At all visits, including Visit 1, **the investigator** was also to assess patients':
(1) # of wheals,
(2) longest diameter of wheals, using the following scale:

Scale	Rating
0	Absent (No wheals)
1	Small (<0.5 cm in diameter)
2	Medium (0.5-2.0 cm in diameter)
3	Large (> 2.0 cm-4.0 cm in diameter)
4	Giant (> 4.0 cm in diameter)

(3) Intensity of erythema on average, using the following scale:

Scale	Rating
0	Absent
1	Slight/pale
2	Definite/red
3	Extreme/bright red

(4) Extent of skin area involved, using the following scale:

Scale	Rating
0	None (wheals absent)
1	Slight (relatively small amt of body involved: 1-10%)
2	Moderate (substantial amt of body involved: 11-30%)
3	Severe (large amt of body involved: 31-50%)
4	Very severe (> 50% of body involved)

Finally, at each visit, including Visit 1, patients were asked to complete the Dermatology Quality of Life Index (DLQI) questionnaire and the Work Productivity Activity Index (WPAI) questionnaire [V1.170:46].

Patients who met all study entrance criteria then underwent the following procedures: randomization to treatment with assignment of a treatment assignment number (TAN) and dispensation of study medication (1st doses were single-blind placebo, all rest were double-blind study medication), the 1st dose of which was to be taken in the evening of Visit 1 at 7:00 p.m. ± 1 hour, and thereafter to take study medication twice daily at 7:00 a.m. ± 1 hour and 7:00 p.m. ± 1 hour [V1.170:47].

After the single-blind placebo lead in, the 4 treatments that patients were randomized to consisted of the following [V1.170:37-38, 237-239]:

Treatment	Dosing
Placebo po bid	1, 180 mg size placebo tablet + 1, 120 mg size placebo tablet + 1, 60 mg size placebo tablet + 1, 20 mg size placebo tablet.
Fexofenadine 20 mg po bid	1, 180 mg size placebo tablet + 1, 120 mg size placebo tablet + 1, 60 mg size placebo tablet + **1, 20 mg size fexofenadine tablet.**
Fexofenadine 60 mg po bid	1, 180 mg size placebo tablet + 1, 120 mg size placebo tablet + **1, 60 mg size fexofenadine tablet +** 1, 20 mg size placebo tablet.
Fexofenadine 120 mg po bid	1, 180 mg size placebo tablet + **1, 120 mg size fexofenadine tablet +** 1, 60 mg size placebo tablet + 1, 20 mg size placebo tablet.
Fexofenadine 240 mg po bid	**1, 180 mg size fexofenadine tablet +** 1, 120 mg size placebo tablet + 1, 60 mg size placebo tablet + 1, 20 mg size placebo tablet.

A quadruple dummy blinding method was instituted in this study, as all placebo tablets were identical in appearance to their respective active drug. Hence, all patients were to take 4 tablets at each dosing, for a total of 8 tablets taken daily (bid dosing).

In addition to completing diaries where urticaria symptoms were rated, patients were also asked to complete the Dermatology Quality of Life Index (DLQI) questionnaire and the Work Productivity Activity Index (WPAI) questionnaire at Visit 1 (and all subsequent visits) [V1.170:46]. Patients were to return to clinic in 15 ± 2 days for Visit 2.

(IV) Visit 1a (24 hours-14 days after Visit 1) [V1.170:47-48, 189-190]:

If a patient met all entrance criteria with the exception of symptom assessment criteria and/or criteria for use of prohibited medications prior to Visit 1, the patient was instructed to return between 24 hours and 14 days following Visit 1 for Visit 1a where eligibility for study entry was reassessed (same symptom score criteria required for study entry as in Visit 1).

(V) Visit 2 (15 ± 2 days after Visit 1 or 1a) [V1.170:48, 190-191]:

The procedures for Visit 2 were essentially the same as for Visit 1/1a (with the exception of the requirement to meet inclusion/exclusion criteria. During visit 2 of the study, random plasma fexofenadine levels were assessed. The time of the blood sample collection and the time of the last dose of study medication were recorded. Compliance with study medication was evaluated and patients whose compliance with study medication was not between 90-110% for the single-blind lead in period were further questioned for possible discontinuation from the study [V1.170:48, 190].

(VI) Visit 3 (Final visit, 15 ± 2 days after Visit 2) [V1.170:48, 191]:

Procedures for Visit 3 were essentially the same as for Visit 2. Again, random plasma fexofenadine levels were measured.

Reviewer's Note: Unlike the adult and pediatric SAR studies, indigenous pollen counts were not collected or noted for this CIU study, which is appropriate given that not all cases of CIU are due to allergens.

8.3.3.2. Clinical Endpoints

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

Primary Efficacy Variables [V1.170:58, 198]:

(1) The change from baseline in the mean reflective pruritus score (MPS) over the 4 week double-blind treatment period.

Reviewer's Note: The range of scores that could be achieved for the primary efficacy endpoint ranged from 0-4 [V1.170:34].

Since the single-blind placebo was administered the evening of Day 1 and the morning of Day 2, baseline symptom scores were defined using the 7:00 a.m. and 7:00 p.m. scores obtained on Day 2. Double-blind treatment scores were collected ~~on Day 3 through the morning of the final visit (or early termination visit)~~. The MPS (also MNW, MTSS; see below in 'Secondary Efficacy ~~Variables' section for definition) was not computed on the day of the final visit~~ since only a 7:00 a.m. score was recorded, hence the daily MPS was computed using the 7:00 a.m. and 7:00 p.m. 12 hour 'reflective' pruritus scores performed on each ~~day of the study beginning~~ on the day following Visit 1 or Visit 1a [V1.170:56]. Missing symptom scores were handled such that if any of the individual symptoms used in calculating the MPS were missing, missing data were not imputed and the patient was excluded from the ITT analysis (of note, this also excluded patients for secondary efficacy parameters in which MPS was used to calculate a symptom score, i.e. MTSS) [V1.170:60].

