assessments of total symptom scores (TSS) during the placebo lead-in period having a TSS ≥ 5 and placed patients into one of 2 categories of symptom severity:

a 'low' category: the number of 7:00 p.m. reflective TSS ≥ 5 ranged from ≤ 4, depending on the number of symptom assessments completed (≤ 4) and
a 'high' category: the number of 7:00 p.m. reflective TSS ≥ 5 ranged from ≥ 5 depending on the number of symptom assessments completed (≥ 5) [V1.225:33].

The TAN, along with patients' sequential number, and the site's study number was used for patient identification. Additionally, the TAN was used to randomize study enrollable patients into 1 of the following 4 treatment arms [V1.225:32, 169]:

Double Blind Treatment Groups:	
STUDY GROUPS	**DOSING**
(1) **Fexofenadine HCl 15 mg po bid**	**1 tablet (fexofenadine HCl 15 mg) +** **1 tablet (placebo;** identical in appearance to the fexofenadine HCl 15 mg tablet) **q a.m. (7 a.m.) and q p.m. (7 p.m.)**
(2) **Fexofenadine HCl 30 mg po bid**	**1 tablet (fexofenadine HCl 30 mg) +** **1 tablet (placebo;** identical in appearance to the fexofenadine HCl 30 mg tablet) **q a.m. (7 a.m.) and q p.m. (7 p.m.)**
(3) **Fexofenadine HCl 60 mg po bid**	**1 tablet (fexofenadine HCl 60mg) +** **1 tablet (placebo;** identical in appearance to the fexofenadine HCl 60 mg tablet) **q a.m. (7 a.m.) and q p.m. (7 p.m.)**
(4) **Placebo bid**	**2 tablets (placebo;** identical in appearance to fexofenadine HCl 60 mg tablet) **+** **q a.m. (7 a.m.) and q p.m. (7 p.m.)**

Patients were instructed to take their initial dose of double-blind study medication at 7:00 p.m. (± 1 hour) on the evening of Visit 1 and subsequent doses at 7:00 a.m. (± 1 hour) and 7:00 p.m. (± 1 hour) daily after completing jointly with their caregivers the instantaneous and reflective symptom assessments and diary entries.

Caregivers of patients at designated study sites were reminded that Visit 3 would be conducted 6-11 hours after the 7:00 a.m. dose of study medication since plasma fexofenadine concentrations would be measured at Visit 3 for these patients.

(IV) Visit 3 (Week 3, 8 ± 1 days after Visit 2) [V1.225:44-45, 184-185]:

During visit 3 of the study, plasma fexofenadine levels were assessed 6-11 hours after the 7:00 a.m. dose of study medication at designated sites. The rest of procedure during Visit 3 was essentially the same as for Visit 2. The time

of the blood sample collection and the time of the last dose of study medication were recorded.

(V) Visit 4 (Week 4, 8 ± 1 days after Visit 3) [V1.225:45-6, 185]:
During visit 4 of the study, patients underwent repeat physical examination, laboratory testing, 12-lead ECG, along with a review of SAR symptoms and concomitant medications by the investigator. Patients were to have taken the 7:00 a.m. dose of study medication and blood samples for fexofenadine HCl concentration were to be taken 1-3 hours after dosing at designated sites. Again, the date and time of blood sample collection and date and time of the last dose of study medication were recorded. At several sites, complete laboratory analysis was performed.

(VI) Collection of ragweed pollen counts [V1.225:41, 178]:
Pollen counts (not specified) for indigenous allergens (to the study site area) were at least 5 days/week beginning 2 weeks prior to the day the 1st patient was qualified at Visit 1 until the last patient enrolled completed Visit 4. Pollen counts were collected on a ~~daily basis on the sponsor-provided~~ pollen count form and kept in the Study File Notebook [V1.225:41].

Reviewer's Note: Similar to study 3081, no mention of who (investigator, sponsor, 3rd party) would be recording the pollen counts is provided in either the study protocol or study report. Neither is provided a quantitative measure (e.g. # grains/m^3) of what would constitute a 'low' vs. 'high' pollen count for any given allergen.

8.2.3.2. Clinical Endpoints

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

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

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

Primary Efficacy Variables [V1.225:54, 195, 328]:
(1) The change from baseline in the average 7:00 p.m. reflective TSS over the 2 week double-blind treatment period [V1.225:54, 195, 328].

Reviewer's Note: Choice of the primary efficacy variable for the pediatric studies was different (i.e. reflective scores) from that chosen for the adult qd SAR study where the end-of-dosing (i.e. 'instantaneous') TSS was evaluated.

Change from baseline was computed by subtracting the average 7:00 p.m. reflective TSS during the placebo lead-in period from the average 7:00 p.m. reflective TSS during the double-blind dosing period. Missing symptom scores were handled such that if any of the individual symptoms used in calculating the TSS were missing, then the average of the non-missing data was computed [V1.225:54].

Secondary Efficacy Variables [V1.225:54, 195]:

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

All primary and secondary efficacy endpoints were analyzed using the 'intent-to-treat population', defined as 'patients with baseline and post-baseline 8:00 p.m. reflective TSS' [V1.225:53], along with the evaluation of the primary efficacy endpoint using 'protocol correct' patients (= 'intent-to-treat' patients with no major protocol violations) [V1.225:53].

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

8.2.3.3. Statistical Analysis [V1.225:52-58, 197-199]

A sample size of 150 patients per treatment arm was calculated based on the primary efficacy endpoint of change in the 7:00 p.m. reflective TSS from baseline between placebo and a treatment to detect a treatment difference of at least 0.72 units in the average change of the 7:00 p.m. reflective TSS symptom score from baseline between placebo and treatment given a standard deviation of no larger than 2.20 units with 80% power, given a 2-sided test with type I α error=0.05. These power calculations were based on previous SAR trials of fexofenadine HCl conducted by the sponsor in adult patients (studies PJPR0023, PJPR0024) in which fexofenadine HCl 60 mg po bid produced an average change

from baseline in 7:00 p.m. reflective TSS of 0.86 units compared to placebo, with an estimated population standard deviation which ranged from 2.03 to 2.36 units [V1.225:52].

As the enrollment period for the 2 pediatric studies 0066 and 0077 was ending, it became apparent to the sponsor that these sample size targets could not be met. With less than 2 weeks remaining before closure of enrollment, the estimate for the combined total # of patients to be randomized in the 2 protocols was between 875-900 patients, or 109-114 patients/treatment arm [V1.225:317-318]. Since these sample sizes would provide only 68-69% power for detecting a significant difference between an individual fexofenadine dose group and placebo under the statistical assumptions, the sponsor determined that the data from the 2 studies could be pooled and analyzed as 1 trial. Such an approach would result in 219-226 patients/treatment group and provide enough power to detect the anticipated treatment differences if they were present. This approach (of pooling studies 0066 and 0077) was discussed with the Agency at a post End-of-Phase-2 teleconference for the ALLEGRA Tablet application and was deemed reasonable, albeit with the caveat that if the combined study should fail to detect a difference between the fexofenadine groups and placebo, the sponsor would need to consider how or why the study failed and would need to analyze efficacy in each study separately for the primary efficacy endpoint [V1.1:201, V1.225:57, Teleconference, HMR and DPDP/FDA, 11/04/97 and Memorandum of Teleconference, HMR and DPDP/FDA, 11/14/97]. It was also noted during these discussions between HMR and DPDP that the effect size would be analyzed closely, in addition to evaluating statistical significance [V1.225:57, Memorandum of Teleconference, HMR and DPDP/FDA, 11/14/97].

ANCOVA was used to compare the effects of fexofenadine HCl 15 mg po bid, 30 mg po bid, 60 mg po bid doses, and placebo. The primary efficacy variable, was included as the dependent variable. In addition, the ANCOVA model contained terms for investigative sites, treatment groups, and the primary efficacy variable as predictor variables. The baseline TSS was included as a continuous covariate.

Pairwise dose comparisons to placebo were made based on a 'closed procedure' so as to protect the overall type I error. In particular, the following comparisons were made sequentially: fexofenadine HCl 60 mg po bid vs. placebo, fexofenadine HCl 30 mg po bid vs. placebo, and fexofenadine HCl 15 mg po bid vs. placebo. If the p-value for a comparison was ≤ 0.05, then the next comparison was performed. If the p-value was > 0.05, then the subsequent comparison was performed only for exploratory purposes. In addition, a linear test across all 4 treatment groups was performed to further characterize the dose response relationship.

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

Sites with fewer than 1 ITT patients with all efficacy variables/dose group were pooled to form 'pseudo-sites' prior to the analysis which are further delineated on [V1.225:55].

Treatment effect was characterized in subgroups of patients defined by investigative site, age, gender, weight, and race. Age was only categorized as 6-11 years of age, with no further subdivision. Race was categorized as Caucasian and other. Weight was categorized as: 15 to < 30 kg, 30 kg to < 45 kg, and ≥ 45 kg [V1.225:96].

No interim analysis was performed for this study.

Evaluation of safety parameters were performed by tabulating the frequency of adverse events (AEs) for each double-blind treatment period. No statistical comparisons were made. Laboratory findings were summarized and baseline and end-study, and change from baseline to end-study for each treatment group. The correlation between fexofenadine HCl dose and change from baseline was assessed using the Spearman-Rank Correlation Coefficient [V1.225:56]. In addition, potentially clinically significant outliers were identified.

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

8.2.3.3.1. Pharmacokinetic Analysis [V1.63:338-341, V1.225:40, 57, 178]

Plasma for measuring fexofenadine levels were obtained at designated sites at Visit 3, 6-11 hours after patients had taken the 7:00 a.m. dose of study medication and at all sites, at the Visit 4/early discontinuation visit 1-3 hours after patients had taken the 7:00 a.m. dose of study medication and fexofenadine levels were determined via an method with an assay range of ng/mL [V1.63:338,V1.225:40]. Plasma fexofenadine concentrations were fitted to the appropriate population pharmacokinetic model by nonlinear mixed effects modeling (NONMEM) and investigated with regard to patient. A multivariate linear regression was used to relate the individual predicted PK parameters and prediction errors from the preliminary population PK model to patient demographics. A natural log transformation of the PK parameters was done to stabilize the variance of the predicted PK parameters and transformed PK parameters were examined using the stepwise multivariate linear regression.

8.2.3.3.2. Pediatric Quality of Life (QOL) Questionnaire Evaluation

For combined studies 0066/0077 a health outcomes survey was conducted in pediatric patients enrolled in these 2 studies using the Juniper 'Pediatric Rhinoconjunctivitis Quality of Life' questionnaire (PRQLQ) during execution of these 2 studies [V1.255:12]. The primary objective of this survey was to assess the impact of treatment on pediatric patients with SAR measured by the overall score of the PRQLQ (note the survey was completed at each of the 4 study visits

and the average change from baseline (Visit 2) was calculated using the average of all 'post-baseline' visits (visits 3 and 4). A secondary objective was to assess the effect of treatment on each of the 5 domains of the PRQLQ: (1) nose symptoms, (2) eye symptoms, (3) practical problems, (4) other symptoms, and (5) activities. Secondary endpoints were defined as the average change from baseline in each of the 5 PRQLQ domains. In addition, a tertiary objective to evaluate the effect of time in the study on the primary and secondary objectives was explored using the following tertiary endpoints: the average change in the overall quality of life (QOL) score and the average change in each of the individual domain scores from baseline to Visit 3 and from baseline to Visit 4 (final/early termination visit). The purpose of these tertiary objectives, as defined by the sponsor, was to examine the robustness of claims within the primary and secondary endpoints [V1.225:12-13].

With regard to the QOL analysis, 2 amendments made to protocols 0066/0077 impacted on the collection of data for the QOL analysis, namely: (1) changing the duration of week 2 and 3 to 7 (± 2 days) and 8 (± 1 day), respectively (which changed the entire study duration from 14-25 to 18-25 days and (2) pooling of results from pediatric SAR separate studies 0066 and 0077 into 1 study such that the analysis would be an a priori (and not post-hoc) analysis [V1.255:14].

