 mg	231	63.7 ± 0.61	64.3 ± 0.65	0.6 ± 0.57	

*P-value is from ANCOVA. Endstudy=last visit for which information was available.

TableII: Average Baseline and Maximum-Postbaseline ECG Values for Fexofenadine 240 mg po qd vs. Placebo [V1.259:90]

ECG Parameter	Treatment (qd)	n	Mean ± Standard Error			*P-value
			Baseline mean ± SE	Maximum mean ± SE	Change from Baseline mean ± SE	
QTc (msec)	Placebo	233	396.9 ± 1.47	417.0 ± 1.28	20.1 ± 1.29	0.0357
	Fexofenadine 240 mg	231	398.4 ± 1.44	414.6 ± 1.33	16.2 ± 1.32	
QT (msec)	Placebo	233	387.4 ± 1.54	406.1 ± 1.66	18.7 ± 1.19	0.5745
	Fexofenadine 240 mg	231	388.7 ± 1.73	406.3 ± 1.68	17.6 ± 1.35	
QRS (msec)	Placebo	233	81.5 ± 0.44	87.7 ± 0.49	6.1 ± 0.40	0.1530
	Fexofenadine 240 mg	231	80.8 ± 0.44	86.2 ± 0.42	5.3 ± 0.38	
PR (msec)	Placebo	233	149.3 ± 1.33	161.9 ± 1.70	12.6 ± 1.24	0.5562
	Fexofenadine 240 mg	231	147.8 ± 1.18	159.5 ± 1.21	11.7 ± 0.84	
HR (bpm)	Placebo	233	63.6 ± 0.60	71.3 ± 0.70	7.8 ± 0.61	0.0247
	Fexofenadine 240 mg	231	63.7 ± 0.61	69.5 ± 0.68	5.8 ± 0.62	

*P-value from 2 sample test from maximum-baseline in ECG values between treatment groups.

With the exception of a statistically significant difference between placebo and fexofenadine for the 2 ECG parameters of change from baseline in maximum QT_c and HR (p=0.0357 and 0.0247, respectively) in which the placebo group, incidentally, demonstrated a slightly greater increase in QT_c and HR than the fexofenadine group, no significant differences between the 2 treatment arms were seen in this 1 year safety study [V1.259:89-90].

Review of data on ECG outlier subjects showed no significant difference between fexofenadine subjects and placebo with respect to QT_c, QRS, and PR ECG values [V1.259:90-92]. No fexofenadine group subjects were identified as having a QT_c outlier value.

With respect to adverse events reported by subjects in this study, 92.8% of subjects in the placebo group and 87.6% of subjects in the fexofenadine group experienced ≥ 1 AE during the course of the 1 year study. The most common AE was headache seen in 36.2% of placebo group subjects and 31.2% of fexofenadine subjects, followed by viral infection (35.7% of placebo subjects and 34.2% of fexofenadine subjects) [V1.259:52]. The incidence of most AEs were comparable between the 2 treatment groups, with a somewhat higher incidence of nasal irritation/inflammation noted in the placebo group compared to the fexofenadine group (8.1% incidence vs. 1.7% incidence) [V1.259:53]. With respect to cardiac AEs, the specific AE categories of palpitation, bradycardia, tachycardia, QT interval prolonged, AV block, arrhythmia, and bundle branch block under the 'heart rate and rhythm' category and chest pain, dizziness, syncope, and ECG abnormality-specific and ECG abnormality-specific were evaluated under 'other AE categories'. The incidence of 'heart rate and rhythm' AEs were similar between the 2 groups [V1.259:58, 59], and with respect to the other categories of cardiovascular AEs, the incidence of syncope, dizziness, and ECG abnormality-specific were slightly higher in the fexofenadine group (incidence for syncope: placebo group-0.4%, fexofenadine group-1.3%, dizziness: placebo group-1.7%, fexofenadine group-3.0%, and ECG abnormality-specific: placebo group-0.4%, fexofenadine group-1.3%) [V1.259:53, 59].

One death was reported in this study (a 29 yo male in the placebo group from a self-inflicted gun-shot wound) [V1.259:66]. Sixteen subjects receiving placebo (6.8%) and 15 subjects (6.4%) receiving fexofenadine discontinued study medication due to adverse events. The only 3 events of note seen in the fexofenadine group were the following: (1) a report of arrhythmia and chest pain (heart pain and "fluttering of the heart") in a 31 yo female who had taken fexofenadine for 69 days and had a normal screening ECG but no follow-up ECG, (2) a report of syncope in a 32 year old male who had taken fexofenadine for 11 days, and (3) a report of dizziness in a 41 year old female who had taken fexofenadine for 13 days [V1.259:67, 68, 69, 74]. Three subjects in the placebo group and 3 subjects in the fexofenadine group were hospitalized (narratives included in [V1.259:69-71]. In none of the cases, was the event due to the study medication. Ten subjects became pregnant while enrolled in the study (5 placebo subjects, 5 fexofenadine subjects) and were discontinued from the study [V1.259:71-72]. No follow-up information is currently available on these subjects, except that 1 of the pregnancies was terminated in spontaneous abortion and 3 were terminated by planned (induced) abortion.