Secondary Efficacy Variables [V1.170:58, 198-199]:

(1) Change from baseline in the patient's reflective self-rated average mean number of wheals (MNW) score over the 4 week double-blind treatment period,
(2) Change from baseline in the patient's reflective self-rated average mean total symptom score (MTSS=the sum of the MPS + MNW score) over the 4 week double-blind treatment period,
(3) Change from baseline in the patient's self-rated average 7:00 a.m. 12 hour reflective mean number of wheals (MNW) score over the 4 week double-blind treatment period,

(4) Change from baseline in the patient's self-rated average 7:00 a.m. 12 hour reflective mean pruritus (MPS) score over the 4 week double-blind treatment period,
(5) Change from baseline in the patient's self-rated average 7:00 a.m. 12 hour MTSS score over the 4 week double-blind treatment period,
(6) Change from baseline in the patient's self-rated average 7:00 p.m. 12 hour reflective mean number of wheals (MNW) score over the 4 week double-blind treatment period,
(7) Change from baseline in the patient's self-rated average 7:00 p.m. 12 hour reflective mean pruritus (MPS) score over the 4 week double-blind treatment period,
(8) Change from baseline in the patient's self-rated average 7:00 a.m. 12 hour MTSS score over the 4 week double-blind treatment period,
(9) Weekly changes from baseline in patient's MPS.
(10) Weekly changes from baseline in patient's MNW.
(11) Change from baseline in patient self-rated average interference of wheals with sleep over the 4-week double-blind treatment period,
(12) Change from baseline in patient self-rated average interference of wheals with normal daily activities over the 4-week double-blind treatment period,
(13) Change from baseline in the average investigator's assessment of the number of wheals at Visit 2 and the final visit (or early termination),
(14) Change from baseline in the average investigator's assessment of the size of wheals at Visit 2 and the final visit (or early termination),
(15) Change from baseline in the average investigator's assessment of intensity of erythema at Visit 2 and the final visit (or early termination),
(16) Change from baseline in the average investigator's assessment of extent of skin area involved at Visit 2 and the final visit (or early termination).

All primary and secondary efficacy endpoints were analyzed using the 'intent-to-treat population', defined as 'patients with baseline and post-12 hour reflective MPS' [V1.170:55], along with the evaluation of the primary efficacy endpoint and the secondary efficacy endpoint of patient self-rated assessment of wheals using 'protocol correct' patients (= 'intent-to-treat' patients with no major protocol violations) [V1.170:55, 200].

Reviewer's Note: The secondary efficacy endpoints were deemed acceptable from the FDA standpoint. In addition, the QOL analysis was considered to be secondary endpoint.

8.3.3.3. Statistical Analysis [V1.170:54, 200-203]

A sample size of 75 patients per treatment arm was calculated based on the primary efficacy endpoint of change in the MPS from baseline between placebo and a treatment to detect a treatment difference of at least 0.32 units in the average change of the MPS symptom score from baseline between placebo

and treatment given a standard deviation of no larger than 0.68 units with 80% power, given a 2-sided test with type I α error=0.05. This power calculation was based on previous CIU trials of once daily dosing of fexofenadine HCl in which the difference in mean scores (average effect over 6 weeks) between fexofenadine HCl and placebo was 0.48 with a standard deviation of 0.68 [V1.170:54, 201].

This sample size likewise provides at least 80% power for the secondary analysis of change from baseline in number of wheals score if difference between fexofenadine HCl and placebo is at least 0.42 units and the population standard deviation is no greater than 0.90 units.

Based on these calculations and taking into account patient discontinuation, the target sample size was 400 randomized patients, which was expected to yield at least 375 ITT patients.

ANCOVA was used to compare the effects of fexofenadine HCl 20 mg po bid, 60 mg po bid, 120 mg po bid doses, 240 mg po bid doses and placebo for the primary efficacy variable, which included terms for investigative sites, treatment groups, and baseline MPS values (as covariate adjustment). The treatment-by investigative site interaction and treatment-by-baseline interaction were assessed separately for inclusion in the model and were included in the final model if significant at the α=0.10 level.

Of note, sites with fewer than 1 ITT patient/dose group were pooled to form 'pseudo-sites' prior to analysis after unblinding of the final database (and did not exceed the largest site in number of patients).

A supportive analysis was performed using ANCOVA of the rank transformed data without testing for normality. The rank analysis was performed on pooled data and pairwise comparisons to placebo were based on a step-down procedure so as to protect the overall type I error. In particular, the following comparisons were made sequentially: fexofenadine HCl 240 mg po bid vs. placebo, fexofenadine HCl 120 mg po bid vs. placebo, fexofenadine HCl 60 mg po bid vs. placebo, and fexofenadine HCl 30 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 5 treatment groups was performed to further characterize the dose response relationship.

The same ANCOVA model used in the primary efficacy analysis was used to analyze all secondary efficacy variables.

Treatment effect was characterized in subgroups of patients defined by investigative site, age, gender, weight, and race. Age was only categorized as < 16 years of age, 16-40 years of age, and $\geq$ 40 years of age. Race was categorized as Caucasian and other. Weight was also categorized as: < 60 kg, 60-90 kg, and $\geq$ 90 kg [V1.170:60].

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 [V1.170:61]. In addition, potentially clinically significant outliers were identified.

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

8.3.3.3.1. Pharmacokinetic Analysis [V1.170:204]

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.

8.3.3.3.2. Dermatology Quality of Life (DLQI) and Work Productivity and Impairment (WPAI) Questionnaire Evaluation

For study 0039, impact of urticaria on patients' quality of life and work/classroom productivity was evaluated using a self-administered questionnaire—the Dermatology Life Quality Index (DLQI) and Work Productivity and Activity Impairment (WPAI) Questionnaire--completed by each patient at the end of each visit (Visit 1/1a, Visit 2, and the final/early termination visit) [V1.217:9, 15]. The primary objective of this evaluation was to assess the impact of treatment on patients with CIU, as measured by the following endpoints: the average change from baseline in the overall DLQI score (a composite score of 6 domains delineated as (1)-(6) below) where is each domain is rated on a 0-10 scale (no effect to complete prevention of performing activity), the average change from baseline % of work/classroom productivity, and the average change from baseline % of work/classroom time missed. A definition of a clinically relevant change (effect size) was not provided in the sponsor's submission of this QOL study. Nor did the sponsor state why the DLQI score is a preferred instrument for the CIU indication. Nonetheless, the sponsor measured the average change from baseline using the average of data from Visit 2 and the final/early termination visit. Of note, work and classroom endpoints were calculated on different patient populations (employees and students, respectively).