A sample case report form for the PRQLQ questionnaire is presented on pages 237-282 of Volume 255 of NDA 20-872. A total of 23 PRQLQ items, outlined below, were scored by the patient on a 7-point scale from 0 (not bothered/none of the time) to 6 (extremely bothered/all of the time) [V1.255:17].

Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) Domains		
Domain	PRQLQ Item Number	Description
Nose Symptoms	1	Stuffy/blocked nose
	2	Sneezing
	3	Runny nose
	4	Itchy nose
Eye Symptoms	5	Itchy eyes
	6	Watery eyes
	7	Swollen/puffy eyes
	8	Sore eyes
Practical Problems	9	Rub nose and ears
	10	Blow nose
	11	Carry Kleenex
	12	Take medications
	20	Feel embarrassed
Other Symptoms	13	Thirst
	14	Scratchy/itchy throat
	15	Headache
	17	Tired
	18	Don't feel well all over
	19	Irritable
Activities	16	Playing outdoors
	21	Hard to get to sleep at night
	22	Wake up during the night
	23	Hard to pay attention

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

A full discussion of statistical approaches in evaluation of the PRQLQ is presented on pages 21-22 of Volume 255, however in summary, sample for this QOL study was dependent on the sample size of the 2 combined SAR studies for ITT patients, at a 2-sided α level of 0.05. Demographic variables and baseline (Visit 2) disease severity was assessed for comparability amongst the 5 treatment groups using the chi-square test for categorical characteristics and the Kruskal-Wallis test for continuous characteristics.

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

8.2.4. Results (presented for combined studies and as separate studies 0066 and 0077, where appropriate (i.e. primary efficacy analysis))

8.2.4.1. Patient Demographics [V1.225:59-63, 65]

(A) A total of 877 patients were randomized into the study, though 2 patients discontinued the study following randomization but prior to receiving double-blind medication. The remaining 875 were exposed to double-blind treatment, and 839 of these patients completed the study. One patient was randomized to double-blind medication at 2 different study sites (patient #852-0005, fexofenadine HCl 15 mg bid group and patient #917-0009, fexofenadine HCl 60 mg bid group) [V1.225:59]. This was discovered by the sponsor after database finalization and assignment of patient disposition codes. The only efficacy analysis affected was the protocol-correct analysis of the primary efficacy variable and the impact was minimal. Thirty-six exposed patients (4.1%) discontinued the study and 839 (95.9%) completed the entire study.

Eight hundred and seventy five (875) patients of the 875 patients were identified as safety evaluable (=exposed to double-blind medication with a post-baseline adverse event (AE) assessment) and were used in the safety analysis. Eight hundred and seventy two (872) patients were identified as 'intent-to-treat' patients (=exposed patients with baseline and post-baseline 7:00 p.m. reflective symptom assessments) and were used in the 'intent-to-treat' analysis. Three patients were excluded from the ITT analyses because they had no post-baseline 7:00 p.m. reflective symptom assessments. Of the 872 ITT patients, 711 had no major protocol violations and were classified as 'protocol correct' [V1.225:60]. A distribution of the patient population is summarized in Table II. below:

Table II. Patient Disposition [V1.225:63]

	Fexofenadine 15 mg	Fexofenadine 30 mg	Fexofenadine 60 mg	Placebo	TOTAL
Randomized	226	209	213	229	877
Intent-to-Treat	223	208	212	229	872
Safety Evaluable	224	209	213	229	875
Protocol Correct	183	167	177	184	711

(B) A total of 36 patients exposed to double-blind medication discontinued the study prior to scheduled completion [V1.225:60]. Two patients discontinued treatment before taking double-blind medication, yielding a total of 38 patients who discontinued prior to study completion [V1.225:60]. The most common reason for early discontinuation was either treatment failure (13 total patients or 1.5% of patients in all 4 treatment groups) or an adverse event (10 total patients or 1.1% of patients in all 4 treatment groups).

This data is summarized in Table III. [V1.225:64].

Table III. Number and Percentage (%) of Randomized Patients for Pediatric Studies 0066 and 0077 Combined Who Discontinued the Study with Reasons for Discontinuation, ITT Population [V1.225:64]

	Fexofenadine 15 mg (n=226)[1]	Fexofenadine 30 mg (n=209)[1]	Fexofenadine 60 mg (n=213)	Placebo (n=229)	TOTAL (n=877)
Number (%) Completed	216 (95.6%)	201 (96.2%)	208 (97.7%)	216 (94.3%)	839 (95.7%)
Reasons for Discontinuation					
Adverse event	1 (0.4%)	3 (1.4%)	1 (0.5%)	5 (2.2%)	10 (1.1%)
Elected to discontinue	2 (0.9%)	0 (0.0%)	1 (0.5%)	4 (1.7%)	7 (0.8%)
Treatment Failure	4 (1.8%)	3 (1.4%)	2 (0.9%)	4 (1.7%)	13 (1.5%)
Lost to follow-up	2 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Patient failed to meet entrance criteria	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Use of prohibited medication(s)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Other	0 (0.0%)	2 (0.9%)	1 (0.5%)	0 (0.0%)	3 (0.3%)
ALL REASONS	12 (5.3%)	8 (3.8%)	5 (2.3%)	13 (5.7%)	38 (4.3%)

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

Reviewer's Note: For all 4 treatment groups, the total % of patient discontinuation was less than 10% of the total number of patients randomized in the study. The overall discontinuation rate for all 4 treatment arms ranged from approximately 2-6% which represents an acceptable rate of premature patient discontinuation. Interestingly, the rates of patient discontinuation were higher with the lower doses of fexofenadine than vice versa. The reasons for early patient discontinuation were deemed acceptable by the medical reviewer.

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

Table IV. Patient Demographics for the ITT Population [V1.225:65]:

Variable	Fexofenadine 15 mg (n=223)	Fexofenadine 30 mg (n=208)	Fexofenadine 60 mg (n=212)	Placebo (n=229)	P-Value
Gender: (n, (%))					
Male	140 (63%)	123 (59%)	112 (53%)	139 (35%)	
Female	83 (37.2%)	85 (41%)	100 (47%)	90 (39%)	.1773[1]
Race: (n, (%))					
Caucasian	196 (88%)	180 (87%)	185 (87%)	187 (82%)	
Black	18 (8%)	16 (8%)	19 (9%)	28 (12%)	
Asian	5 (2%)	2 (1%)	3 (1%)	7 (3%)	
Multiracial	4 (2%)	10 (5%)	5 (2%)	7 (3%)	.3743
Age: (yrs)					
Mean ± SD	9.14 ± 1.63	9.09 ± 1.51	9.04 ± 1.65	9.24 ± 1.55	
Range	5-12	5-12	5-11	6-11	.5954
Weight: (kg)					
Mean ± SD	36.68 ± 11.22	35.01 ± 11.02	34.39 ± 10.27	36.56 ± 11.13	
Range	18.6-93.0	17.7-84.8 kg	18.1-72.6 kg	21.0-77.1	.0334
Height: (cm)					
Mean ± SD	138.55 ± 12.25	137.49 ± 11.01	137.25 ± 11.41	138.81 ± 11.30	
Range	106.7-167.6	105.4-166.4	112-170.2	106.7-167.6	.3192

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

Reviewer's Note: It was noted that patient demographics were similar amongst the 4 treatment groups, with the majority of patients Caucasian and a greater proportion of male:female patients. No statistically significant differences or trends were noted between the treatment groups with regard to demographic factors except for a statistically significant difference in weight (p=0.0334) in which the placebo and fexofenadine 15 mg group had a broader range of weights than the other 2 treatment groups.

(D) Patient distribution by disease severity at baseline in the ITT population was provided by the sponsor and no statistically significant difference was noted between the 3 ITT treatment groups for the 7:00 p.m. reflective symptom assessment (p-value=0.3521; used for determining the primary efficacy variable): the 7:00 a.m. reflective TSS (excluding nasal congestion, p-value=0.3626), and the 7:00 a.m. and 7:00 p.m. instantaneous individual SAR symptom scores (nasal

congestion, sneezing, rhinorrhea, itchy nose, mouth, throat and/or ears, and itchy, watery, red eyes) [V1.225:66]. The difference in 7:00 p.m. reflective TSS for the ITT population ranged from 7.71-8.04 with a standard deviation ranging from 2.307-2.523 [V1.225:67]. Neither were statistically significant differences noted between the 3 ITT treatment groups for the baseline 7:00 a.m. and 7:00 p.m. instantaneous symptom assessments (TSS and individual SAR symptom scores, $p>0.32$ for all assessments with the exception of the 7:00 p.m. instantaneous sneezing assessment where a p-value across groups of 0.08 was noted) [V1.225:69].

(E) Patient Validity [V1.225:63]

One hundred and sixty three patients (or 18.6% of all exposed patients) (40 treated with fexofenadine HCl 15 mg, 42 treated with fexofenadine HCl 30 mg, 36 treated with fexofenadine HCl 60 mg, and 45 treated with placebo) valid for efficacy had a 'major' protocol violation. The most common 'major' protocol violations consisted of the following: use of prohibited medications (7.9% of total patients), followed by missing efficacy data (7.5% of total patients). The % of patients with a violation of: 'failure to meet entrance criteria' was comparable among the 4 treatment groups, with a slightly higher preponderance in the placebo group. A summary of invalidated patients and the reasons for invalidation are summarized in Table 7 of the study report for studies 0066/0077 [V1.225:63].

Reviewer's Note: Criteria for invalidation of patient data were comparable to those seen in other SAR trials and thus deemed reasonable by the medical reviewer. In addition, the overall degree of patient invalidation was slightly lower for the fexofenadine HCl 60 mg arm but comparable in terms of % amongst the other 3 treatment arms.

(G) Duration of Study Medication Exposure [V1.225:70]

The mean duration of double-blind exposure to study treatment for the safety population was 14.49 days (± 2 days) for all 4 treatment groups. The range of duration of exposure was 2-21 days for the placebo group (n=229 patients), 2-21 days for the fexofenadine HCl 15 mg group (n=223), 1-18 days for the fexofenadine HCl 30 mg group (n=209), and 3-19 days for the fexofenadine HCl 60 mg group (n=213). Duration of exposure was calculated using days between randomization and last dosing day of the double-blind treatment.

(H) Patient Compliance [V1.225:70-71]

Assessment of patient compliance with double-blind medication was evaluated by the sponsor by dividing the total # of tablets taken during the double-blind dosing period (i.e. the total # of tablets dispensed – the total # of tablets returned) by the total # of tablets that should have been taken based on the # of days the patients participated in the double-blind period. Average compliance was found to be 99.58% for the placebo group, 99.72% for the fexofenadine HCl

15 mg group, 99.69% for the fexofenadine HCl 30 mg group, and 99.07% for the fexofenadine HCl 60 mg group [V1.225:71]. Four patients had compliance < 80% and 2 patients had compliance above 120%. Based on these measurements, compliance was noted to be acceptable according to the sponsor's original protocol and protocol amendments.

8.2.4.2. Efficacy Endpoint Outcomes

(I) Primary Efficacy Variables:

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=223 for fexofenadine HCl 15 mg group, n=208 for fexofenadine HCl 30 mg group, n=212 for fexofenadine HCl 60 mg group, and n=229 for placebo) for the primary efficacy variable the change from baseline in the average 7:00 p.m. reflective TSS; where the primary comparison of interest was the response of the 3 fexofenadine doses vs. placebo. Unlike the adult SAR study 3081, choice of a reflective TSS as the primary efficacy endpoint did not provide information about the end-of-dosing interval efficacy (or duration of drug effect) but rather was chosen in order to give information about patients' response in total SAR symptoms over the preceding 12 hours.