Review of laboratory tests and vital signs showed no clinically significant difference between treatment groups [V1.259:76-88].

Population PK of fexofenadine in study 0027 was included in a combined analysis of study 0031/0027 in which study 0031 also analyzed population PK of 60 mg p.o bid for 6 months [V1.63:349-350]. For both studies, plasma concentration of fexofenadine was measured via , with a standard curve range of 1-200 pg/mL [V1.63:350-351]. Observed fexofenadine plasma

concentration time data were analyzed by nonlinear mixed effects modeling (NONMEM) to develop appropriate PK models. Potential covariates included: age, weight, height, body surface area (BSA), gender, dose, and race. Covariates showing evidence of influence were evaluated sequentially using NONMEM by comparing the full model (with covariate included) with the model from which the covariate being evaluated was deleted.

Based upon NONMEM, the 2-compartment oral model was established as the base model with oral clearance based upon BSA. For the fexofenadine 240 mg qd dose, results of this analysis revealed: a Cl_{po} (L/h) of 14.2•BSA or ~ 26.7 L/h, a V2/F (L) of 380, a Q (L/h) of 149, a V3 (L) of 4210, and a K_a (1/h) of 0.844 [V1.63:352].

No identifiable gender or race differences were noted for fexofenadine. There was a sizable residual (prediction) variability in the base model (CV%=71.2%) which was not substantially reduced by the addition of covariates (CV%=64.2%). The modeled variability across subjects for apparent oral clearance (Cl_{po}) was 46.7%, and the modeled variability across subjects for apparent volume of distribution (V) was 135.2% [v1.63:352].

8.8.4. Conclusion

This 1 year safety study revealed no significant increase in QTc prolongation, or other cardiac outliers, and no increased incidence of cardiac tachyarrhythmias in patients treated with fexofenadine 240 mg qd, compared to placebo treatment.

Table 3. Schedule of Study Procedures

Study Procedures	*Treatment Period*					
	Screening Visit	*Visit 1*	*Visits 2 and 3*	*Visits 4, 7, and 10*	*Visits 5, 6, 8, 9, 11, and 12*	*Visit 13* (Final Visit)*
Informed Consent	X					
Demographics	X					
Medical History	X					
Entrance Criteria	X	X				
Physical Examination	X					X
Medication History	X	X				
Clinical Lab and Urine Samples	X			X		X
Urine Drug Screen	X			X		X
Vital Signs	X	X	X	X	X	X
Pregnancy Test (u=urine s=serum)	X(s)	X (u + s)	X(s)	X(s)	X(s)	X(s)
12-Lead ECG	X		X	X		X
Review Labs, ECG, and Urine Drug Screen		X				
Issue Compliance Diary, Adverse Event Card, and Concomitant Medication Card		X	X	X	X	
Review Concomitant Medications			X	X	X	X
Dispense Medication		X	X	X	X	
Compliance Assessment			X	X	X	X
Assess for Adverse Events			X	X	X	X
Obtain MDL 16,455A Blood Sample 1-3 Hours Postdose			X	X		X †
Obtain MDL 16,455A Blood Sample at Random Hours					X	

* Final visit or early discontinuation.

† If the subject had an early discontinuation visit, the MDL 16,455A blood sample may have been obtained at any time.

9.0. Integrated Summary of Efficacy

A total of 3 separate clinical indications were sought in this NDA application for ALLEGRA: (1) treatment of adult SAR with a qd dosing regimen, (2) treatment of CIU in adults (12-65 years of age) and children (6-11 years of age) with a bid dosing regimen, and (3) treatment of pediatric SAR with a bid dosing regimen. Data presented for each clinical indication are done so with the intent-to-treat population (ITT). While no pediatric CIU trials were conducted, the sponsor pursued application of the Pediatric Rule for the indication of the treatment of CIU in the pediatric population based on the similarity of CIU in both adults and children in terms of pathophysiology, symptomatology, and treatment and based on bridging PK from the adult population to pediatric PK data.

For the adult SAR indication a total of 3, phase 3 placebo-controlled trials were performed (3081, 0061, and 0032), 1 of which was pivotal (study 3081). Two of these 3 trials (3081, 0032) evaluated fexofenadine 120 mg and 180 mg doses vs placebo (study 0061 evaluated fexofenadine 80 mg qd and 120 mg qd doses vs. placebo). Two placebo-controlled pediatric SAR trials were performed (0066 and 0077) which were combined into 1 large trial (0066/0077) by the sponsor which was considered the 'pivotal' trial. Studies 0066 and 0077 were identical in design and evaluated fexofenadine 15, 30, and 60 mg bid vs. placebo. The 15 mg dose was chosen as a possible 'minimally effective dose' in order to gain greater information about the dose response of fexofenadine in children. Three adult, placebo-controlled CIU trials were performed (0039, 0067, and 0019), 2 of which were pivotal (0039 and 0067). The CIU studies examined doses of fexofenadine ranging from 20 mg to 240 mg bid. And finally, one, 1-year safety study performed in normal healthy controls (0027) specifically evaluated cardiac effects of fexofenadine (QT, QT_c interval, arrhythmias) when given at a total daily dose of 240 mg qd.