Secondary objectives included an assessment of the following secondary endpoints: (1) DLQI symptoms/feeling domain, (2) DLQI daily activities domain, (3) DLQI leisure domain, (4) DLQI work/school domain, (5) DLQI personal relations domain, (6) DLQI treatment domain, (7) overall work/classroom productivity, and (8) regular activity [V1.217:15]. Secondary endpoints were defined as the average change from baseline in each of the 6 PRQLQ domains (#1-6 above). In addition, a tertiary objective to evaluate the effect of time enrollment in the study on the primary and secondary objectives which was explored using average change from baseline to Visit 2 and from baseline to the 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 [V1.217:16].

A sample case report form for the DLQI questionnaire and sample form of the WPAI questionnaire is presented on pages 142-143 and pages 145-146, respectively of Volume 217 of NDA 20-872. For the DLQI questionnaire, items were generally rated as either: very much, a lot, a little, not at all, or not relevant (pertaining to skin condition) [V1.217:142-143]. For the WPAI questionnaire, work, productivity, and resource utilization were generally rated on a scale of 1-10 [V1.217:145-146]. The specific scoring method for each of the domains was calculated using an equation, which is discussed on page 26 of Volume 217. In these computations, the higher the score, the greater the impairment of quality of life.

The DLQI was designed to be a short and simple measure of the impact of various skin diseases on patients. This specialty-specific focus was to be created in the DLQI by asking patients to attribute the causes of their negative life experiences to the skin disease rather than to adverse experiences caused by other health and non health-related factors. The random error or reliability of the DLQI was assessed using a test-retest procedure, with responses found to be highly correlated. Information provided by the sponsor regarding the DLQI's internal consistency, reliability, and validity are summarized as follows: The internal consistency of the DLQI items was assessed by examining the bivariate inter-correlations among all items. The correlations ranged from a low of 0.23 to a high of 0.70; none were negative. This correlation matrix appeared to provide evidence in support of the scale's internal consistency. Scores on the DLQI were compared to a control group to test known groups validity and all individual questions showed significantly higher scores on the clinical group than the control group. The responsiveness of the DLQI to clinical change has been examined in 3 published studies, where it was shown that the change scores paralleled the measure of clinical severity in all studies [V1.217:21]. 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 DLQI and the WPAI is presented on pages 25-31 of Volume 217, however in summary, sample size for these QOL study was dependent on the sample size of the CIU study (375 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 analysis of primary outcomes variables (with terms for treatment, investigative site, and baseline values as covariate adjustment). 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 life and work/classroom productivity observations [V1.217:30]. No discussion of adjustment for multiple comparisons wass addressed in the DLQI protocol.

8.3.4. Results

8.3.4.1. Patient Demographics [V1.170:62-70, V1.177:164-165]

(A) A total of 468 patients were randomized into the study, though 19 patients discontinued the study following randomization but prior to receiving double-blind medication. The remaining 449 were exposed to double-blind treatment, and 332 of these patients completed the study.

Four hundred and thirty seven (437) patients of the 468 randomized 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. For the 12 patients excluded from the safety analysis who received double-blind study medication, no record of possible AEs experienced was provided by the sponsor since as the sponsor states, no post-baseline AE assessment was performed [V1.170:113]. Whether any of these 12 patients may have experienced an AE is not addressed in the sponsor's submission. Nineteen (19) patients discontinued the study before receiving double-blind medication and 12 patients had no post-baseline AE assessment [V1.170:63]. Four hundred and eighteen (418) patients were identified as 'intent-to-treat' patients (=exposed patients with baseline and post-12 hour reflective MPS scores [V1.170:55]) and were used in the 'intent-to-treat' analysis (31 patients from the safety evaluable population were excluded for ITT because they had no baseline or post-baseline 12 hour reflective MPS assessments [V1.170:63]). Three patients were excluded from the ITT analyses because they had no post-baseline 7:00 p.m. reflective symptom assessments. Of the 418 ITT patients, only 261 had no major protocol violations and were classified as 'protocol correct' [V1.225:63] (i.e. a large number of patients in this study had protocol violations). A distribution of the patient population is summarized in Table II. below:

Table II. Patient Disposition [V1.170:66]

	Fexofenadine 20 mg bid	Fexofenadine 60 mg bid	Fexofenadine 120 mg bid	Fexofenadine 240 mg bid	Placebo	TOTAL
Randomized	98	101	85	91	93	468
Intent-to-Treat	90	90	77	82	79	418
Safety Evaluable	92	97	79	84	85	437
Protocol Correct	55	58	47	54	47	261

(B) A total of 136 patients exposed to double-blind medication discontinued the study prior to scheduled completion [V1.225:68]. The most common reason for early discontinuation was treatment failure (61/468 total patients or 13% of patients in all 5 treatment groups). Of the 61 treatment failures, 19 were from the placebo group and 15 were from the 20 mg treatment group—indicating that not all patients responded adequately in the 20 mg treatment group. The lowest frequency of discontinuation was noted in the fexofenadine 60 mg bid treatment group.

This data is summarized in Table III. [V1.170:68].

Table III. Number and Percentage (%) of Randomized Patients for CIU 0039 Who Discontinued the Study with Reasons for Discontinuation, ITT Population [V1.170:68]

	Fexo 20 mg (n=98)[1]	Fexo 60 mg (n=101)[1]	Fexo 120 mg (n=85)	Fexo 240 mg (n=91)	Placebo (n=98)	TOTAL (n=468)
Number (%) Completed	66 (67.3%)	79 (78.2%)	64 (75.3%)	66 (72.5%)	57 (61.3%)	332 (70.9%)
Reasons for Discontinuation						
Adverse event	4 (4.1%)	6 (5.9%)	5 (5.9%)	1 (1.1%)	2 (2.2%)	18 (3.8%)
Elected to discontinue	2 (2.0%)	1 (1.0%)	3 (3.5%)	1 (1.1%)	4 (4.3%)	11 (2.4%)
Treatment Failure	15 (15.3%)	8 (7.9%)	10 (11.8%)	9 (9.9%)	19 (20.4%)	13 (1.5%)
Lost to follow-up	0 (0.0%)	1 (1.0%)	1 (1.2%)	3 (3.3%)	2 (2.2%)	7 (1.5%)
Patient elected to discontinue after exposure	2 (2.0%)	1 (1.0%)	3 (3.5%)	1 (1.1%)	4 (4.3%)	11 (2.4%)
Use of prohibited medication(s)	2 (2.0%)	1(1.0%)	1 (1.2%)	0 (0.0%)	1 (1.1%)	5 (1.1%)
Other	9 (9.2%)	5 (5.0%)	1 (1.2%)	10 (11.0%)	7 (7.5%)	32 (6.8%)
ALL REASONS	32 (32.7%)	22 (21.8%)	21 (24.7%)	25 (27.5%)	36 (38.7%)	136 (29.1%)

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

Reviewer's Note: For all 5 treatment groups, the total % of patient discontinuation was significantly higher than that noted in any of the other trials in this NDA (>20%) and was higher than normally deemed acceptable in such a study (i.e. ≤ 10%), though CIU-perhaps being a more systemic illness than SAR, might in general be less responsive to antihistamine therapy. The highest discontinuation rate was seen in the placebo and fexofenadine 20 mg bid group, with slightly lower rates at the medium to

high doses of fexofenadine (60 mg, 120 mg and 240 mg bid). The predominant reason for patient discontinuation was treatment failure.