Results of the primary efficacy analysis for studies 0066/0077 combined and the individual studies 0066 and 0077 are summarized in Table V. For the combined studies 0066/0077, a statistically significant decrease in the primary efficacy endpoint for all 3 fexofenadine doses compared to placebo was not demonstrable, although a numerical trend for decrease in 7:00 p.m. reflective TSS compared to placebo was seen across all 3 fexofenadine doses. The greatest numerical decrease in the primary efficacy endpoint for the combined studies 0066/0077 was seen for the fexofenadine 60 mg po bid group (-1.55 units ± 0.167), very closely followed by the fexofenadine 30 mg po bid group (-1.54 units ± 0.169) [V1.225:75].

Post-hoc analysis of the individual studies (analysis post-unblinding of the 2 studies) revealed that pediatric study 0066 failed to demonstrate a statistically significant improvement in the primary efficacy endpoint compared to placebo but conversely study 0077 did indeed show a statistically significant improvement in the primary efficacy endpoint compared to placebo for all 3 fexofenadine doses. Of note, in study 0066, a large placebo response was noted, which was indeed greater than that seen in all 3 fexofenadine groups (15 mg, 30 mg, and 60 mg). In study 0077, no dose response in treatment effect was noted, with the fexofenadine 15 mg po bid arm (-1.83 units ± 0.246) showing the greatest numerical difference from baseline symptom scores, followed by the fexofenadine 60 mg po bid arm (-1.73 units ± 0.277).

Reviewer's Note: The sponsor had no specific explanation for this finding/discrepancy of efficacy between study 0066 and 0077. Additional analyses were conducted in an effort to better explain the differences in efficacy results between these 2 protocols. Evaluation of baseline

demographics, (age, weight, gender, and race), baseline allergy symptom severity, pollen counts at each investigative site, and rates of screen and randomization failures at each investigative site was performed with regard to treatment effect but failed to explain the difference in efficacy results between the 2 protocols.

Nonetheless, difficulty in demonstrating efficacy in the treatment of SAR in the pediatric population is well known and has been seen in other trials of similar design. This difficulty is thought to be due to the use of symptom diaries where the successful demonstration of treatment effects depends on the ability of young children to perform daily evaluations of their symptoms in a thoughtful and consistent manner. Numerically, trends in study 0066 indicated a greater effect with regard to symptom control in fexofenadine treated patients than placebo, with no significant dose response demonstrable amongst the 3 fexofenadine doses (15 mg, 30 mg, and 60 mg po bid). Clearly however, it is likely that the large placebo response in study 0066 (which in turn, influenced combined studies 0066/0077) may be a major factor responsible for this discrepancy in efficacy results between 0066 and 0077.

Similar results were seen with analysis of the 'protocol correct' group for combined studies 0066/077, although there was a slight numerical increase in response in all 4 treatment groups including the placebo group (however none of the responses in the 3 fexofenadine groups were statistically significantly greater than placebo) [V1.225:80].

Of note, one of the investigators in study 0066-Dr. Edwards (site PPJST0854) was disqualified; in which a total of 17 patients comprised the ITT population at this site (5, 5, 3, and 4 patients were treated with placebo, fexofenadine 15 mg, 30 mg, and 60 mg, respectively. The sponsor submitted results of the primary efficacy variable analysis for combined studies 0066/0077 and the individual study 0066 which excluded this site and which failed to show any significant numerical or statistical difference in the final efficacy results [NDA 20872 subsequent submission, HMR, 08/13/98, section SAR PJPR0066/0077 and PED SAR PJPR0066]. After exclusion of this one study site, conclusions reached about efficacy for the primary endpoint for both studies 0066/0077 combined and study 0066 were not altered.

Treatment-by-investigative site and treatment-by-baseline 7 p.m. reflective TSS interactions were assessed using ANCOVA with the baseline 7 p.m. reflective TSS, treatment, investigative site, treatment-by-investigative site and treatment-by-baseline 7 p.m. reflective TSS at a significance level of 0.1 [V1.225:73]. The treatment-by-baseline TSS interaction (without treatment-by-site) was found to be statistically significant for combined studies 0066/0077 (p=0.0392) [V1.225:73, 234:11, 13]. There was no statistical evidence of dependence of treatment effect on the investigative site (p=0.5465) [V1.234:11].

Reviewer's Note: In summary, evaluation of the primary efficacy endpoint indicated lack of a statistically significant difference for either of the 3 fexofenadine doses in decreasing the 7 p.m. reflective TSS compared to placebo treatment, though greater numerical improvement was noted for the active treatments. Pediatric SAR study 0066 was a failed study, although again this may have been due to a strong placebo response. Conversely, study 0077 did show efficacy of all 3 fexofenadine doses in decreasing the 7 p.m. reflective TSS compared to placebo treatment, though no distinct dose response was noted.

Table V.
Efficacy of Fexofenadine HCl 15 mg, 30 mg, and 60 mg, vs. Placebo
Primary Efficacy Variable: Intent-to-Treat (ITT) Population [V1.225:75-78]

Primary Efficacy Variable	TREATMENT GROUP (A) Fexo 15 mg bid	(B) Fexo 30 mg bid	(C) Fexo 60 mg bid	(D) Placebo	P-value A-D	B-D	C-D
STUDIES 0066/0077 Combined: **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=223)	**(n=208)**	**(n=212)**	**(n=229)**			
Baseline TSS	7.72 ± 0.169	7.78 ± 0.162	7.71 ± 0.158	8.04 ± 0.163			
Double-blind Treatment Period TSS	6.33 ± 0.201	6.36 ± 0.208	6.29 ± 0.203	6.84 ± 0.190			
Change from baseline in average 7 p.m. reflective TSS	**-1.49 ± 0.163**	**-1.54 ± 0.169**	**-1.55 ± 0.167**	**-1.21 ± 0.161**	0.2197	0.1585	0.2227
Mean Difference ± SE					-.28±.22	-.32±.23	-.33±.23
STUDY 0066: **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=118)	**(n=108)**	**(n=111)**	**(n=124)**			
Baseline TSS	7.90 ± 0.236	7.96 ± 0.226	7.75 ± 0.224	8.19 ± 0.221			
Double-blind Treatment Period TSS	6.73 ± 0.285	6.53 ± 0.290	6.49 ± 0.293	6.68 ± 0.285			
Change from baseline in average 7 p.m. reflective TSS	-1.30 ± 0.248	-1.53 ± 0.258	-1.44 ± 0.256	-1.59 ± 0.236	0.3559	0.8470	0.6442
Mean Difference ± SE					-.29±.31	-.06±.32	-.15±.32
STUDY 0077: **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=105)	**(n=100)**	**(n=101)**	**(n=105)**			
Baseline TSS	7.50 ± 0.241	7.58 ± 0.232	7.66 ± 0.225	7.87 ± 0.241			
Double-blind Treatment Period TSS	5.88 ± 0.277	6.17 ± 0.298	6.07 ± 0.277	7.03 ± 0.241			
Change from baseline in average 7 p.m. reflective TSS	**-1.83 ± 0.246**	**-1.65 ± 0.253**	**-1.73 ± 0.277**	**-0.84 ± 0.241**	**0.0023**	**0.0138**	**0.0318**
Mean Difference ± SE					-.99±.32	-.81±.33	-.89±.33

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

Subgroup Analysis of the Primary Efficacy Variable:

A subgroup analysis of the primary efficacy variables to examine treatment interactions was performed by the sponsor on the basis of gender [V1.225:93], race [V1.225:94], weight [V1.225:95], study site [V1.225:93], and baseline symptom severity (as determined by the average 7:00 p.m. reflective TSS during the placebo lead-in period. Analysis by further sub-grouping of age (e.g. 6-8 years, 9-11 years) was not performed as there was no regulatory or clinical reason to do so. The statistical model used for this analysis was ANCOVA with a significance level of 0.1 [V1.225:93].

With regard to baseline symptom scores, patients were categorized into 'low' or 'high' baseline symptom groups based on whether their baseline 7:00 p.m. reflective TSS was ≤ to or ≥ to the median baseline 7:00 p.m. reflective TSS of 7.3 for the ITT population [V1.225:97].

Based on these subgroup analyses, no statistical significance was noted for the study site by treatment interaction (p=.5465) although the main effect of site (p=0.0043) was statistically significant [V1.225:93], no statistical significance was noted for the gender by treatment interaction (p=0.2029) or main effect of gender (p=0.9361) for the change in the average 7:00 p.m. reflective TSS [V1.225:93-94], no statistical significance was noted for weight by treatment (p=0.8542) or main effect of weight (p=0.5926) for the change in the average 7:00 p.m. reflective TSS, along with no statistical significance noted for race by treatment interaction (p=0.9336) or main effect of race (p=0.4117) for the change in the average 7:00 p.m. reflective TSS; indicating that the treatment effects were consistent across these demographic variables. In other words, the effect of the 3 treatment groups was not statistically significantly different among subgroups of patients defined by these factors.

Evaluation of the level of baseline symptoms by treatment interaction revealed a statistically significant effect at the 0.1 level (p=0.0629), indicating that treatment effect varies with the level of baseline symptoms. A larger treatment effect was noted for 'high' baseline patients who had larger reductions than the 'low' baseline patients for all 4 treatment groups [V1.225:97] but especially for the placebo group ('low' placebo group change from baseline in 7:00 p.m. reflective TSS=-0.27 units ± 0.233 and 'high' placebo group change from baseline in 7:00 p.m. reflective TSS=-2.26 units ± 0.231) [V1.225:97].

(II). Secondary Efficacy Variables:

Analysis of secondary efficacy variables was submitted by the sponsor for combined studies 0066/0077 in the medical volumes and for the separate studies 0066 and 0077 in the statistical volumes.

A summary of analysis of the secondary efficacy variables for the ITT population is provided in Table VI. below for combined study 0066/0077 and indicates that for the majority of secondary efficacy endpoints, a statistically significant difference in symptom scores was not seen for the 3 fexofenadine doses compared to placebo, although review of numerical trends did generally

show a greater decrease in symptoms with active treatment for the majority of secondary endpoints [V1.225:82-93]. With regard to dose response (based on numerical change between the 3 fexofenadine doses and placebo) for combined studies 0066/0077, no consistent trend was noted between fexofenadine dose and numerical response for the secondary efficacy endpoints [V1.225:82-93]. Review of the summary of secondary efficacy endpoints for individual studies 0066 and 0077 is presented in Tables VII. and VIII. and showed that for 'failed' study 0066, no statistically significant differences between placebo and any of the 3 active treatment groups was seen, despite a slight numerical trend toward efficacy [V1.297:6, 8, 10, 12, 14, 16]. Conversely, analysis of the secondary efficacy endpoints for study 0077—the 'successful' SAR trial, statistically significant efficacy was demonstrable for almost all endpoints for the 3 fexofenadine treatment arms, with the exception of the individual symptoms of rhinorrhea, nasal congestion, and itchy, watery, red eyes [V1.297:7, 9, 11, 13, 15, 17]. Importanly, no consistent dose response was seen across secondary efficacy endpoints for the 3 fexofenadine arms in study 0077.

Specifically with regard to analysis of the week 1 vs. week 2 change in average 7:00 p.m. reflective TSS for combined studies 0066/0077 (Table IX.), only the fexofenadine 60 mg treatment group showed a statistically significantly greater decrease compared to placebo treatment for week 1 of treatment ($p=0.0286$ for the 60 mg group) with the other 2 fexofenadine doses showing a marginally significant decrease ($p=0.0642$ for the fexofenadine 15 mg group and $p=0.0569$ for the fexofenadine 30 mg group). Furthermore, although the numerical difference in 7:00 p.m. reflective TSS was greater for all 3 fexofenadine groups at week 2 of treatment (compared to placebo) than at week 1, for neither of the 3 groups was the decrease statistically significant. Again, it was difficult to extrapolate a dose response for the combined studies 0066/0077 since 1 of the studies had failed but based on the numerical change from baseline in average 7:00 p.m. reflective TSS for week 1 vs. week 2, a very shallow dose response was noted for week 1 and no dose response noted for week 2. When this endpoint was evaluated by individual study, again no statistically significant difference was seen for any of the 3 fexofenadine doses vs. placebo in study 0066 but statistically significant differences were seen for all 3 fexofenadine doses vs. placebo, except the fexofenadine 30 mg po bid dose at week 2 [V1.297:7, 9].