In addition to evaluation of efficacy by symptom scoring, for all 3 clinical indications in this NDA, quality of life (QOL) studies were performed in which patient health outcomes were evaluated by a variety of instruments. The Juniper adult and pediatric questionnaires were utilized as disease-specific instruments for the adult and pediatric SAR trials, while CIU was evaluated using the 'Dermatology Quality of Life Index'—an instrument designed for skin diseases in general, but not specific for CIU.

A summary of clinical trials reviewed in NDA 20-872 for ALLEGRA tablets is provided in Table I below.

Table I. Summary of all Controlled Clinical Trials Reviewed in NDA 20-872: ALLEGRA Tablets

STUDY	TREATMENT DURATION	TREATMENT ARMS:
Adult SAR		
3081-Pivotal Trial	2 weeks	Fexo: 120, 180 mg qd Placebo
0032	2 weeks	Fexo: 120, 180 mg qd, Cetirizine 10 mg qd, Placebo
0061	7-10 days	Fexo 80, 120 mg qd, Placebo
Pediatric SAR		
0066-Pivotal Trial	2 weeks	Fexo: 15, 30, 60 mg bid, Placebo
0077-Pivotal Trial	2 weeks	"
Combined 0066/0077	2 weeks	"
Adult Chronic Idiopathic Urticaria (CIU)		
0039-Pivotal Trial	4 weeks	Fexo: 20, 60, 120, 240 mg bid, Placebo
0067-Pivotal Trial	4 weeks	Fexo: 20, 60, 120, 240 mg bid, Placebo
0019	6 weeks	Fexo: 60, 120, 240 mg qd, Placebo
Controlled, 1 year Safety Study		
0027	1 year	Fexo 240 mg qd, Placebo
Quality of Life Studies		
Adult qd SAR (3081): Juniper Rhinoconjunctivitis Questionnaire (RQLQ), Work Productivity and Activity Impairment (WPAI), and SF-36 Questionnaire	2 weeks	Fexo: 120, 180 mg qd Placebo
Pediatric SAR (0066/0077): Juniper Pediatric Rhinoconjunctivitis (PRQLQ) Questionnaire	2 weeks	Fexo: 15, 30, 60 mg bid, Placebo
Adult CIU (0039, 0067): Dermatology Life Quality Index (DLQI), WPAI Questionnaire	4 weeks	Fexo: 20, 60, 120, 240 mg bid, Placebo

While the 'to-be-marketed' formulation of ALLEGRA in this NDA submission is the tablet formulation, and all pivotal trials used the tablet, the non-pivotal SAR studies 0032 and 0061, non-pivotal CIU study 0019, and the 1 year safety study 0027 all utilized fexofenadine capsules. Pivotal PK studies 0045 and 0094 demonstrated the bioequivalence of the 180 mg 'to-be-marketed' lactose-free tablet dose to 3 of the currently marketed 60 mg capsules (using the 'downward waiver' to support bioequivalence) and between the 60 mg fexofenadine capsule and 60 mg fexofenadine tablet, respectively [V1.63:250-253, 258-261]. For pediatric PK, evaluation of 2, 30 mg capsules and 1, 30 mg capsule in a 2-period crossover design indicated that fexofenadine 30 mg or 60 mg bid would provide systemic exposure for pediatric patients comparable to, or somewhat greater than the range of exposures associated with the 60 mg bid

approved dose for adult SAR patients (~ a 56% higher $AUC_{(0-\tau)}$ in pediatric SAR patients compared to adults for the 60 mg capsule bid approved dose) [V1.63:211, 284-289].

Patient exposure to study medication by dose is summarized in Table II. below and reveals a reasonable number of patients exposed to the 'to-be-marketed' dosing regimens of fexofenadine: 30 mg bid, 60 mg bid, 120 mg qd, 180 mg qd, and 240 mg qd.

Table II. Patient Exposure By Dose to ALLEGRA
All Multiple-Dose Clinical Pharmacology and Controlled Clinical Trials [NDA 20-872, V1.298:47]

Treatment	Clinical Pharmacology (n=24)	Controlled Studies				All Studies
		Adult SAR (n=1889)	Adult CIU (n=897)	Pediatric SAR (n=646)	Normal Subjects (n=240)	(n=3822)
Placebo	0	945	234	229	237	1645
Fexofenadine QD Dosing						
60 mg qd	0	0	44	0	0	44
80 mg qd	0	457	0	0	0	457
120 mg qd	0	960	38	0	0	998
180 mg qd	23	493	50	0	0	566
240 mg qd	0	0	39	0	240	279
Fexofenadine BID Dosing						
15 mg bid	0	0	0	224	0	224
20 mg bid	0	0	188	0	0	188
30 mg bid	0	0	0	209	0	209
40 mg bid	23	0	0	0	0	23
60 mg bid	0	0	191	213	0	404
90 mg bid	24	0	0	0	0	24
120 mg bid	0	0	173	0	0	173
240 mg bid	0	0	174	0	0	174
Total Fexo	24	1889	897	646	240	3693