(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 [V1.170:70]:

Variable	Fexo 20 mg (n=90)	Fexo 60 mg (n=90)	Fexo 120 mg (n=77)	Fexo 240 mg (n=82)	Placebo (n=79)	P-Value
Gender: (n, (%))						
Male	28 (31%)	26 (29%)	25 (33%)	22 (27%)	24 (30%)	
Female	62 (69%)	64 (71%)	52 (68%)	60 (73%)	55 (70%)	.9480[1]
Race: (n, (%))						
Caucasian	80 (89%)	82 (91%)	66 (86%)	67 (82%)	74 (94%)	
Black	4 (4%)	5 (6%)	6 (8%)	8 (10%)	2 (3%)	
Asian	3 (3%)	2 (2%)	3 (4%)	7 (9%)	1 (1%)	
Multiracial	3 (3%)	1 (1%)	2 (3%)	0 (0%)	2(3%)	.2533
Age: (yrs)						
Mean ± SD	38.14 ± 12.34	39.78 ± 10.59	40.40 ± 11.51	37.18. ± 11.59	38.51 ± 13.39	
Range	12-63	13-64	17-66	12-64	13-70	.4142
Age: (yrs, n%)						
<16	2 (2%)	1 (1%)	0 (0%)	2 (2%)	5 (6%)	
16-<40	51 (57%)	46 (51%)	36 (47%)	45 (55%)	39 (49%)	.3369
≥ 40	37 (41%)	43 (48%)	41 (53%)	35 (43%)	35 (44%)	
Weight: (kg)						
Mean ± SD	76.52 ± 19.20	77.26 ± 18.78	79.69 ± 18.24	75.69 ± 18.34	76.66 ± 21.10	
Range	41.3-155.1 kg	49.0-131.5 kg	52.2-131.5 kg	52.2-131.5 kg	48.5 -149.1 kg	.5382
Height: (in)						
Mean ± SD	65.66 ± 4.03	66.17 ± 3.83	66.69 ± 3.69	65.82 ± 3.60	66.07 ± 3.64	
Range	54.5-74.0	60.0-77.0	60.0-77.0	51.8-74.0	57-73	.5012

[1]P-value comparing the 5 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 5 treatment groups, with the majority of patients Caucasian and a greater proportion of female:male patients. No statistically significant differences or trends were noted between the treatment groups with regard to demographic factors.

(D) Patient distribution by disease severity at baseline in the ITT population was provided by the sponsor for a number of patient and investigator-rated efficacy parameters [V1.170:71-74] and no statistically significant difference was noted between the 5 ITT treatment groups for any of these parameters, including the primary efficacy endpoint—the MPS (p=0.2415), although the highest score was seen in placebo group patients [V1.170:73]. The range of the MPS score for the baseline period ranged from 0.5-4.0 (std. dev.=0.864) for the placebo group, 0-4.0 (std. dev.=0.893) for the fexofenadine 20 mg group, 0-4.0 (std. dev.=0.930) for the fexofenadine 60 mg group, 0-4.0 (std. dev.=0.892) for the fexofenadine 120 mg group, and 0-3.5 (std. dev.=0.903) for the fexofenadine 240 mg group. In summary, these ranges in MPS were similar between the 5 treatment arms.

(E) Patient Validity [V1.170:67-68, 77]

One hundred and eighty eight patients (or 41.9% of all exposed patients) (37 treated with fexofenadine HCl 20 mg, 42 treated with fexofenadine HCl 60 mg, 34 treated with fexofenadine HCl 120 mg, 33 treated with fexofenadine HCl 240 mg and 42 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 (27.6% of total patients). The % of patients with a violation tended to be higher for the placebo group for all categories of 'major protocol violation' with the exception of: 'failure to meet entrance criteria' which was highest in the fexofenadine 240 mg group, closely followed by the fexofenadine 20 mg group. With respect to use of prohibited medications, 21 patients (23.6%) in the placebo group, 26 patients (28.3%) in the fexofenadine HCl 20 mg group, 33 patients (33.0%) in the fexofenadine HCl 60 mg group, 26 patients (32.0%) in the fexofenadine HCl 120 mg group, and 17 patients (19.5%) in the fexofenadine HCl 240 mg group used ≥ 1 prohibited medication [V1.170:76]. Hence, use of prohibited medications was slightly higher in the fexofenadine 60 mg and 120 mg groups. The most commonly used prohibited medications consisted of aspirin, NSAIDs, and narcotic analgesics across all 5 groups, with a slightly higher incidence of use of other H_1 antagonists in the placebo group patients than either of the 4 active treatment groups [V1.170:77]. A summary of invalidated patients and the reasons for invalidation are summarized in Table 11 of the study report for CIU study PJPR0039 [V1.170:67].

Reviewer's Note: Criteria for invalidation of patient data were comparable to those seen in the SAR trials and thus deemed reasonable by the medical reviewer, although the overall numbers of invalidated patients per exposed patients was significantly higher across all treatment arms. This finding was driven by the high incidence of prohibited medication use amongst CIU patients.

(F) Duration of Study Medication Exposure [V1.170:75]

The mean duration of double-blind exposure to study treatment for the safety population was 24.80 days (± 9 days) for all 5 treatment groups. The mean/range of duration of exposure was 22.22 days/3-34 days for the placebo group (n=86 patients), 24.39/2-35 days for the fexofenadine HCl 20 mg group (n=92), 26.06/2-37 days for the fexofenadine HCl 60 mg group (n=97), 25.81 /3-33 days for the fexofenadine HCl 120 mg group (n=79), and 25.48/2-35 days for the fexofenadine HCl 240 mg group (n=85). There were 10 patients without duration of exposure information. Duration of exposure was calculated using days between randomization and last dosing day of the double-blind treatment.