The end-of-dosing interval (i.e. duration of effect) for the 3 fexofenadine doses was assessed by 2 secondary efficacy endpoints: (1) the change from baseline in the average 7:00 a.m. instantaneous TSS (over the 2 week double-blind treatment period) and (2) the change from baseline in the average 7:00 p.m. instantaneous TSS (over the 2 week double-blind treatment period). Analysis of these 2 endpoints (i.e. 7 a.m. and 7 p.m. scoring) for all 3 fexofenadine doses for combined studies 0066/0077 failed to reveal a statistically significant decrease compared to placebo treatment, but did show numerical trends that all 3 active treatments decreased the instantaneous TSS more than placebo treatment, with a trend toward statistical significance [V1.225:86-87]. Again, based on combined

studies 0066/0077, a consistent dose response with respect to fexofenadine dose was not seen for either of these 2 endpoints. When the end-of dosing interval was evaluated for each of the 2 instantaneous TSS in studies 0066 and 0077 separately for the double-blind treatment period, study 0077 demonstrated that the 3 fexofenadine doses had statistically significant improvements in the 7 a.m. and 7 p.m. 'trough' instantaneous TSS [V1.297:12-15].

With regard to the other secondary efficacy endpoints, a statistically significant difference was only noted for the fexofenadine 60 mg group vs. placebo for the individual symptom score of itchy, watery, red eyes when looking at the data for combined studies 0066/0077 [V1.225:82]. Again, assessment of the individual studies revealed a greater number of endpoints with statistically significant differences for the fexofenadine treatments compared to placebo in study 0077 exclusively.

Review of onset of action for daily change from baseline change from baseline in the 7:00 p.m. reflective TSS for the double-blind treatment period (the primary efficacy variable) for the intent-to-treat population was performed by the sponsor for studies 0066/0077 combined (not studies 0066 and 0077 separately and failed to illustrate a statistically significant sustained decrease for all 3 doses of fexofenadine HCl (15 mg, 30 mg, and 60 mg) compared to placebo for the double-blind period of treatment (days 2-16). Results are summarized in Table XIV. below. For each of the 3 fexofenadine doses, sporadic statistically significant decreases in the primary efficacy endpoint (compared to placebo) were seen, but again these were not consistently maintained thereafter. Importantly, for the fexofenadine 15 mg and 60 mg doses, a statistically significant improvement in the 7:00 p.m. reflective TSS was shown at day 2, although based on previous chamber onset of action studies conducted with fexofenadine in adults and based on the mechanism of action of this H_1 antihistamine, onset of action would be anticipated to occur much sooner than 2 days (i.e. 1 hour).

Reviewer's Note: Analysis of the onset of action for the 3 fexofenadine doses (15, 30, and 60 mg) failed to show a consistent sustained statistically significant decrease in the primary efficacy endpoint on a daily basis for the 2 week double-blind treatment period.

Table VI: Secondary Efficacy Variables for the ITT Population for Studies 0066/0077 Combined and Treatment with Fexofenadine HCl 15 mg, Fexofenadine HCl 30 mg, Fexofenadine HCl 60 mg, and Placebo [V1.225:82-93].

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No		
	Fexo 15 mg qd	Fexo 30 mg qd	Fexo 60 mg qd
Secondary Efficacy Variables			
1. Δ from baseline week 1 average 7:00 p.m. reflective TSS	No (p=0.0642)	No (p=0.0569)	***Yes*** (p=0.0286)
2. Δ from baseline week 2 average 7:00 p.m. reflective TSS	No (p=0.6231)	No (p=0.6587)	No (p=0.6302)
3. Δ from baseline in average daily 7:00 p.m. reflective TSS:			
Day 2:	***Yes*** (p=0.0326)	No (p=0.4544)	***Yes*** (p=0.0445)
Day 3:	No (p=0.6277)	No (p=0.9490)	No (p=0.2988)
Day 4:	No (p=0.1154)	No (p=0.24247)	No (p=0.1283)
Day 5:	No (p=0.1935)	***Yes*** (p=0.0037)	No (p=0.0676)
Day 6:	No (p=0.2588)	No (p=0.1804)	***Yes*** (p=0.0278)
Day 7:	No (p=0.1439)	***Yes*** (p=0.0168)	No (p=0.1423)
Day 8:	***Yes*** (p=0.0480)	No (p=0.4021)	No (p=0.1098)
Day 9:	No (p=0.7316)	No (p=0.8887)	No (p=0.2212)
Day 10:	No (p=.3030)	No (p=0.6912)	No (p=0.7574)
Day 11:	No (p=0.9001)	No (p=0.8461)	No (p=0.7278)
Day 12:	No (p=0.9167)	No (p=0.5351)	No (p=0.9996)
Day 13:	No (p=0.9068)	No (p=0.8694)	No (p=0.7061)
Day 14:	No (p=0.7928)	No (p=0.5342)	No (p=0.5949)
Day 15:	No (p=0.5746)	No (p=0.2932)	No (p=0.4031)
Day 16:	No (p=0.3311)	***Yes*** (p=0.0258)	No (p=0.0932)
4. Δ from baseline in average 7:00 p.m. instantaneous TSS (over the 2 week double-blind treatment period).	No (p=0.2935)	No (p=0.1156)	No (p=0.1625)
5. Δ from baseline in average 7:00 a.m. instantaneous TSS (over the 2 week double-blind treatment period).	No (p=0.1213)	No (p=0.2919)	No (p=0.2479)
6. Δ from baseline in average 7:00 a.m. reflective TSS (over the 2 week double-blind treatment period).	No (p=0.2815)	No (p=0.4603)	No (p=0.2219)
7. Δ from baseline in average individual 7:00 p.m. reflective symptom scores (over the 2 week double-blind period):			
–Sneezing	No (p=0.1234)	No (p=0869)	No (p=0.1044)
–Rhinorrhea	No (p=0.9320)	No (p=0.7858)	No (p=0.7803)
–Itchy nose, mouth, and/or throat	No (p=0.1154)	No (p=0.0834)	No (p=0.2953)
–Itchy, watery, red eyes.	No (p=0.1904)	No (p=0.0651)	***Yes*** (p=0.0268)
–Nasal congestion	No (p=0.3507)	No (p=0.9417)	No (p=0.6204)

Δ=Change, TSS=Total symptom score

Table VII: Secondary Efficacy Variables for the ITT Population for Study 0066 Treatment with Fexofenadine HCl 15 mg, Fexofenadine HCl 30 mg, Fexofenadine HCl 60 mg, and Placebo [V1.297:6, 8, 10, 12, 14, 16]

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No		
	Fexo 15 mg qd	Fexo 30 mg qd	Fexo 60 mg qd
Secondary Efficacy Variables			
1. Δ from baseline week 1 average 7:00 p.m. reflective TSS	No (p=0.5187)	No (p=0.9530)	No (p=0.9764)
2. Δ from baseline week 2 average 7:00 p.m. reflective TSS	No (p=0.1953)	No (p=0.4520)	No (p=0.2565)
3. Δ from baseline in average 7:00 p.m. instantaneous TSS (over the 2 week double-blind treatment period).	No (p=0.6391)	No (p=0.5468)	No (p=0.6598)
4. Δ from baseline in average 7:00 a.m. instantaneous TSS (over the 2 week double-blind treatment period).	No (p=0.7473)	No (p=0.6574)	No (p=0.5991)
5. Δ from baseline in average 7:00 a.m. reflective TSS (over the 2 week double-blind treatment period).	No (p=0.5391)	No (p=0.4043)	No (p=0.6299)
6. Δ from baseline in average individual 7:00 p.m. reflective symptom scores (over the 2 week double-blind period):			
–Sneezing	No (p=0.4456)	No (p=0.7050)	No (p=0.9939)
–Rhinorrhea	No (p=0.1593)	No (p=0.3930)	No (p=0.1998)
–Itchy nose, mouth, and/or throat	No (p=0.4316)	No (p=0.9583)	No (p=0.5105)
–Itchy, watery, red eyes.	No (p=0.8053)	No (p=0.3192)	No (p=0.3786)
–Nasal congestion	No (p=0.0895)	No (p=0.4395)	No (p=0.4700)

Δ=Change, TSS=Total symptom score

Table VIII: Secondary Efficacy Variables for the ITT Population for Study 0077 Treatment with Fexofenadine HCl 15 mg, Fexofenadine HCl 30 mg, Fexofenadine HCl 60 mg, and Placebo [V1.297:7, 9, 11, 13, 15, 17]

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No		
	Fexo 15 mg qd	Fexo 30 mg qd	Fexo 60 mg qd
Secondary Efficacy Variables			
1. Δ from baseline week 1 average 7:00 p.m. reflective TSS	*Yes* (p=0.0005)	*Yes* (p=0.0054)	*Yes* (p=0.0014)
2. Δ from baseline week 2 average 7:00 p.m. reflective TSS	*Yes* (p=0.0121)	No (p=0.0789)	*Yes* (p=0.0366)
3. Δ from baseline in average 7:00 p.m. instantaneous TSS (over the 2 week double-blind treatment period).	*Yes* (p=0.0168)	*Yes* (p=0.0484)	*Yes* (p=0.0116)
4. Δ from baseline in average 7:00 a.m. instantaneous TSS (over the 2 week double-blind treatment period).	*Yes* (p=0.0018)	*Yes* (p=0.0175)	*Yes* (p=0.0104)
5. Δ from baseline in average 7:00 a.m. reflective TSS (over the 2 week double-blind treatment period).	*Yes* (p=0.0102)	*Yes* (p=0.0309)	*Yes* (p=0.0122)
6. Δ from baseline in average individual 7:00 p.m. reflective symptom scores (over the 2 week double-blind period):			
–Sneezing	*Yes* (p=0.0012)	*Yes* (p=0.0035)	*Yes* (p=0.0170)
–Rhinorrhea	No (p=0.1310)	No (p=0.5466)	No (p=0.0581)
–Itchy nose, mouth, and/or throat	*Yes* (p=0.0006)	*Yes* (p=0.0051)	*Yes* (p=0.0155)
–Itchy, watery, red eyes.	No (p=0.0665)	No (p=0.0613)	*Yes* (p=0.0209)
–Nasal congestion	No (p=0.5103)	No (p=0.2944)	No (p=0.8691)

Δ=Change, TSS=Total symptom score

Table IX.
Efficacy of Fexofenadine HCl 15 mg, 30 mg, and 60 mg vs. Placebo
Secondary Efficacy Variable: **7:00 p.m. Reflective TSS**;
Studies 0066/0077 Combined: ITT Population
WEEK 1 vs. WEEK 2 of Treatment
[V1.225:84-85]

	TREATMENT GROUP						
Primary Efficacy Variable	**(A) Fexo 15 mg bid**	**(B) Fexo 30 mg bid**	**(C) Fexo 60 mg bid**	**(D) Placebo**	**P-value**		
					A-D	**B-D**	**C-D**
WEEK 1 **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=223)	**(n=208)**	**(n=212)**	**(n=229)**			
Baseline TSS	7.72 ± 0.169	7.78 ± 0.162	7.71 ± 0.158	8.04 ± 0.163			
Double-blind Treatment Period TSS	6.57 ± 0.211	6.64 ± 0.206	6.51 ± 0.208	7.24 ± 0.193			
Change from baseline in average 7 p.m. reflective TSS	**-1.23 ± 0.158**	**-1.25 ± 0.165**	**-1.31 ± 0.163**	**-0.83 ± 0.157**	0.0642	0.0569	**0.0286**
Mean Difference ± SE					-.40±.22	-.42±.22	-.48±.22
WEEK 2 **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=214)	**(n=204)**	**(n=207)**	**(n=222)**			
Baseline TSS	7.67 ± 0.171	7.80 ± 0.1665	7.68 ± 0.160	8.06 ± 0.166			
Double-blind Treatment Period TSS	6.01 ± 0.218	6.12 ± 0.234	6.03 ± 0.219	6.40 ± 0.212			
Change from baseline in average 7 p.m. reflective TSS	-1.82 ± 0.196	-1.80 ± 0.202	-1.81 ± 0.199	-1.68 ± 0.193	0.6231	0.6587	0.6302
Mean Difference ± SE					-.13±.27	-.12±.27	-.13±.27