Analysis of patient/subject duration of exposure is presented in Table III. below and reveals that most patients/subjects received < 30 days of fexofenadine treatment; and indeed most received close to 2 weeks of fexofenadine treatment since most trials reviewed in this NDA were designed with a 2 week duration of double-blind treatment. Of note, 598 patients/subjects received fexofenadine ≥ 30 days and of this group, 216 of these subjects belonged to the 1-year safety study (0027).). In the 1- year safety study the mean duration of exposure was 285.9 days for the placebo group and 271.2 days for the fexofenadine group [V1.259:48].

Table III: Duration of Fexofenadine Exposure [V1.298:45]

Duration of Exposure	Clinical Pharmacology		Controlled Studies				All Studies
	Normal Subjects (n=138)	Pediatric SAR (n=15)	Adult SAR (n=1889)	Adult CIU (n=897)	Pediatric SAR (n=646)	Normal Subjects (n=240)	(n=3822)
Single dose	123	15	0	0	0	0	138
Multiple dose < 30 days	24	0	1889	517	646	16	3092
Multiple dose ≥ 30 days	0	0	2	371	0	216	589
Unknown	0	0	21	10	0	8	39
N, Mean Days ± AD, Range	147, 6.3 ± 6.09, 1-20	15, 1.9 ± .35, 1-2	1891, 12.6 ± 2.97, 1-46	888, 28.0 ± 10.14, 1-73	646, 15.5 ± 1.98, 1-22	232, 272.2 ± 120.18, 2-377	3819, 32.2 ± 68.48, 1-377

9.1. Patient Demographics

A total of 4740 adult patients were enrolled in the various studies in NDA 20-872, of whom 3161 received various doses of fexofenadine. A summary of patient characteristics for the adult trials is summarized in Table IV. and overall indicates similar patient demographics across treatments. A similar analysis performed in pediatric patients is summarized in Table V and also indicates similar demographic characteristics across treatments.

Table IV. Patient Demographics of All [1]Adult Studies Combined (Clinical Pharmacology and Controlled Studies) [V1.298:51]

	Adult Clinical Pharmacology and Controlled Studies			
Characteristics	Placebo (n=1416)	Fexofenadine (n=3161)	Cetirizine (n=209)	Total (n=4740)
Gender (n, %)				
Male	632 (44.6%)	1426 (45.1%)	102 (48.8%)	2128 (44.9%)
Female	784 (55.4%)	1735 (54.9%)	107 (51.2%)	2612 (55.1%)
Age (Years)				
n	1416	3161	209	4740
Mean ± SD	33.6 ± 12.2	34.0 ± 12.6	32.8 ± 11.9	33.8 ± 12.5
Range	12-81	12-84	12-62	12-84
12 to < 16	87 (6.1%)	172 (5.4%)	7 (3.3%)	266 (5.6%)
16 to < 40	892 (63.0%)	1973 (62.4%)	140 (67.0%)	2979 (62.8%)
40 to < 65	427 (30.2%)	982 (31.1%)	62 (29.7%)	1451 (30.6%)
≥ 65	10 (0.7%)	34 (1.1%)	0 (0.0%)	44 (0.9%)
Race (n, %)				
Caucasian	1297 (91.6%)	2860 (90.5%)	186 (89.0%)	4298 (90.7%)
Black	54 (3.8%)	136 (4.3%)	5 (2.4%)	195 (4.1%)
Asian	31 (2.2%)	97 (3.1%)	7 (3.3%)	134 (2.8%)
Multiracial	34 (2.4%)	68 (2.2%)	11 (5.3%)	113 (2.4%)
Weight (kg)				
n	1411	3157	209	4731
Unknown n	5	4	0	9
Mean ± SD	72.7 ± 17.0	72.8 ± 16.5	71.7 ± 16.5	72.7 ± 16.1
Range	32.2-167	31-155.1	43-147	31-167
< 60	328 (23.2%)	698 (22.1%)	50 (23.9%)	1069 (22.6%)
60 to > 90	881 (62.4%)	1983 (62.8%)	135 (64.6%)	2969 (62.8%)
≥ 90	202 (14.3%)	476 (15.1%)	24 (11.5%)	693 (14.6%)

[1]Adult studies summarized in this table include: clinical pharmacology studies 033, part 2, 045, 062, 071, 068, 022, controlled SAR trials 3081, 0032, 0061, CIU studies 0039, 0067, 0019, and controlled normal subject 1 year safety study 0027.