(G) Patient Compliance [V1.170:75-76]

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 from Visit 1/1a to the final study visit/early termination visit (the double-blind period). Average compliance was found to be 98.31% for the placebo group, 98.43% for the fexofenadine HCl 20 mg group, 97.15% for the fexofenadine HCl 60 mg group, 98.24% for the fexofenadine HCl 120 mg group, and 98.45% for the fexofenadine HCl 240 mg group [V1.170:75]. Eight 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 (compliance was to be between 90-110%) [V1.170:40].

8.3.4.2. Efficacy Endpoint Outcomes

(I) Primary Efficacy Variables:

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=90 for fexofenadine HCl 20 mg group, n=90 for fexofenadine HCl 60 mg group, n=77 for fexofenadine HCl 120 mg group, n=82 for fexofenadine HCl 240 mg group, and n=79 for placebo) for the primary efficacy variable of the change from baseline in the mean pruritus score (MPS); where the primary comparison of interest was the response of the 4 fexofenadine doses vs. placebo. Choice of a reflective MPS 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 decreasing pruritus symptoms over the preceding 12 hours.

Results of the primary efficacy analysis for CIU study 0039 are summarized in Table V. A statistically significant decrease in the primary efficacy endpoint for all 4 fexofenadine doses compared to placebo was demonstrable, with the greatest numerical decrease in MPS over the 4 week double-blind period noted for the fexofenadine 240 mg bid group (change of -1.08 units), closely followed by the fexofenadine 60 mg bid group (change of -1.00 units). A consistent and progressive numerical trend for decrease in the MPS was not seen with increasing fexofenadine dose.

Similar results were seen with analysis of the 'protocol correct' group for study 0039, although there was a greater response in the placebo group which tended to obscure response of the fexofenadine 20 mg group, thus making comparison between the 2, statistically insignificant [V1.170:82].

Of note, one of the investigators in study 0039-Dr. Edwards (site PPJST0283) was disqualified; in which a total of 19 patients comprised the ITT population at this site 3, 3, 5, 3, and 5 patients were treated with placebo, fexofenadine 20 mg, 60 mg, 120 mg, and 240 mg, respectively. The sponsor submitted results of the primary efficacy variable analysis study 0039 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 CIU Study PJPR 0039]. After exclusion of this one study site, conclusions reached about efficacy for the primary endpoint study 0039 was not altered.

Treatment-by-investigative site and treatment-by-baseline mean reflective MPS interactions were assessed using ANCOVA with the baseline reflective MPS, treatment, investigative site, treatment-by-investigative site and treatment-by-baseline reflective MPS at a significance level of 0.1 [V1.170:78-79]. The test for the covariate baseline MPS was statistically significant, indicating that patients with a higher baseline MPS were likely to show a larger reduction in MPS [V1.170:78-79]. The treatment-by-baseline TSS interaction (without treatment-by-site) was also found to be statistically significant (p=0.0190) [V1.170:78]. There was no statistical evidence of dependence of treatment effect on the investigative site (p=0.1879) [V1.170:79].

Reviewer's Note: Based on evaluation of the primary efficacy endpoint, the fexofenadine 60 mg bid dose offered a clinical response greater than either the 20 mg bid or 120 mg bid dose, and one which was very similar to the 240 mg bid dose. Hence, based of these clinical data, the 60 mg bid dose appears the most appropriate initial dose for the treatment of CIU in adults patients age 12 years and older.

Table V.
Efficacy of Fexofenadine HCl 20 mg, 60 mg, 120 mg, and 240 mg, vs. Placebo
Primary Efficacy Variable: Intent-to-Treat (ITT) Population [V1.170:79, V1.178:12]

	TREATMENT GROUP								
Primary Efficacy Variable	**(A) Fexo 20 mg bid**	**(B) Fexo 60 mg bid**	**(C) Fexo 120 mg bid**	**(D) Fexo 240 mg bid**	**(E) Placebo**	**[1]P-value**			
						A-E	**B-E**	**C-E**	**D-E**
Change from Baseline in the Mean Pruritis Score (MPS, Mean ± Standard Error)									
	(n=90)	**(n=90)**	**(n=77)**	**(n=82)**	**(n=79)**				
Baseline MPS	1.80 ± 0.094	1.86 ± 0.098	1.94 ± 0.102	1.91 ± 0.102	2.13 ± 0.097				
Double-blind Treatment Period MPS	1.13 ± 0.089	0.90 ± 0.079	1.07 ± 0.092	0.83 ± 0.078	1.62 ± 0.098				
Change from baseline in MPS	**-0.68 ± 0.076**	**-1.00 ± 0.075**	**-0.84 ± 0.081**	**-1.08 ± 0.079**	**-0.40 ± 0.082**	**0.0098**	**0.0001**	**0.0001**	**0.0001**
Mean Difference ± SE						-.29±.11	-.60±.11	-.44±.11	-.68±.11

[1]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 variable to examine treatment interactions was performed by the sponsor on the basis of gender [V1.170:10-111], race [V1.170:111-112], weight [V1.170:112-113], and study site [V1.170:106-109]. Baseline symptom severity (as determined by the mean reflective MPS during the placebo lead-in period was not included in this covariate analysis (as had been done in the SAR trials for fexofenadine). Analysis by further sub-grouping by age (i.e. < 16 years, 16- <40 years of age, and ≥ 40 years of age) was performed [V1.170:110]. The statistical model used for this analysis was ANCOVA with a significance level of 0.1 [V1.170:106].

Based on these subgroup analyses, no statistical significance was noted for the study site by treatment interaction (p=0.7383) or main effect of site for mean change from baseline in MPS (p=0.2122); indicating that the treatment effects were consistent across investigative sites [V1.170:109]. Furthermore, no statistical significance was noted for the treatment-by-age interaction for mean change from baseline in MPS (p=0.7186) The main effect of age was statistically significant (p=0.0114), with generally larger decrease in MPS from baseline noted in patients < 40 years of age. No statistically significant difference was noted in the gender-by-treatment interaction (p=0.2559) or main effect of gender (p=0.9657) for the change in the mean reflective MPS over the double-blind period [V1.170:110-111], no statistical significance was noted for weight by treatment (p=0.4425) or main effect of weight (p=0.4552) for the change in the mean reflective MPS [V1.170:112-113], along with no statistical significance noted for race by treatment interaction (p=0.4435) or main effect of race (p=0.9572) [V1.170:111-112]; indicating that the treatment effects were consistent across these demographic variables. In other words, the effect of the 4 treatment groups was not statistically significantly different among subgroups of patients defined by these factors.