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

Table X.
Efficacy of Fexofenadine HCl 15 mg, 30 mg, and 60 mg vs. Placebo
Secondary Efficacy Variable: **7:00 p.m. Reflective TSS**
Study 0066: ITT Population
WEEK 1 vs. WEEK 2 of Treatment
[V1.297:6, 8]

	TREATMENT GROUP						
Primary Efficacy Variable	**(A) Fexo 15 mg bid**	**(B) Fexo 30 mg bid**	**(C) Fexo 60 mg bid**	**(D) Placebo**	**P-value**		
					A-D	**B-D**	**C-D**
WEEK 1 **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=118)	**(n=108)**	**(n=111)**	**(n=124)**			
Baseline TSS	7.90 ± 0.236	7.96 ± 0.226	7.96 ± 0.226	8.19 ± 0.221			
Double-blind Treatment Period TSS	6.96 ± 0.301	6.79 ± 0.287	6.79 ± 0.287	7.02 ± 0.284			
Change from baseline in average 7 p.m. reflective TSS	**-1.23 ± 0.228**	**-1.25 ± 0.249**	**-1.25 ± 0.249**	**-1.23 ± 0.228**	0.5187	0.9530	0.9764
Mean Difference ± SE					.19±.30	-.02±.30	.01±.30
WEEK 2 **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=115)	**(n=106)**	**(n=111)**	**(n=121)**			
Baseline TSS	7.90 ± 0.241	7.98 ± 0.230	7.75 ± 0.224	8.23 ± 0.222			
Double-blind Treatment Period TSS	6.44 ± 0.311	6.25 ± 0.330	6.28 ± 0.314	6.21 ± 0.309			
Change from baseline in average 7 p.m. reflective TSS	-2.12 ± 0.282	-1.83 ± 0.307	-1.69 ± 0.302	-2.12 ± 0.282	0.1953	0.4520	0.2565
Mean Difference ± SE					.48±.37	.28±.38	.42±.37

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

Table XI.
Efficacy of Fexofenadine HCl 15 mg, 30 mg, and 60 mg vs. Placebo
Secondary Efficacy Variable: **7:00 p.m. Reflective TSS**;
Study 0077: ITT Population
WEEK 1 vs. WEEK 2 of Treatment
[V1.297:7, 9]

Primary Efficacy Variable	TREATMENT GROUP (A) Fexo 15 mg bid	(B) Fexo 30 mg bid	(C) Fexo 60 mg bid	(D) Placebo	P-value A-D	B-D	C-D
WEEK 1 **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=105)	(n=100)	(n=101)	(n=105)			
Baseline TSS	7.50 ± 0.241	7.58 ± 0.232	7.66 ± 0.225	7.87 ± 0.241			
Double-blind Treatment Period TSS	6.13 ± 0.288	6.47 ± 0.296	6.34 ± 0.284	7.49 ± 0.255			
Change from baseline in average 7 p.m. reflective TSS	**-1.51 ± 0.244**	**-1.29 ± 0.251**	**-1.42 ± 0.250**	**-0.38 ± 0.239**	**0.0005**	**0.0054**	**0.0014**
Mean Difference ± SE					-1.1±.32	-.9±.33	-1.0±.32
WEEK 2 **7 p.m. Reflective Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=99)	(n=98)	(n=96)	(n=101)			
Baseline TSS	7.41 ± 0.239	7.61 ± 0.236	7.61 ± 0.228	7.87 ± 0.249			
Double-blind Treatment Period TSS	5.51 ± 0.296	5.97 ± 0.332	5.75 ± 0.301	6.62 ± 0.285			
Change from baseline in average 7 p.m. reflective TSS	-2.22 ± 0.296	-1.93 ± 0.301	-2.06 ± 0.301	-1.24 ± 0.288	**0.0121**	0.0789	**0.0366**
Mean Difference ± SE					-.98 ±.4	-.68±.40	-.82±.4

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

Table XII.
Efficacy of Fexofenadine HCl 15 mg, 30 mg, and 60 mg, vs. Placebo
Secondary Efficacy Variable: 7 a.m. Instantaneous Total Symptom Score for the Double-Blind Treatment Period
Intent-to-Treat (ITT) Population [V1.225:89, 297:12, 13]

	TREATMENT GROUP						
Primary Efficacy Variable	**(A) Fexo 15 mg bid**	**(B) Fexo 30 mg bid**	**(C) Fexo 60 mg bid**	**(D) Placebo**	**P-value**		
					A-D	**B-D**	**C-D**
STUDIES 0066/0077 Combined: **7 a.m. Instantaneous Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=223)	**(n=205)**	**(n=210)**	**(n=229)**			
Baseline TSS	6.78 ± 0.208	6.85 ± 0.183	6.83 ± 0.203	7.12 ± 0.198			
Double-blind Treatment Period TSS	5.91 ± 0.206	6.08 ± 0.206	6.03 ± 0.206	6.48 ± 0.191			
Change from baseline in average 7 a.m. instantaneous TSS	**-0.98 ± 0.153**	**-0.89 ± 0.160**	**-0.91 ± 0.158**	**-0.66 ± 0.151**	0.1213	0.2919	0.2479
Mean Difference ± SE					-.33±.21	-.23±.29	-.25±.21
STUDY 0066: **7 a.m. Instantaneous Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=118)	**(n=107)**	**(n=109)**	**(n=124)**			
Baseline TSS	7.15 ± 0.289	7.12 ± 0.266	7.00 ± 0.289	7.28 ± 0.277			
Double-blind Treatment Period TSS	6.33 ± 0.304	6.32 ± 0.286	6.28 ± 0.308	6.33 ± 0.280			
Change from baseline in average 7 a.m. instantaneous TSS	-0.87 ± 0.241	-0.83 ± 0.251	-0.81 ± 0.250	-0.97 ± 0.229	0.7473	0.6574	0.5991
Mean Difference ± SE					.10 ±.3	.14±.3	.16±.3
STUDY 0077: **7 a.m. Instantaneous Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=105)	**(n=98)**	**(n=101)**	**(n=105)**			
Baseline TSS	6.36 ± 0.296	6.55 ± 0.248	6.65 ± 0.285	6.94 ± 0.282			
Double-blind Treatment Period TSS	5.44 ± 0.267	5.81 ± 0.297	5.75 ± 0.270	6.64 ± 0.254			
Change from baseline in average 7 a.m. instantaneous TSS	**-1.22 ± 0.223**	**-1.00 ± 0.233**	**-1.05 ± 0.229**	**-0.29 ± 0.219**	**0.0018**	**0.0175**	**0.0104**
Mean Difference ± SE					-.92±.29	-.71±.30	-.76±.30

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

Table XIII.
Efficacy of Fexofenadine HCl 15 mg, 30 mg, and 60 mg, vs. Placebo
Secondary Efficacy Variable: 7 p.m. Instantaneous Total Symptom Score for the Double-Blind Treatment Period
Intent-to-Treat (ITT) Population [V1.225:86, 297:14, 15]

	TREATMENT GROUP						
Primary Efficacy Variable	**(A) Fexo 15 mg bid**	**(B) Fexo 30 mg bid**	**(C) Fexo 60 mg bid**	**(D) Placebo**	**P-value**		
					A-D	**B-D**	**C-D**
STUDIES 0066/0077 Combined: **7 p.m. Instantaneous Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=118)	**(n=107)**	**(n=109)**	**(n=124)**			
Baseline TSS	6.56 ± 0.211	6.59 ± 0.195	6.70 ± 0.158	6.98 ± 0.202			
Double-blind Treatment Period TSS	5.76 ± 0.211	5.68 ± 0.208	5.77 ± 0.209	6.27 ± 0.203			
Change from baseline in average 7 p.m. instantaneous TSS	**-0.94 ± 0.162**	**-1.06 ± 0.170**	**-1.02 ± 0.167**	**-0.70 ± 0.160**	0.2935	0.1156	0.1625
Mean Difference ± SE					-.23±.22	-.36±.23	-.32±.23
STUDY 0066: **7 p.m. Instantaneous Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=118)	**(n=107)**	**(n=109)**	**(n=124)**			
Baseline TSS	6.96 ± 0.292	7.02 ± 0.261	6.67 ± 0.278	7.07 ± 0.276			
Double-blind Treatment Period TSS	6.23 ± 0.304	5.93 ± 0.294	6.01 ± 0.313	6.19 ± 0.304			
Change from baseline in average 7 p.m. instantaneous TSS	-0.79 ± 0.278	-1.13 ± 0.261	-0.79 ± 0.261	-0.93 ± 0.238	0.6391	0.5468	0.6598
Mean Difference ± SE					.15 ±.31	-.19±.32	.14±.32
STUDY 0077: **7 p.m. Instantaneous Total Symptom Score (Excluding the Nasal Congestion Score, Mean ± Standard Error)**							
	(n=105)	**(n=98)**	**(n=101)**	**(n=105)**			
Baseline TSS	6.10 ± 0.302	6.11 ± 0.286	6.11 ± 0.286	6.86 ± 0.297			
Double-blind Treatment Period TSS	5.22 ± 0.283	5.41 ± 0.294	5.51 ± 0.274	6.37 ± 0.275			
Change from baseline in average 7 p.m. instantaneous TSS	**-1.17 ± 0.243**	**-1.04 ± 0.253**	**-1.21 ± 0.249**	**-0.40 ± 0.238**	**0.0168**	**0.0484**	**0.0116**
Mean Difference ± SE					-.77±.32	-.64±.33	-.82±.32

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

Table XIV.
Efficacy of Fexofenadine HCl 15 mg, 30 mg, and 60 mg vs. Placebo
DAILY CHANGE FROM BASELINE IN THE 7:00 p.m. REFLECTIVE TOTAL SYMPTOM SCORE (TSS) FOR THE DOUBLE-BLIND TREATMENT PERIOD, ITT Population [V1.225:91-93]