Table 8–202. Demographic characteristics of study population by adult clinical pharmacology and controlled studies
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Characteristics	Clinical pharmacology	Controlled studies									
		SAR patients				CIU patients			Normal subjects		
	Fex HCl (N=138)	Placebo (N=945)	Fex HCl (N=1889)	Cetirizine (N=209)	Total (N=2997)	Placebo (N=234)	Fex HCl (N=897)	Total (N=1131)	Placebo (N=237)	Fex HCl (N=240)	Total (N=477)
Gender n(%)											
Male	138 (100%)	459 (48.6%)*	914 (48.4%)	102 (48.8%)	1443 (48.1%)	71 (30.3%)	275 (30.7%)	346 (30.6%)	102 (43.0%)	99 (41.3%)	201 (42.1%)
Female	0 (0.0%)	486 (51.4%)	975 (51.6%)	107 (51.2%)	1554 (51.9%)	163 (69.7%)	622 (69.3%)	785 (69.4%)	135 (57.0%)	141 (58.8%)	276 (57.9%)
Age (years) n(%)											
N	138	945	1889	209	2997	234	897	1131	237	240	477
Mean ± SD	27.7 ± 6.7	32.2 ± 11.7	31.8 ± 12.0	32.8 ± 11.9	31.9 ± 11.9	39.3 ± 13.4	39.5 ± 12.7	39.5 ± 12.8	33.4 ± 11.4	34.7 ± 13.0	34.0 ± 12.2
Range	18,44	12,65	12,70	12,62	12,70	13,81	12,84	12,84	12,65	12,64	12,65
12–<16	0 (0.0%)	64 (6.8%)	141 (7.5%)	7 (3.3%)	212 (7.1%)	8 (3.4%)	15 (1.7%)	23 (2.0%)	15 (6.3%)	16 (6.7%)	31 (6.5%)
16–<40	130 (94.2%)	627 (66.3%)	1256 (66.5%)	140 (67.0%)	1997 (66.6%)	113 (48.3%)	447 (49.8%)	560 (49.5%)	152 (64.1%)	142 (59.2%)	294 (61.6%)
40–<65	8 (5.8%)	251 (26.6%)	482 (25.5%)	62 (29.7%)	775 (25.9%)	107 (45.7%)	411 (45.8%)	518 (45.8%)	69 (29.1%)	82 (34.2%)	151 (31.7%)
≥ 65	0 (0.0%)	3 (0.3%)	10 (0.5%)	0 (0.0%)	13 (0.4%)	6 (2.6%)	24 (2.7%)	30 (2.7%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Race n(%)											
Caucasian	126 (91.3%)	866 (91.6%)	1714 (90.7%)	186 (89.0%)	2721 (90.8%)	216 (92.3%)	799 (89.1%)	1015 (89.7%)	215 (90.7%)	223 (92.9%)	438 (91.8%)
Black	7 (5.1%)	36 (3.8%)	79 (4.2%)	5 (2.4%)	120 (4.0%)	10 (4.3%)	43 (4.8%)	53 (4.7%)	8 (3.4%)	7 (2.9%)	15 (3.1%)
Asian	3 (2.2%)	22 (2.3%)	48 (2.6%)	7 (3.3%)	77 (2.6%)	4 (1.7%)	36 (4.3%)	43 (3.8%)	5 (2.1%)	7 (2.9%)	12 (2.5%)
Multiracial	2 (1.4%)	21 (2.2%)	47 (2.5%)	11 (5.3%)	79 (2.6%)	4 (1.7%)	16 (1.8%)	20 (1.8%)	9 (3.8%)	3 (1.3%)	12 (2.5%)

Clinical pharmacology = Protocols 033 Part 2, 045, 062, 071, 068, 022
Controlled SAR = Protocols 061, 032, 061
Controlled CIU = Protocols 039, 067, 019
Controlled normal subjects = Protocol 027
* In the database for the SAR Protocol 061, one placebo patient was inadvertently reported as a male, but should be female.