(II). Secondary Efficacy Variables:

A summary of analysis of the secondary efficacy variables for the ITT population is provided in Table VI. below and indicates that for the clear majority of secondary efficacy endpoints, a statistically significant difference in symptom scores was seen for the 4 fexofenadine doses compared to placebo in study 0039. Review of numerical trends generally showed a greater decrease in symptoms with active treatment for the fexofenadine 240 mg bid group, very closely followed by the fexofenadine 60 mg bid group for the most of the secondary endpoints [V1.170:83-106]. As seen with the primary efficacy endpoint, no consistent trend was noted for the dose response (based on numerical change between the 4 fexofenadine doses and placebo) between fexofenadine dose and numerical change in symptom scores for the secondary efficacy endpoints [V1.170:83-106].

Specifically with regard to analysis of the week 1 vs. week 2 vs. week 3, vs. week 4 change in mean reflective MPS, only the fexofenadine 60 mg bid treatment group showed a statistically significantly greater decrease compared to

placebo treatment for all 4 weeks of treatment [V1.170:89-90]. Similar results were also seen for the weekly analysis of the mean average MNW (mean # of wheals) scores where only the fexofenadine 60 mg bid group demonstrated a statistically significant decrease in MNW during all 4 weeks of the study.

The end-of-dosing interval (i.e. duration of effect) for the 4 fexofenadine doses was not formally assessed by any of the patient-self rated endpoints, nor was it critical for evaluation of efficacy for the CIU indication. Nonetheless, the investigator's assessment at Visit 2 and the final Visit of: (1) the # of wheals, (2) the size of wheals, (3) the intensity of erythema, and (4) the extent of skin area involved were which were a close approximation to an end-of-dosing interval assessment or 'instantaneous' measurement since these were obtained at a defined point in time (i.e. during the office visit) and did not involve any measurements over a prior time period. Based on these endpoints, again, the fexofenadine 60 mg bid group demonstrated the most consistent statistically significant difference compared to placebo (for 3 out of the 4 endpoints, with a trend for significance with the 4th efficacy endpoint) [V1.170:105-106]. The numerical difference in change for the fexofenadine 60 mg bid group was generally equal to or greater than that afforded by the fexofenadine 240 mg bid group, whose symptom scores were most similar to that of the 60 mg bid group. Based on review of the secondary efficacy endpoints for 0039, a consistent dose response with respect to fexofenadine dose was not seen.

Review of onset of action for daily change from baseline change from baseline in the mean reflective MPS for the double-blind treatment period (the primary efficacy variable) for the intent-to-treat population was not performed by the sponsor for study 0039 and was not deemed to be as important an analysis for the CIU indication, as say, for the SAR indication because of the greater chronicity of urticaria.

Reviewer's Note: Review of the secondary efficacy endpoints for CIU study 0039 indicates that fexofenadine 60 mg bid dose is the most appropriate dose for treatment of CIU in patients ≥ 12 years of age. Analysis of onset of action and evaluation of the end-of-dosing interval for the 4 fexofenadine doses was not performed and was not deemed important from the clinical perspective for the CIU indication.

Table VI: Secondary Efficacy Variables for the ITT Population for CIU Study 0039: Fexofenadine HCl 20 mg, Fexofenadine HCl 60 mg, Fexofenadine HCl 120 mg, Fexofenadine HCl 240 mg, vs. Placebo [V1.170:83-89, 92-102, V.178:20-33]
Continued on next page

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No			
	Fexo 20 mg qd	Fexo 60 mg qd	Fexo 120 mg qd	Fexo 240 mg qd
Secondary Efficacy Variables				
1. Δ from baseline in patient self-rated average MNW over the 4 week double-blind period	Yes (p=0.0115)	Yes (p=0.0001)	Yes (p=0.0068)	Yes (p=0.0001)
2. Δ from baseline in patient self-rated average MTSS over the 4 week double-blind period	Yes (p=0.0109)	Yes (p=0.0001)	Yes (p=0.0011)	Yes (p=0.0001)
3. Δ from baseline in patient self-rated average 7:00 a.m. 12 hr reflective MNW over the 4 week double-blind period.	Yes (p=0.0015)	Yes (p=0.0001)	Yes (p=0.0040)	Yes (p=0.0001)
4. Δ from baseline in patient self-rated average 7:00 a.m. 12 hr reflective MPS over the 4 week double-blind period.	Yes (p=0.0009)	Yes (p=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)
5. Δ from baseline in patient self-rated average 7:00 a.m. 12 hr reflective MTSS over the 4 week double-blind period.	Yes (p=0.0008)	Yes (p=0.0001)	Yes (p=0.0004)	Yes (p=0.0001)
6. Δ from baseline in patient self-rated average 7:00 p.m. 12 hr reflective MNW over the 4 week double-blind period.	Yes (p=0.0412)	Yes (p=0.0001)	Yes (p=0.0079)	Yes (p=0.0001)
7. Δ from baseline in patient self-rated average 7:00 p.m. 12 hr reflective MPS over the 4 week double-blind period.	Yes (p=0.0113)	Yes (p=0.0001)	Yes (p=0.0003)	Yes (p=0.0001)
8. Δ from baseline in patient self-rated average 7:00 p.m. 12 hr reflective MTSS over the 4 week double-blind period.	Yes (p=0.0336)	Yes (p=0.0001)	Yes (p=0.0020)	Yes (p=0.0001)
9. Weekly Δs from baseline in patient's MPS:				
Week 1	Yes (p=0.0008)	Yes (p=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)
Week 2	No (p=0.1125)	Yes (p=0.0001)	Yes (p=0.0012)	Yes (p=0.0001)
Week 3	No (p=0.2423)	Yes (p=0.0002)	Yes (p=0.0414)	Yes (p=0.0007)
Week 4	No (p=0.5121)	Yes (p=0.0196)	No (p=0.5677)	Yes (p=0.0137)

Δ=Change, MPS=Mean pruritus score, MNW=Mean number of wheals, MTSS=Mean total symptom score