Efficacy Variable	TREATMENT GROUP (A) Fexo 15 mg qd	(B) Fexo 30 mg qd	(C) Fexo 60 mg qd	(D) Placebo	[1]P-value A-D	B-D	C-D
Change from Baseline in 8 a.m. instantaneous Total Symptom Score: (N, Mean ± Standard Error)							
DAY 2	223 -1.16 ± 0.183	207 -0.81 ± 0.190	210 -1.13 ± 0.188	228 -0.62 ± 0.181	**0.0326**	0.4544	**0.0445**
DAY 3	222 -1.07 ± 0.189	208 -0.96 ± 0.196	209 -1.22 ± 0.195	226 -0.94 ± 0.188	0.6277	0.9490	0.2988
DAY 4	222 -1.29 ± 0.191	208 -1.19 ± 0.198	211 -1.28 ± 0.196	226 -0.88 ± 0.190	0.1154	0.2427	0.1283
DAY 5	222 -1.08 ± 0.203	207 -1.55 ± 0.211	211 -1.24 ± 0.208	228 -0.72 ± 0.200	0.1935	**0.0037**	0.0676
DAY 6	221 -1.13 ±0.210	207 -1.20 ± 0.218	210 -1.45 ± 0.216	227 -0.81 ± 0.208	0.2588	0.1804	**0.0278**
DAY 7	218 -1.33 ± 0.210	203 -1.61 ± 0.218	210 -1.33 ± 0.214	224 -0.91 ± 0.207	0.1439	**0.0168**	0.1423
DAY 8	216 -1.68 ± 0.208	203 -1.36 ± 0.216	205 -1.58 ± 0.214	223 -1.11 ± 0.205	**0.0480**	0.4021	0.1098
DAY 9	214 -1.46 ± 0.220	201 -1.40 ± 0.229	205 -1.73 ± 0.225	221 -1.36 ± 0.218	0.7316	0.8887	0.2212
DAY 10	205 -1.94 ± 0.226	198 -1.74 ± 0.231	203 -1.72 ± 0.227	215 -1.62 ± 0.221	0.3030	0.6912	0.7574
DAY 11	209 -1.70 ± 0.222	200 -1.80 ± 0.228	205 -1.84 ± 0.224	215 -1.74 ± 0.219	0.9001	0.8461	0.7278
DAY 12	210 -1.95 ± 0.224	199 -1.78 ± 0.231	205 -1.98 ± 0.227	214 -1.98 ± 0.223	0.9167	0.5351	0.9996
DAY 13	211 -1.88 ± 0.228	201 -1.86 ± 0.235	203 -1.80 ± 0.232	212 -1.92 ± 0.228	0.9068	0.8694	0.7061
DAY 14	205 -2.09 ± 0.231	189 -2.20 ± 0.244	197 -1.83 ± 0.237	208 -2.00 ± 0.230	0.7928	0.5342	0.5949
DAY 15	103 -2.39 ± 0.362	85 -2.64 ± 0.400	95 -2.53 ± 0.384	104 -2.12 ± 0.367	0.5746	0.2932	0.4031
DAY 16	54 -2.06 ± 0.480	39 -3.06 ± 0.574	52 -2.55 ± 0.498	44 -1.38 ± 0.547	0.3311	**0.0258**	0.0932

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

8.2.4.2.1. Quality of Life (QOL) Analysis

Evaluation of the health outcome parameters in studies 0066/0077 combined indicated that at either of the 3 doses of fexofenadine, no significant effect on QOL compared to placebo was seen in pediatric patients. Clinical and demographic characteristics and baseline symptoms were very similar for most parameters in the 857 patients who had a baseline and at least 1 follow-up PRQLQ score (and who comprised the quality of life ITT population), with the exception of a statistically significant difference in weight ($p=0.0256$) and itchy, watery, red eyes at baseline ($p=0.0142$) [V1.255:26-28].

No statistically significant differences among treatments with respect to average change from baseline in the overall QOL score was noted ($p \geq 0.4298$) [V1.255:29-30]. With respect to the summary of change from baseline in PRQLQ domains, the fexofenadine 60 mg po bid group was found to be statistically superior to placebo with respect to average change from baseline in the 'other symptoms' domain of the PRQLQ ($p=0.0459$) [V1.255:32, 36]. There were no other statistically significant differences between treatments with respect to average change form baseline in individual PRQLQ domains [V1.255:32-35, 37].

8.2.4.3. Safety Analysis

Safety analysis for studies 0066/0077 consisted of an evaluation of adverse events, standard laboratory tests, 12-lead ECGs, and vital signs pre-and post-treatment in patients randomized into the study and 'exposed' to study medication (the safety evaluable population). Two hundred and twenty four (224) patients comprised the fexofenadine HCl 15 mg, 209 patients comprised the fexofenadine HCl 30 mg, 213 patients comprised the fexofenadine HCl 60 mg, and 229 patients comprised the placebo group safety evaluable populations [V1.225:63]. In this trial, the safety evaluable population was almost the same as the ITT population with the addition of 1 patient each to the fexofenadine 15 mg, 30 mg, and 60 mg groups, respectively.

8.2.4.3.1. Demographics of the Exposed Population

Demographics of the exposed population was almost the same as that of the ITT population that was presented in section 8.1.4.1 ('Patient Demographics') of the medical officer review of NDA 20-872 and is re-summarized in Table IX below. All 4 treatment groups were similar in baseline characteristics, with the exception of a statistically significant difference in weight between the 4 treatment groups.

Table IX. Patient Demographics for the ITT Population [V1.225:65]:

Variable	Fexofenadine 15 mg (n=223)	Fexofenadine 30 mg (n=208)	Fexofenadine 60 mg (n=212)	Placebo (n=229)	P-Value
Gender: (n, (%))					
Male	140 (63%)	123 (59%)	112 (53%)	139 (35%)	
Female	83 (37.2%)	85 (41%)	100 (47%)	90 (39%)	.1773[1]
Race: (n, (%))					
Caucasian	196 (88%)	180 (87%)	185 (87%)	187 (82%)	
Black	18 (8%)	15 (8%)	19 (9%)	28 (12%)	
Asian	5 (2%)	2 (1%)	3 (1%)	7 (3%)	
Multiracial	4 (2%)	10 (5%)	5 (2%)	7 (3%)	.3743
Age: (yrs)					
Mean ± SD	9.14 ± 1.63	9.09 ± 1.51	9.04 ± 1.65	9.24 ± 1.55	
Range	5-12	5-12	5-11	6-11	.5954
Weight: (kg)					
Mean ± SD	36.68 ± 11.22	35.01 ± 11.02	34.39 ± 10.27	36.56 ± 11.13	
Range	18.6-93.0	17.7-84.8 kg	18.1-72.6 kg	21.0-77.1	.0334
Height: (cm)					
Mean ± SD	138.55 ± 12.25	137.49 ± 11.01	137.25 ± 11.41	138.81 ± 11.30	
Range	106.7-167.6	105.4-166.4	112-170.2	106.7-167.6	.3192

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

8.2.4.3.2. Duration of Patient Exposure/Patient Disposition

Also reiterated in Section 8.1.4.1 of the NDA review, the mean duration of double-blind exposure to study treatment for the safety population was 14.49 days (± 2 days) for all 4 treatment groups. The range of duration of exposure was 2-21 days for the placebo group (n=229 patients), 2-21 days for the fexofenadine HCl 15 mg group (n=223), 1-18 days for the fexofenadine HCl 30 mg group (n=209), and 3-19 days for the fexofenadine HCl 60 mg group (n=213).

8.2.4.4. Adverse Events (AE's)

The overall incidence of all 'treatment emergent' adverse events (i.e. those AE's occurring during treatment) were generally similar for the 4 treatment groups (including placebo) and was ~ 35% for all AEs combined [V1.225:99-102, V1.244:51-54]. As seen in adult study 3081, the most frequent adverse event for all 4 treatment groups consisted of headache (with an incidence of 8.0% in the fexofenadine HCl 15 mg group, an incidence of 7.2% in the fexofenadine HCl 30 mg group, an incidence of 9.4% in the fexofenadine HCl 60 mg group, and an incidence of 6.6% in the placebo group), followed by upper respiratory tract infection (an incidence of 4.9% in the fexofenadine HCl 15 mg group, an incidence of 4.3% in the fexofenadine HCl 30 mg group, an incidence of 1.4% in the fexofenadine HCl 60 mg group, and an incidence of 1.7% in the placebo group) [V1.225:99]. With the minor exception of a progressively slightly higher incidence of wheezing, injury accident, and vomiting across the 3 active treatment groups, no dose response for AE frequency was noted across treatment groups. Of note, the incidence of somnolence was very low for all 4 treatment groups (fexofenadine 15 mg: 0%, 30 mg: 0.5%, 60 mg: 0%, and placebo: 0.9% [V1.225:100].

Compared with the labeling for ALLEGRA™ (fexofenadine hydrochloride 60 mg capsules, n=679), AEs in the pediatric population in studies 0066/0077 combined which occurred at a ≥ 1% frequency and which were more common than in the placebo group consisted of coughing, epistaxis, wheezing, injury accident, and vomiting, n=646 total patients).

A summary of all reported adverse events ('treatment emergent') for placebo treatment, as compared to the fexofenadine HCl 15 mg, fexofenadine HCl 30 mg, fexofenadine HCl 60 mg treatments in studies 0066/0077 combined, is presented in Table X.

Table X. Adverse Event (AE) Frequency:
AE's ≥ 1% for ALLEGRA (Fexofenadine 15 mg, 30 mg, and 60 mg bid vs. Placebo), by Organ System and Preferred Term; Safety Evaluable Population [V1.225:99-102, 244:51-54]

BODY SYSTEM	Preferred Term	Fexo 15 mg (n=224) n (%)	Fexo 30 mg (n=209) n (%)	Fexo 60 mg (n=213) n (%)	Placebo (n=229) n (%)
All Systems	Any AE	79 (35.3%)	77 (36.8%)	74 (34.7%)	83 (36.2%)
Neurologic	**Headache**	**18 (8.0%)**	**15 (7.2%)**	**20 (9.4%)**	**15 (6.6%)**
Respiratory	Upper respiratory tract infection	11 (4.9%)	9 (4.3%)	3 (1.4%)	4 (1.7%)
	Pharyngitis	9 (4.0%)	6 (2.9%)	6 (2.8%)	9 (3.9%)
	Coughing	3 (1.3%)	8 (3.8%)	5 (2.3%)	3 (1.3%)
	Epistaxis	4 (1.8%)	3 (1.4%)	3 (1.4%)	3 (1.3%)
	Wheezing	0 (0.0%)	3 (1.4%)	4 (1.9%)	1 (0.4%)
Body as a Whole-General	Injury Accident	4 (1.8%)	6 (2.9%)	9 (4.2%)	3 (1.3%)
	Abdominal Pain	6 (2.7%)	4 (1.9%)	5 (2.3%)	8 (3.5%)
	Fever	4 (1.8%)	5 (2.4%)	4 (1.9%)	2 (0.9%)
	Pain	0 (0.0%)	5 (2.4%)	4 (1.9%)	1 (0.4%)
	Chest Pain	1 (0.4%)	3 (1.4%)	2 (0.9%)	0 (0.0%)
Gastrointestinal	Dyspepsia	2 (0.9%)	4 (1.9%)	1 (0.5%)	0 (0.0%)
	Tooth Disorder	3 (1.3%)	2 (1.0%)	2 (0.9%)	1 (0.4%)
	Nausea	1 (0.4%)	3 (1.4%)	2 (0.9%)	0 (0.0%)
	Diarrhea	2 (0.9%)	3 (1.4%)	0 (0.0%)	1 (0.4%)
	Vomiting	1 (0.4%)	1 (0.5%)	3 (1.4%)	2 (0.9%)
Hearing and Vestibular	Otitis media	1 (0.4%)	5 (2.4%)	2 (0.9%)	0 (0.0%)
	Ear Disorder (not otherwise specified)	1 (0.4%)	2 (1.0%)	1 (0.5%)	1 (0.4%)
Infectious Disease	Infection viral	2 (0.9%)	1 (0.5%)	3 (1.4%)	0 (0.0%)
	Influenza	2 (0.9%)	2 (1.0%)	1 (0.5%)	6 (2.6%)
Dermatologic	Rash	2 (0.9%)	3 (1.4%)	3 (1.4%)	1 (0.4%)

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

8.2.4.4.2. Cardiac Adverse Events

Cardiovascular adverse events in the pediatric Allegra bid SAR safety database (studies 0066/0077) for patients 6-11 years of age were specifically recorded under the 'cardiovascular' category for the clinical endpoints of arrhythmia, ventricular arrhythmia, ECG abnormal, and tachycardia; however the additional adverse events of: dizziness and chest pain were added to the list of cardiovascular adverse events by the medical reviewer even though AE

frequencies for these 2 categories were < 1% for across all 4 treatment groups (with the exception of a 1.4% incidence of chest pain in the fexofenadine 30 mg group which was not seen in the other 2 fexofenadine treatment groups) [V1.225:100]. The incidence of the above 4 cardiovascular adverse events was < 1% across all 4 treatment groups, and generally, the incidence was between 0-0.5% for the 4 treatment groups [V1.225:101].