Table 8–202. Demographic characteristics of study population by adult clinical pharmacology and controlled studies
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Characteristics	Clinical pharmacology	Controlled studies									
		SAR patients				CIU patients			Normal subjects		
	Fex HCl (N=138)	Placebo (N=945)	Fex HCl (N=1889)	Cetirizine (N=209)	Total (N=2997)	Placebo (N=234)	Fex HCl (N=897)	Total (N=1131)	Placebo (N=237)	Fex HCl (N=240)	Total (N=477)
Gender n(%)											
Male	138 (100%)	459 (48.6%)*	914 (48.4%)	102 (48.8%)	1443 (48.1%)	71 (30.3%)	275 (30.7%)	346 (30.6%)	102 (43.0%)	99 (41.3%)	201 (42.1%)
Female	0 (0.0%)	486 (51.4%)	975 (51.6%)	107 (51.2%)	1554 (51.9%)	163 (69.7%)	622 (69.3%)	785 (69.4%)	135 (57.0%)	141 (58.8%)	276 (57.9%)
Age (years) n(%)											
N	138	945	1889	209	2997	234	897	1131	237	240	477
Mean ± SD	27.7 ± 6.7	32.2 ± 11.7	31.8 ± 12.0	32.8 ± 11.9	31.9 ± 11.9	39.3 ± 13.4	39.5 ± 12.7	39.5 ± 12.8	33.4 ± 11.4	34.7 ± 13.0	34.0 ± 12.2
Range	18,44	12,65	12,70	12,62	12,70	13,81	12,84	12,84	12,65	12,64	12,65
12–<16	0 (0.0%)	64 (6.8%)	141 (7.5%)	7 (3.3%)	212 (7.1%)	8 (3.4%)	15 (1.7%)	23 (2.0%)	15 (6.3%)	16 (6.7%)	31 (6.5%)
16–<40	130 (94.2%)	627 (66.3%)	1256 (66.5%)	140 (67.0%)	1997 (66.6%)	113 (48.3%)	447 (49.8%)	560 (49.5%)	152 (64.1%)	142 (59.2%)	294 (61.6%)
40–<65	8 (5.8%)	251 (26.6%)	482 (25.5%)	62 (29.7%)	775 (25.9%)	107 (45.7%)	411 (45.8%)	518 (45.8%)	69 (29.1%)	82 (34.2%)	151 (31.7%)
≥ 65	0 (0.0%)	3 (0.3%)	10 (0.5%)	0 (0.0%)	13 (0.4%)	6 (2.6%)	24 (2.7%)	30 (2.7%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Race n(%)											
Caucasian	126 (91.3%)	866 (91.6%)	1714 (90.7%)	186 (89.0%)	2721 (90.8%)	216 (92.3%)	799 (89.1%)	1015 (89.7%)	215 (90.7%)	223 (92.9%)	438 (91.8%)
Black	7 (5.1%)	36 (3.8%)	79 (4.2%)	5 (2.4%)	120 (4.0%)	10 (4.3%)	43 (4.8%)	53 (4.7%)	8 (3.4%)	7 (2.9%)	15 (3.1%)
Asian	3 (2.2%)	22 (2.3%)	48 (2.6%)	7 (3.3%)	77 (2.6%)	4 (1.7%)	36 (4.3%)	43 (3.8%)	5 (2.1%)	7 (2.9%)	12 (2.5%)
Multiracial	2 (1.4%)	21 (2.2%)	47 (2.5%)	11 (5.3%)	79 (2.6%)	4 (1.7%)	16 (1.8%)	20 (1.8%)	9 (3.8%)	3 (1.3%)	12 (2.5%)

Clinical pharmacology = Protocols 033 Part 2, 045, 062, 071, 068, 022
Controlled SAR = Protocols 061, 032, 061
Controlled CIU = Protocols 039, 067, 019
Controlled normal subjects = Protocol 027
* In the database for the SAR Protocol 061, one placebo patient was inadvertently reported as a male, but should be female.

Table 8-204: Demographic Characteristics of the Pediatric Population
(Studies 0066/0077 combined) [V1.298:52]

Table 8–202. Demographic characteristics of study population by adult clinical pharmacology and controlled studies
Page 2 of 2

Characteristics	Clinical pharmacology	Controlled studies									
		SAR patients				CIU patients			Normal subjects		
	Fex HCl (N=138)	Placebo (N=945)	Fex HCl (N=1889)	Cetirizine (N=209)	Total (N=2997)	Placebo (N=234)	Fex HCl (N=897)	Total (N=1131)	Placebo (N=237)	Fex HCl (N=240)	Total (N=477)
Weight (kg) n(%)											
Unknown (N)	0	3	3	0	6	2	1	3	0	0	0
N	138	942	1886	209	2991	232	896	1128	237	240	477
Mean ± SD	76.7 ± 9.7	71.7 ± 16.5	71.4 ± 16.0	71.7 ± 16.5	71.5 ± 16.2	76.0 ± 18.9	75.4 ± 18.1	75.5 ± 18.2	73.5 ± 16.5	72.3 ± 16.0	72.9 ± 16.2
Range	57.15,99.34	32.2,167	31,145	43,147	31,167	46.9,149.7	32.2,155.1	32.2,155.1	42.525,131.4	44.1,124.65	42.525,131.4
<60	6 (4.3%)	226 (24.0%)	453 (24.0%)	50 (23.9%)	723 (24.2%)	48 (20.7%)	183 (20.4%)	231 (20.5%)	54 (22.8%)	57 (23.8%)	111 (23.3%)
60–<90	117 (84.8%)	597 (63.4%)	1180 (62.6%)	135 (64.6%)	1879 (62.8%)	136 (58.6%)	536 (59.8%)	672 (59.6%)	148 (62.4%)	152 (63.3%)	300 (62.9%)
≥90	15 (10.9%)	119 (12.6%)	253 (13.4%)	24 (11.5%)	389 (13.0%)	48 (20.7%)	177 (19.8%)	225 (19.9%)	35 (14.8%)	31 (12.9%)	66 (13.8%)

Clinical pharmacology = Protocols 033 Part 2, 045, 062, 071, 068, 022
Controlled SAR = Protocols 081, 032, 061
Controlled CIU = Protocols 039, 067, 019
Controlled normal subjects = Protocol 027
* In the database for the SAR Protocol 081, one placebo patient was inadvertently reported as a male, but should be female.