Table VI: CONTINUED:
Secondary Efficacy Variables for the ITT Population for CIU Study 0039
Fexofenadine HCl 20 mg, Fexofenadine HCl 60 mg, Fexofenadine HCl 120 mg,
Fexofenadine HCl 240 mg, vs. Placebo [V1.170:89-90, 102-106]

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No			
	Fexo 20 mg qd	Fexo 60 mg qd	Fexo 120 mg qd	Fexo 240 mg qd
Secondary Efficacy Variables				
10. Weekly Δs from baseline in patient's MNW:				
Week 1	Yes (p=0.0060)	Yes (p=0.0003)	Yes (p=0.0010)	Yes (p=0.0001)
Week 2	No (p=0.1463)	Yes (p=0.0003)	Yes (p=0.0432)	Yes (p=0.0013)
Week 3	No (p=0.2548)	Yes (p=0.0018)	No (p=0.3300)	Yes (p=0.0384)
Week 4	No (p=0.8480)	Yes (p=0.0224)	No (p=0.4928)	No (p=0.1129)
11. Δ from baseline in patient self-rated average interference of wheals with sleep over the 4 week double-blind period	Yes (p=0.0011)	Yes (p=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)
12. Δ from baseline in patient self-rated average interference of wheals with normal daily activities over the 4 week double-blind period.	Yes (p=0.0014)	Yes (p=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)
13. Δ from baseline in the average investigator's assessment of the # of wheals at Visit 2 and the final visit.	No (p=0.7478)	No (p=0.1430)	Yes (p=0.0358)	No (p=0.8087)
14. Δ from baseline in the average investigator's assessment of the size of wheals at Visit 2 and the final visit.	Yes (p=0.0027)	Yes (p=0.0012)	No (p=0.0826)	No (p=0.0007)
15. Δ from baseline in the average investigator's assessment of intensity of erythema at Visit 2 and the final visit.	Yes (p=0.0016)	Yes (p=0.0001)	Yes (p=0.0472)	Yes (p=0.0002)
16. Δ from baseline in the average investigator's assessment of extent of skin area involved at Visit 2 and the final visit.	No (p=0.0808)	Yes (p=0.0057)	No (p=0.2817)	Yes (p=0.0100)

Δ=Change, MNW=Mean number of wheals, #=Number.

8.3.4.2.1. Quality of Life (QOL) Analysis

Evaluation of the health outcome parameters in CIU study 0039 indicated that on average, all fexofenadine treatment groups reported an improvement in health-related quality of life (QOL), as measured by average change from baseline in overall DLQI score. All active treatment groups were statistically superior to placebo with respect to average change from baseline in overall DLQI score for the 403 patients that constituted the QOL ITT population ($p \leq 0.0386$) [V1.217:31, 42]. Treatment comparisons (active treatment-placebo) for average change from baseline in overall DLQI were –1.650 units in the fexofenadine 20 mg bid group, -2.959 units in the fexofenadine 60 mg bid group, -2.420 units in the fexofenadine 120 mg bid group, and –3.706 units in the fexofenadine 240 mg bid group [V1.217:44]. Of note, in the final statistical model for average change from baseline in the overall DLQI score, there was a significant treatment-by-baseline interaction and this indicated that the treatment effect on change in

overall DLQI score differed with varying baseline overall DLQI scores (i.e. smaller improvements from baseline seen for patients with low baseline DLQI scores and vice versa).

Analyses of changes in the 6 individual DLQI domains (symptoms/feelings, daily activities, leisure, work/school, personal relations, and treatment) were performed to explore the extent of the differences observed in the overall DLQI score and showed improvement in most domains for all 4 fexofenadine groups compared to placebo, with the exception of the fexofenadine 20 mg bid group ($p \leq 0.0169$ for the symptoms/feelings domain, $p \leq 0.0116$ for the daily activities domain, $p \leq 0.0104$ for the leisure domain, $p \leq 0.0208$ for the work/school domain [V1.217:48-49]. There were no statistically significant differences among treatments with respect to the treatment domain. The fexofenadine 20 mg, 60 mg, and 240 mg bid groups had significantly greater improvement than placebo in the personal relations domain ($p \leq 0.0382$). The domains which appeared to contribute the most to the determination of the overall DLQI score (the primary endpoint) for each of the 4 fexofenadine treatment groups consisted of: the symptoms/feelings domain, the daily activities domain, and the leisure domain. These results are summarized in Table 8 of Volume 217 of NDA 20-872 [V1.217:49] and are presented below in Table VII.

With respect to the change from baseline in the Work Productivity and Activity Impairment (WPAI) assessment, all fexofenadine doses except for the 20 mg bid group were statistically significantly superior to placebo with respect to average change from baseline in percent work productivity ($p \leq 0.0266$) [V1.217:52]. These results are summarized in Table 9 of Volume 217 of NDA 20-872 [V1.217:54]. Of note, in the final statistical model for average change from baseline in % work productivity, there was a significant treatment-by-baseline interaction which indicated that the treatment effect on change in % work differed with varying baseline work productivity values (i.e. patients with low % work productivity at baseline had larger increases from baseline, in contrast to patients with high % work productivity at baseline who had smaller increases from baseline in all treatment groups) [V1.217:55]. For the endpoint of change from baseline in % work time missed, there were no statistically significant differences among treatments with respect to average change from baseline in % work time missed as compared to placebo [V1.217:57-58]. For the endpoint of change from baseline in overall work productivity, improvement from baseline in overall work productivity was shown in all treatment groups, although all treatment groups except the fexofenadine 20 mg bid group showed results that were statistically significantly greater than placebo treatment ($p \leq 0.0347$) [V1.217:58-59]. Results for this domain are summarized in Table 11 of Volume 217 of NDA 20-872 [V1.217:59].

For the classroom productivity domain, all treatment groups reported an increase in classroom productivity compared to baseline, however no statistically significant difference amongst the active treatments was seen with respect to average change from baseline in % classroom productivity as shown in Table 13,

however, given the small number of patients (range 9-15) per treatment group, the comparison may have been sufficiently underpowered to detect a statistical difference [V1.217:61-62]. Furthermore, no statistically significant differences among treatment groups with respect to average change from baseline in % of classroom time missed or change from baseline in overall classroom productivity was seen, as noted in Tables 14 and 15 [V1.217:62-64]. And finally, with respect to average change from baseline in regular activity, all treatment groups reported an increase in regular activity that was statistically significantly superior to placebo ($p \leq 0.0116$) [V1.217:66]. These results are presented in Table 17 of Volume 217 of NDA 20-872 [V1.217:66].