A total of 4 patients experienced cardiovascular adverse events, which related specifically to cardiac arrhythmia or cardiac conduction disturbance (2 patients in the fexofenadine 15 mg treatment group and 1 patient each, respectively, in the fexofenadine 30 mg and 60 mg groups) [V1.225:109-110]. One patient in the fexofenadine 15 mg group (# 900-006)—a 7 year old male, was found to have a final visit (visit 4) ECG that was interpreted as showing left anterior hemiblock (LAH), but on retest 3 days later was not found to have LAH [V1.225:100]. A second patient in the fexofenadine 15 mg group (# 916-004)—a 9 year old male, was noted on his final visit ECG to have normal sinus rhythm with occasional unifocal PVCs, which were interpreted as being clinically irrelevant but met criteria as a QT_c outlier [V1.225:109]. The patient was asymptomatic and on retest 5 days later, the ECG no longer noted to show PVCs [V1.225:110]. A patient in the fexofenadine 30 mg group (# 900-021)—a 9 year old female developed tachycardia to 160 beats/minute secondary to β-agonist therapy for asthma exacerbation [V1.225:110]. And finally, one patient in the fexofenadine 60 mg group (# 925-018)—a 9 year old female, reported that her heart "skipped a beat" while on 'some physical apparatus at school' though her ECG was found to be within normal limits [V1.225:110]. No patients in the placebo treatment group were noted to have any cardiovascular adverse events.

Of note, sudden cardiac death were not specifically recorded or tabulated in the cardiac adverse event database by the sponsor.

Means and mean changes from baseline to endstudy in the ECG parameters: PR interval, QT interval, QT_c interval, QRS interval, and RR interval were presented by the sponsor [V1.225:130] and failed to reveal statistically significant differences between the 4 treatment groups with respect to mean change from baseline to endstudy for any of the ECG parameters [V1.225:130]. Of the 875 safety evaluable patients, 855 patients had ECGs performed at the final visit or early termination visit. Of these 855 patients, 7 patients in the placebo group (7/221 or 3.2%), and 15 patients in the 3 fexofenadine groups (15/634 or 2.4%) had QT_c intervals at the final visit/early termination visit that met criteria as outliers [V1.225:131]. No dose response with respect to fexofenadine dose was seen with regard to the number patients with a QT_c outlier or the degree of QT_c prolongation (in fact, the fexofenadine 60 mg bid dose had the lowest number of outliers) [V1.225:131].

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 amongst the 4 treatment groups (of note: a

slightly greater incidence of mild AEs was seen in the 3 fexofenadine groups as compared to placebo treatment [V1.225:104-105, V1.244:59-66].

8.2.4.5. Adverse Event Stratification by Duration of Treatment

Again, although adverse event stratification by duration of treatment was not performed by the sponsor, given the study's entire duration of 2 weeks, performance of AE stratification by duration of treatment would not be deemed clinically relevant for an H_1 antihistamine whose onset of action is well within 12 hours. Many of the adverse events described in the safety database for studies 0066/0077 combined are ones which would not be anticipated to occur with drug accumulation (i.e. liver function abnormalities) but rather AEs related to the drug's direct pharmacologic activity or due to an idiosyncratic (unpredictable) reaction(s).

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

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

8.2.4.7. Patient Discontinuation due to Adverse Events

A total of 5 patients treated with either of the 3 doses of fexofenadine HCl (1 fexofenadine 15 mg patient, 2 fexofenadine 30 mg patients, and 1 fexofenadine 60 mg patient; 0.01%) and 5 patients treated with placebo (0.02%) discontinued treatment prematurely due to adverse events [V1.225:107, V1.244:264]. On review of the adverse event summaries by the medical reviewer, none of the patients in the fexofenadine treatment groups appeared to have discontinued medication due to a drug related event—the reasons for discontinuation were upper respiratory tract infection, upper respiratory congestion, otitis media, ear disorder (not otherwise specified), and asthma [V1.225:108, V1.244:264, 270-272]. Similar reasons for study medication discontinuation were noted in the 5 placebo group patients (i.e. asthma in 3 patients, sinusitis in 2 patients) [V1.225:108, V1.244:264, 270-272].

8.2.4.8. Serious Adverse Events and Death

No deaths were reported during this SAR trial for any of the 4 treatment groups. The sponsor's definition of [2]serious treatment emergent adverse events was modified somewhat in these 2 studies (similar to that specified in study 3081) to include, in addition to the standard regulatory criteria for a 'serious' adverse event (listed in the footnote below), additional criteria of: (1) an adverse event which resulted in withdrawal from the study, (2) temporary interruption of study medication, or (3) treatment with a counteractive medication [V1.225:105].

[2] 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.

Reviewer's Note: The addition of the latter 3 criteria to the definition of AEs, especially the 'treatment with a counteractive medication' criteria increased the number of serious AEs, though the majority of these cases occurred in patients treated with a counteractive medication (usually for treatment of headache [V1.225:109, V1.244:68, 70-72, 229-262]. When the 'treated with counteractive medication' cases were removed as serious AE criteria, the frequency of patients experiencing a treatment-related serious AE other than patient discontinuation of medication decreased to 1 patient in the fexofenadine 30 mg group (patient # PJST0900-0021: a 9 year old female in protocol 0077 with a history of allergic rhinitis and mild asthma was discontinued from treatment after 14 days and hospitalized for an asthma exacerbation after exposure to seasonal allergens while camping; the AE was not deemed to be related to study medication by the principal investigator) [V1.225:107, V1.244:270].

8.2.4.9. Laboratory Test Results

Laboratory tests performed during visit 1 (pre-randomization) and visit 4 (completion of treatment) of the study at several sites (complete laboratory analysis was not required at visit 4) and which consisted of a complete blood count with differential count, blood chemistries (to include cholesterol, triglycerides, total globulin and albumin:globulin ratio), liver function tests (SGOT (AST), SGPT (ALT), alkaline phosphatase, total protein, albumin, and total bilirubin, and LDH), urinalysis (to include screening for drugs of abuse), and serum pregnancy test (for all women) did not reveal any unexpected abnormalities in fexofenadine HCl or placebo treated patients. The effects of the 4 treatments on laboratory parameters were analyzed (with the exception of serum pregnancy tests) using average baseline, endstudy and change from baseline laboratory values, along with a tabulation of outlier values for individual patients in order to identify potentially clinically important changes [V1.225:111]. The sponsor's criteria for an abnormal laboratory value or outlier was a value outside the limits of normal for that parameter, as defined by the sponsor's laboratory outlier criteria [V1.225:124-125, V1.244:276-308]. These criteria were the same as those for evaluation of laboratory outliers in the adult SAR trials [V1.225:123, V1.244:276-308]. Summary statistics for each laboratory value was computed using an ANOVA model with adjustment for site as had been done in previous NDA submissions (e.g. ALLEGRA-D, NDA 20-786) [V1/225:278]. Likewise shift tables were performed in this study as a method of presenting laboratory data [V1.225:119].

No clinically meaningful change from baseline values in any laboratory parameter was noted, however statistically significant differences were seen for the laboratory parameters of WBC, lymphocyte count, chloride, and magnesium [V1.225:115, 117, V1.244:379-384]. With the exception of a slight increase in serum chloride with increasing fexofenadine dose, no dose response was seen in either of the other 3 laboratory parameters with increasing fexofenadine dose.

Evaluation of shift tables (having both baseline and endstudy values) for each laboratory parameter failed to reveal any trends and results were overall unremarkable across the 4 treatment arms [V1.225:120-123, V1.244:318-377].

Evaluation of individual outliers (marked abnormalities in laboratory parameters, as based on a set percentage of the lower/higher limit of normal for a given laboratory value and a set decrease/increase from the baseline value [V1.123-127]) for each laboratory test showed no significant numerical difference in the number of patients with outliers between the 4 treatment groups, nor any obvious dose-related trends for laboratory outlier trends. These data are summarized in Table 40 of the study report of combined trials 0066/0077 and Appendix K2 [V1.225:126-127, V1.244:311-316]. A slightly greater number of 'low' outliers was noted for WBC, lymphocyte, and serum glucose parameters (seen in all 4 treatment groups) [V1.225:126, 127] and conversely, a slightly greater number of 'high' outliers was noted across all 4 treatment arms for the laboratory parameters of hematocrit and triglycerides [V1.225:126, 127].

Two 'low outlier' values worthy of noting were reported in 1 fexofenadine 15 mg patient (# 921-0009; baseline WBC=2.98 x $10^3/\mu L$, post-baseline WBC=0.71 x $10^3/\mu L$) and in 1 fexofenadine 30 mg patient (# 860-0018; baseline WBC=1.65 x $10^3/\mu L$, post-baseline WBC=0.71 x $10^3/\mu L$) [V1.244:314]. Both of these 2 patients already manifested WBC at the lower limit of normal at baseline (not clear if they had an ongoing viral infection). No additional information was provided by the sponsor.

8.2.4.10. Vital Signs and Weight

Vital signs (blood pressure (systolic and diastolic), and heart rate were monitored in this study at baseline and the final study visit (visit 4). Review of the mean change from baseline in all vital signs for the safety evaluable population revealed no statistically significant change at final visit from baseline between the 4 treatment groups [V1.225:127-129]. These data are summarized in Table 41 of the study report for trials 0066/0077 combined [V1.225:128].

Reviewer's Note: With regard to safety data, review of the disqualified investigator's (Dr. Edwards, study site PJST0854) safety data from the total safety listings failed to detect any inconsistencies or abnormalities that might be potentially noted in the adverse event, laboratory test, vital sign, or ECG listings that differed from those seen at the other study sites for study 0066. Hence, safety data reviewed for Dr. Edward's site appeared to be consistent with all other safety data, with normal variability and similar AE frequencies

and outliers for labs/vital signs [Correspondence from HMR to FDA, Regarding Dr. Edward's Study Site, Wayne F. Vallee, R. Ph., HMR, U.S. Drug Regulatory Affairs, 08/13/98].

8.2.4.4. Pharmacokinetic Studies

Population pharmacokinetic studies of fexofenadine HCl in pediatric patients age 6-11 years with SAR was performed in order to characterize this population PK and to determine the impact of covariates on PK parameter estimates for fexofenadine HCl. Re-iterating the study design, patients had blood samples collected on Visit 3 (week 3) and Visit 4 (week 4). Plasma fexofenadine levels were analyzed for fexofenadine (MDL 16,455) using with an assay sensitivity of ng/mL [V1.63:338-341].

A total of 730 fexofenadine plasma samples were collected from 593 patients (from the 3 fexofenadine treatment groups) all of whom were included in the population PK analysis. Demographic data for all participating fexofenadine patients were analyzed (Table 8-49, [V1.63:299, Amendment to NDA 20-872, Wayne F. Vallee, R.Ph., HMR, U.S. Drug Regulatory Affairs, 11/17/98] and revealed very similar patient demographics for the data set used in the NON-MEM (nonlinear mixed-effects modeling) population PK analysis as compared to the full data set. Based upon population PK modeling results, the PK of fexofenadine in pediatric SAR patients appeared to be affected by patient demographics. The population PK model best describing the data was a 2-compartment oral model with apparent oral clearance (Cl_{po}/F) based upon height (which was different from the adult model) [V1.63:341]. There was no identifiable gender, race or dose differences in the PK of fexofenadine.