Supporting Data: *Page*

Table V. Patient Demographics of All [1]Pediatric Studies Combined (Clinical Pharmacology and Controlled Studies) [V1.298:52]

Characteristics	Pediatric Clinical Pharmacology and Controlled Studies		
	Placebo (n=229)	Fexofenadine (n=661)	Total (n=4740)
Gender (n, %)			
Male	139 (60.7%)	391 (60.7%)	530 (59.6%)
Female	90 (39.3%)	270 (40.8%)	360 (40.4%)
Age (Years)			
n	229	661	890
Mean ± SD	9.2 ± 1.6	9.1 ± 1.6	9.1 ± 1.6
Range	6-11	5-12	5-12
6 to < 9	77 (33.6%)	217 (32.8%)	294 (33.0%)
9 to 12	152 (66.4%)	444 (67.2%)	596 (67.0%)
Race (n, %)			
Caucasian	187 (81.7%)	577 (87.3%)	764 (85.8%)
Black	28 (12.2%)	53 (8.0%)	81 (9.1%)
Asian	7 (3.1%)	12 (1.8%)	19 (2.1%)
Multiracial	7 (3.1%)	19 (2.9%)	26 (2.9%)
Weight (kg)			
n	229	656	885
Unknown n	0	5	5
Mean ± SD	36.6 ± 11.1	35.3 ± 10.8	35.6 ± 10.9
Range	21-77.1	0 (0%)	17.7-93
< 15	0 (0%)	17.7-93	0 (0%)
15 to < 30	76 (33.2%)	239 (36.4%)	315 (35.6%)
30 to < 45	112 (48.9%)	321 (48.9%)	433 (48.9%)
≥ 45	41 (17.9%)	96 (14.6%)	137 (15.5%)

[1]Pediatric studies summarized in this table include: clinical pharmacology study 037, and controlled SAR trials 0066 and 0077.

Slightly more female than male patients participated in the adult studies, while in contrast slightly more male than female patients participated in the pediatric studies. For both the adult and pediatric populations, the majority of patients were Caucasian. For the adult group, most ranged from 16 to < 40 years of age. In the pediatric age group, a greater proportion (~ 2/3) of enrolled patients belonged to an older (age 9-12 year) age group, however children ≥ 6 years of age were present in each of the treatment groups.

A more complete break down of adult and pediatric population demographics by study type (i.e. controlled SAR, CIU studies, etc). is provided in attached Tables 8-202 and 8-204 from the NDA submission [V1.298:49-50, 52].

9.2. Summary of the Primary Efficacy Data (including the end-of dosing interval) for the Adult Studies

Evaluation of the primary efficacy data for the 3 adult qd fexofenadine SAR studies, one of which (study 3081) was considered a pivotal trial by the medical reviewer, consisted of an evaluation of the end-of-dosing interval—the patient self-rated change from baseline in the average 8:00 a.m. instantaneous total symptom score (=composite score of: sneezing, rhinorrhea, itchy nose, mouth, throat and/or ears, and itchy, watery red eyes) over the 2 week double-blind period. For the non-pivotal trials (0032 and 0061), while the primary efficacy endpoint was defined in both studies a priori as the change from baseline in the

patient self-rated average 24 hour reflective TSS, the change from baseline in the average trough 8:00 a.m. instantaneous TSS over the 2 week double-blind period (the end-of dosing period) was also evaluated.

Hence, in this integrated summary of efficacy for adult SAR trials both endpoints (24 hour reflective TSS and instantaneous 8:00 a.m. TSS) are presented concurrently.

Important study design issues for these 3 studies included: (1) a single-blind placebo lead in period ranging from 3-7 days (depending on study), (2) enrollment of adult SAR patients 12-65 years of age with a minimum symptom severity at both the screening (Visit 1, patient's reflective TSS for the previous 12 hours had to be ≥ 6 (excluding nasal congestion and ≥ 2 additional SAR symptoms (excluding nasal congestion) were to be rated as 'moderate' or 'severe' on a 0-4 scale [0=none, 1=mild, 2=moderate, 3=severe, 4=very severe], and no symptom was to be rated 'very severe') and baseline visits (Visit 2, these criteria depended on the study but generally required a TSS ≥ 5 with 2 or more symptoms (excluding nasal congestion) with a score of "2" or "3" (instantaneous TSS was utilized for pivotal study 3081 and 24 hour reflective TSS was utilized for non-pivotal studies 0032 and 0061), (3) utilization of the 'to-be-marketed' ALLEGRA formulation in study 3081 only (tablets) and utilization of fexofenadine capsules in the 2 non-pivotal adult SAR trials, and (4) evaluation of fexofenadine 120 mg and 180 mg doses in studies 3081 and 0032, but evaluation of fexofenadine 80 mg and 120 mg in study 0061. Since the TSS was comprised of 4 SAR symptoms, each of which was rated on a 0-4 scale in all 3 SAR studies, patients could achieve a TSS ranging from 0 to a maximum score of 16. Thus, both the instantaneous and reflective TSS could have a maximum score of 16. Rescue medication use was not allowed in any of these 3 studies.