Results of this analysis in the pediatric population (which differed from results seen in adult population PK for fexofenadine showed the following:

1. an apparent oral clearance (Cl_{po}/F (L/h)) of: 41.3 L/h (for a 135 cm patient)
   9.306 L/h/cm
2. an apparent volume of distribution (V2/F) of: 79.3 L
3. an inter-compartmental clearance (L/h) of: 10.3
4. a peripheral compartment model (L) of: 270
5. an absorption rate constant (1/h) of: K_a=0.356
6. an inter-subject variance (ω^2) of: CV=37.1%
7. a residual variance (σ^2) of: CV=73.2%

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

While the results of combined studies 0066 and 0077 were not able to support efficacy of ALLEGRA in the pediatric population for the treatment of SAR symptoms and it is not entirely clear why data in study 0066 ('failed efficacy trial') were so different from those in 0077 except that study 0066 displayed a

large placebo response, along with the difficulty in demonstrating efficacy in the treatment of SAR in the pediatric population is well known and has been seen in other trials of similar design, separation of the combined study into its individual components: 0077 and 0066 revealed that one of the studies-0077, did support the safety of twice daily ALLEGRA in the pediatric population at either the fexofenadine HCl 15, 30, or 60 mg dose for the treatment of symptoms of SAR (excluding nasal congestion) in children 5 years of age and older (children age 5-12 years received fexofenadine in these studies). The more effective doses in this study in terms of the primary efficacy endpoint and many of the secondary efficacy endpoints were either the 15 mg or the 60 mg doses, which demonstrated a greater numerical and more consistent improvement in the various efficacy parameters evaluating SAR symptoms and demonstrated improvement in a greater number of these parameters than did the 30 mg dose.

For the end-of dosing interval, perhaps the more clinically relevant efficacy endpoint for an antihistamine, all 3 doses of ALLEGRA in study 0077 demonstrated a statistically significant improvement compared to placebo.

Overall, ALLEGRA tablets were safe and well-tolerated given once a day, at doses of 15 mg, 30 mg, and 60 mg po bid. No serious related adverse events occurred in patients treated with ALLEGRA tablets, nor were any deaths reported. No QT_c interval prolongation or significant ECG findings were seen across treatment arms. Similar to placebo treatment, headache was the most common adverse event, followed by upper respiratory tract infection. No abnormal trends or worrisome laboratory findings were noted in studies 0066/0077. No significant changes in vital signs were noted at the final study visit in safety evaluable patients.

Summary:

Based on numerical trends in combined pediatric trials 0066/0077 and trial 0066, and statistically significant results noted in pediatric SAR trial 0077, ALLEGRA tablets 15 mg, 30 mg, or 60 mg bid demonstrated adequate evidence of efficacy and safety compared with placebo, for the twice daily treatment of SAR symptoms in children 6-11 years of age. However, as discussed in the 'Clinical Background' section: Human Pharmacology, pharmacokinetics, pharmacodynamics' (section 6.0), based on PK data in children, the fexofenadine 30 mg dose demonstrated a plasma fexofenadine concentration (AUC and C_{max}) most comparable to that of 60 mg in adult and adolescent patients. Based on these data, the 30 mg bid dose appears the most appropriate dose for treatment of SAR symptoms in children 6-11 years of age.

Table 3. Table of Study Procedures

Study Procedure	Visit			
	1 (Entry)	2 (Randomization)	3 (Interim)	4 (Final or Early Discontinuation)
Informed Consent	X			
Demographics	X			
Medical History	X			
Skin Test	X			
Entrance Criteria	X	X		
Single-blind Unit Dose Card Dispensed	X			
Physical Exam (including vital signs)	X			X
Clinical Labs (including serum pregnancy test for all post-menarchal females)	X			X*
Medication History	X			
Fexofenadine Blood Sample Collection			X†	X*
12-Lead ECG		X		X*
Qualifying SAR Assessment for Single-blind Placebo Lead-In	X			
Qualifying SAR Assessment for Double-blind Medication		X		
Daily Symptom Diary Issued	X	X	X	
Adverse Event and Concomitant Medication Diary Issued	X	X	X	
Double-Blind Unit Dose Card Dispensed		X	X	
Assess Use of Concomitant Medications		X	X	X
Collect Unit Dose Card and Diaries		X	X	X
Determine Study Drug Compliance		X	X	X
Adverse Event Assessment		X	X	X‡
Quality of Life Assessment	X	X	X	X

* Not required if patient had not received double-blind study medication. Could be obtained for safety concerns if determined necessary by investigator. Blood sample and ECG obtained 1 to 3 hours post final AM dose.
† Designated study sites only (6 to 11 hours post AM dose).
‡ Adverse events were to be reported if experienced within 72 hours after last dose of study medication.

CHRONIC IDIOPATHIC URTICARIA IN ADULT PATIENTS (BID Dosing, Pivotal Trial (0039):

8.3. Protocol No. PJPR0039: A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 4 dosage strengths of fexofenadine HCl 20 mg, 60 mg, 120 mg, and 240 mg bid in adult patients (ages 12-65 years) in the treatment of chronic idiopathic urticaria.

Principal Investigator: None, multi-center study.

Participating Centers: 37 U.S. and Canadian centers

8.3.1. Objective

The primary objective of this study was to investigate the safety and efficacy of fexofenadine HCl at 20 mg po bid, 60 mg po bid, 120 mg po bid, and 240 mg po bid, compared to placebo treatment in patients age 12-65 years for the treatment of symptoms of chronic idiopathic urticaria (CIU).

A secondary objective of the study was to characterize the population pharmacokinetics of fexofenadine bid in adult patients with CIU and assess the quality of life and work and classroom productivity.

8.3.2. Study Design

The basic study design for study PJPR0039 was almost identical to that of the adult and pediatric SAR trials, albeit with modifications in the study protocol for the CIU indication. This was a phase III, multi-center, randomized, double-blind, parallel group, with a 24-hour single-blind placebo lead-in, safety and efficacy study of the treatment of fexofenadine HCl 20 mg po bid, 60 mg po bid, 120 mg po bid, and 240 mg po bid, vs. placebo in at least 400 randomized adult CIU patients (468 actually randomized). The study consisted of 3 or 4 patient visits: 2 screening visits (visits 1 and 1a (a 2nd opportunity to qualify for randomization; weeks 1 and 2), and 2 treatment visits (visits 3 and 4; 15 ± 2 days post-treatment and 30 ± 4 days post-treatment/early termination visit) such that patients received study medication for approximately 4 weeks. A table of study procedures is provided in Appendix 1 [V1.170:49, 192].

8.3.3. Protocol

8.3.3.1.a. Population: Male or female adult patients, 12-65 years of age, with a diagnosis of CIU (made or confirmed by the investigator and documented in the case report form) [V1.170:33, 175].

(A) Inclusion Criteria [V1.170:33-34, 175]:

1. History or urticarial wheals (hives) for at least 3 days/week for the 6 consecutive weeks prior to Visit 1 (or Visit 1a).
2. At visit 1 (or Visit 1a) a 12 hour reflective total symptom score (TSS) ≥ 3.

(II) Exclusion Criteria [V1.170:34-35, 176-177]:

1. A diagnosis of the following as a primary diagnosis: physical urticaria (e.g. cold, heat, sun-induced, pressure or dermatographism), cholinergic urticaria, urticaria due to medications, insect bites, food, or other known etiology, hereditary angioedema or known C_1 immunodeficiency, urticaria associated with an underlying disease (e.g. neoplasm, Hodgkin's disease, vasculitits, hyperthyroidism, clinical thyroiditis, rheumatoid arthritis, complement abnormalities, SLE, hepatitis, mast cell disease, mixed connective tissue syndrome, mononucleosis, or other acute or chronic infections). Of note, dermatographism associated with chronic urticaria would not have excluded the patient from the study.
2. Any disease state or surgery known to affect the GI absorption of drugs.
3. Known history or lack of a positive response to an antihistamine for urticaria.
4. Urine drug screen positive for recreational drugs: cocaine, phencyclidine hydrochloride, or cannabinoids.

Reviewer's Note: The clinical criteria for inclusion/exclusion for this CIU trial were deemed appropriate by the medical officer.

(III). Concurrent Medication Restrictions [V1.170:36, 178-179]: The list of medications to be discontinued within the indicated time periods prior to visit 1, and not allowed for the duration of the study:

Medication	Time Discontinued Prior to Visit 1
1. Parenteral corticosteroids (IM, Intra-articular)	≥ 90 days
2. Oral corticosteroids	≥ 30 days
3. Topical corticosteroids	≥ 14 days
4. Inhaled corticosteroids	≥ 30 days
5. Short-acting IV push corticosteroids (e.g. Solu-Cortef, Solumedrol)	≥ 14 days
6. Astemizole	≥ 60 days

Medication	Time Discontinued Prior to Visit 1
7. Loratidine	≥ 7 days
8. Cetirizine	≥ 72 hours
9. Terfenadine	≥ 72 hours
10. Fexofenadine	≥ 72 hours
11. Hydroxyzine	≥ 72 hours
12. Ebastine	≥ 72 hours
13. Azatadine	≥ 72 hours
14. Ketotifen	≥ 14 days
15. Nedocromil or cromolyn	≥ 14 days
16. H_2 antagonists	≥ 72 hours
17. Other H_1 antagonists	≥ 24 hours
18. Cough/cold preparations	≥ 24 hours
19. Sleep aids	≥ 24 hours
20. Antacids	≥ 24 hours
21. Sedatives or hypnotics	≥ 72 hours
22. Tricyclic antidepressants	≥ 21 days
23. Phenothiazines, benzodiazepines	≥ 21 days
24. Oral and parenteral macrolide antibiotics (erythromycin, clarithromycin, troleandomycin, azithromycin)	≥ 30 days
25. Oral/parenteral ketoconazole, fluconazole, itraconazole, miconazole, or metronidiazole	≥ 90 days
26. Aspirin (except low dose: ≤ 325 mg qd), NSAIDS, and narcotic analgesics	≥ 72 hours
27. Calcium channel blockers	≥ 24 hours
28. β-agonsits	≥ 24 hours
29. Methylxanthines (e.g. theophylline)	≥ 7 days

8.3.3.1.b. Procedure

(III) Screening Visit (Visit 1) [V1.170:40-42, 46-48, 187-189]:

The procedure for Visit 1 was similar to those performed in the other studies of ALLEGRA in this NDA, with a complete medical history, physical examination (including vital signs), laboratory and urine evaluation, assessment of adverse events performed at the screening visit. 12-lead ECGs were not performed in this study. For this CIU study, confirmation of the patient's diagnosis of CIU by the PI was also ascertained and documented. As per the inclusion criteria, patients were required to have ≥ 1 wheal present at the time of randomization (score of ≥ 1), and at least a moderate severity of pruritus (score of ≥ 2), for a total symptom score (TSS) ≥ 3. The TSS was defined as a composite score of the number of wheals (0-4 scale) and the pruritus score (scale 0-4), with

equal weight being given to both endpoints. The **patient self-rated symptoms** (which were collected twice daily, ~ 12 hours apart) and rating scale is listed below:

Wheal Rating Scale (reflective; i.e. over previous 12 hours):

Scale	Rating
0	None
1	1-5 wheals (hives)
2	6-15 wheals
3	16-25 wheals
4	> 25 wheals

Pruritus Rating Scale (reflective; i.e. over previous 12 hours):

Scale	Rating
0	**None** (no itching present)
1	**Mild** (minor irritation, hardly noticeable; not annoying or troublesome
2	**Moderate** (annoying and troublesome, may have interfered somewhat with normal daily activity and/or sleep)
3	**Severe** (very annoying and troublesome, substantially interfered with normal daily activity and/or sleep)
4	**Very severe** (warranted a visit to the physician)

In addition, at the screening visit, patients were asked to assess the interference of wheals (hives) with sleep (recorded in the 7:00 a.m. 12 hour reflective assessment) and the interference of wheals (hives) with normal daily activities (recorded in the 7:00 p.m. 12 hour reflective assessment) [V1.170:41] using the following scales:

Interference of skin condition with sleep scale:
(reflective; i.e. over previous 12 hours)

Scale	Rating
0	None
1	Mild
2	Moderate
3	Severe

Interference of skin condition with normal daily activities scale:
(reflective; i.e. over previous 12 hours)

Scale	Rating
0	None
1	Mild
2	Moderate
3	Severe