A summary of efficacy results using the 2 primary endpoints is provided in Table VI. below. Review of the instantaneous and reflective TSS for these 3 SAR studies revealed a statistically significant decrease in symptoms compared to placebo for the fexofenadine 120 mg and 180 mg qd doses, but the 180 mg dose consistently showed a greater numerical difference in TSS. In the pivotal trial 3081, the 120 mg dose was marginally effective at the end-of-dosing interval and these data also appeared to be substantiated by PK data in which a comparison of qd and bid dosing of ALLEGRA was performed. Thus a shallow dose response from the fexofenadine 120 mg to 180 mg dose was evident on analysis of these 2 endpoints.

Subgroup analysis of the primary efficacy variable did not show any significant effect of demographic factors (e.g. age, gender, race, weight) in any of the 3 studies but in pivotal SAR study 3081, although a statistically significant baseline-by-treatment interaction (p=0.0256) was seen, indicating that treatment effect varied with baseline symptom severity via ANCOVA [V1.64:116].

In summary, based on these efficacy findings (and the PK data from modeling of plasma profiles for fexofenadine 60 mg, 120 mg, 180 mg, and 240 mg given once daily under steady-state conditions which indicated that the fexofenadine

120 mg dose were likely to have a marginal plasma concentrations (of at least 290 ng/mL) at the end-of-dosing interval) [V1.63:212], a recommended dose of fexofenadine for the treatment of SAR in adults and adolescents ≥ 12 years of age of 120 mg would be acceptable, though the 180 mg qd should afford greater efficacy, particularly at the end-of-dosing interval.

Table VI. Summary of Primary Efficacy Data for the in the 3 Adult SAR Studies: 3081, 0032, and 0061
[V1.64:91, 102, V1.83:83, 107, V1.136:76, 77, Response to FDA Request, 05/24/99, Wayne F. Vallee, Drug Regulatory Affairs, Quintiles]

	TREATMENT GROUPS					P-value:		
	Fexo 80 mg qd	Fexo 120 mg qd	Fexo 180 mg qd	Cetirizine 10 mg qd	Placebo	Fexo 80 mg qd c/w placebo	Fexo 120 mg qd c/w placebo	Fexo 180 mg qd c/w placebo
Change from baseline in patient rated 8:00 a.m. instantaneous TSS (Mean Difference ± [2]SE, % Δ from baseline) (Primary efficacy endpoint for 3081 only)								
Pivotal Adult SAR study 3081	[1]NA	-1.17 ± .11 (-15.2%)	-1.36 ± .11 (-17.7%)	NA	-0.87 ± .11 (-11.4%)	NA	0.0505	0.0016
[3]Study 0032-uncorrected	NA	-2.6 ± .2 (-37.1%)	-2.6 ± .2 (-37.7%)	-2.6 ± .2 (-36.6%)	-1.9 ± .2 (-26.8 %)	NA	0.0238	0.0443
[3]Study 0032-corrected	NA	-2.22	-2.31	-2.41	-1.45	NA	0.0021	0.0003
Study 0061	-0.8 ± .1 (-14.0%)	-0.9 ± .1 (-15.8%)	NA	NA	-0.6 ± .1 (-10.9%)	0.2133	0.0379	NA
Change from baseline in 24 hour in patient rated 24 hour reflective TSS (Mean Difference ± SE, % Δ from baseline) (Primary endpoint for 0032, 0061)								
Pivotal Adult SAR study 3081	NA	-1.29 ± .11 (-17.2%)	-1.38 ± .11 (-18.6%)	NA	-0.66 ± .11 (-8.9%)	NA	0.0001	0.0001
[3]Study 0032-uncorrected	NA	-3.0 ± .2 (-41.7%)	-3.3 ± .2 (-44.6%)	-3.3 ± .2 (-45.2%)	-1.9 ± .2 (-26.0%)	NA	0.0001	0.0001
[3]Study 0032-corrected	NA	-2.76	-3.01	-2.93	-1.74	NA	0.0001	0.0001
Study 0061	-1.7 ± .1 (-25.0%)	-1.7 ± .1 (-25.4%)	NA	NA	-0.7 ± .2 (-10.6%)	0.0001	0.0001	NA

[1]NA=Not applicable. [2]SE=Standard Error. [3]Study 0032 was re-analyzed after excluding site #21 and accounting for transcription errors Statistical significance compared to placebo was seen in the cetirizine treatment group P-values, means and associated std errors from an ANCOVA model containing adjustment for site, treatment, and baseline symptom severity.

9.3. Summary of the Primary Efficacy Data (including the end-of dosing interval) for the Pediatric SAR Studies

The overall study design for the 2 pediatric SAR trials (0066 and 0077) was similar to the adult SAR trials, and patients likewise received a 2-week course of double-blind study medication. A single-blind placebo lead-in period of 5-7 days preceded the double-blind period in both studies. Like the adult SAR study, enrollable patients were required to have minimum symptom severity at both the