In summary, results of the DLQI and WPAI questionnaire indicate that fexofenadine at doses of 60 mg, 120 mg, and 240 mg bid appeared to improve most domains of health-related quality of life, productivity, and regular activity significantly more than placebo. In general, no consistent improvements were seen for the fexofenadine 20 mg bid dose as compared to placebo for the majority of domains tested. Because of inherent problems regarding choice of the instrument and current reliance upon symptom scores and not QOL measures to assess response of CIU to treatment by the Agency [Response to Dermatology Quality of Life Question, HFD-540, FDA, Dr. Jonathan Wilkin, 02/05/99], at the present time all dermatologic non-disease specific instruments not deemed acceptable as measures of QOL.

Table VII: DLQI SUMMARY: [1]Average Change from Baseline [V1.217:49]

DOMAINS	Treatment Comparison, Mean ± Std. Error (Change from baseline, as compared with placebo)			
	Fexo 20 mg qd	Fexo 60 mg qd	Fexo 120 mg qd	Fexo 240 mg qd
1. Overall DLQI Score **(Planned Primary Analysis)**	-1.6590 ± .74947 **(p=0.0386)**	-2.959 ± .7982 **(p=0.0002)**	-2.420 ± .8227 **(p=0.0035)**	-3.706 ± .8170 **(p=0.0001**
2. Symptoms/Feelings Domain	-0.371 ± .2084 (p=0.0761)	-0.826 ± .2082 **(p=0.0001)**	-0.515 ± .2146 **(p=0.0169)**	-1.027 ± .2134 **(p=0.0001)**
3. Daily Activities Domain	-0.314 ± .1858 (p=.0921)	-0.645 ± .1861 **(p=0.0006)**	-0.488 ± .1925 **(p=0.0116)**	-0.697 ± .1906 **(p=0.0003)**
4. Leisure Domain	-0.291 ± .2193 (p=0.1861)	-0.675 ± .2204 **(p=0.0024)**	-0.582 ± .2258 **(p=0.0104)**	-0.807 ± .2248 **(p=0.0004)**
5. Work/school Domain	-0.132 ± .1041 (p=0.2043)	-0.376 ± .1053 **(p=0.0004)**	-0.251 ± .1082 **(p=0.0208)**	-0.469 ± .1071 **(p=0.0001)**
6. Personal Relations Domain	-0.435 ± .2091 **(p=0.0382)**	-0.448 ± .2100 **(p=0.0336)**	-0.390 ± .2161 (p=0.0721)	-0.531 ± .2149 **(p=0.0140)**
7. Treatment Domain	-0.114 ± .0938 (p=0.2236)	-0.118 ± .0945 (p=0.2122)	-0.067 ± .0969 (p=0.4909)	-0.164 ± .0974 (p=0.0939)

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

8.3.4.3. Safety Analysis

Safety analysis for study 0039 was essentially the same as that conducted for other fexofenadine trials (adult qd SAR, pediatric bid SAR) and 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).

Ninety two (92) patients comprised the fexofenadine HCl 20 mg, 97 patients comprised the fexofenadine HCl 60 mg, 79 patients comprised the fexofenadine HCl 120 mg, 84 patients comprised the fexofenadine HCl 120 mg, and 85 patients comprised the placebo group safety evaluable populations (i.e. exposed to double-blind medication with at least 1 postbaseline AE assessment) [V1.170:113]. In this trial, the safety evaluable population was slightly higher than the ITT population (patients with baseline and postbaseline 12 hour reflective MPS assessments; 418 patients total) [V1.170:65].

8.3.4.3.1. Demographics of the Exposed Population

Demographics of the exposed population was almost the same as that of the ITT population which was previously presented in section 8.1.4.1 ('Patient Demographics') of the medical officer review of NDA 20-872 and will not be re-summarized here [V1.177:164-165, 167-168, 170-171]. In summary, all 5 treatment groups were similar with respect to baseline characteristics.

8.3.4.3.2. 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 24.80 days (± 9 days) for all 5 treatment groups [V1.170:75]. The mean/range of duration of exposure was 22.22 days/3-34 days for the placebo group (n=86 patients), 24.39/2-35 days for the fexofenadine HCl 20 mg group (n=92), 26.06/2-37 days for the fexofenadine HCl 60 mg group (n=97), 25.81 /3-33 days for the fexofenadine HCl 120 mg group (n=79), and 25.48/2-35 days for the fexofenadine HCl 240 mg group (n=85). There were 10 patients without duration of exposure information. Duration of exposure was calculated using days between randomization and last dosing day of the double-blind treatment.

8.3.4.4. 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 5 treatment groups (including placebo), with a slightly higher preponderance for the active treatment groups and ranged from ~ 52-62% for all AEs combined [V1.170:114-115, V1.182:45-49]. As previously noted for other clinical indications, the most frequent adverse event for all 5 treatment groups consisted of headache (with an incidence of 28.3% in the fexofenadine HCl 20 mg group, an incidence of 22.7% in the fexofenadine HCl 60 mg group, an incidence of 25.3% in the fexofenadine HCl 120 mg group, an incidence of 23.8% in the fexofenadine HCl 120 mg group, and an incidence of 20.0% in the placebo group), followed by upper respiratory tract infection (an incidence of 7.6% in the fexofenadine HCl 20 mg group, an incidence of 8.2% in the fexofenadine HCl 60 mg group, an incidence of 7.6% in the fexofenadine HCl 120 mg group, an incidence of 9.5% in the fexofenadine HCl 240 mg group, and an incidence of 9.4% in the placebo group) [V1.170:115, V1.182:45]. In both cases, the incidence of these 2 AEs was ~ twice as high as

that noted in the SAR trials, with unclear reasons for this. With the minor exception of a progressively slightly higher incidence of dysmenorrhea across the 4 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 20 mg: 2.2%, 60 mg: 3.1%, 120 mg: 1.3%, 240 mg: 1.2%, and placebo: 0.0%) [V1.170:115].

A summary of all reported adverse events ('treatment emergent') for placebo treatment, as compared to the fexofenadine HCl 20 mg, fexofenadine HCl 60 mg, fexofenadine HCl 120 mg, and fexofenadine HCl 240 mg treatments in CIU study 0039 ≥ 3% (chosen as a cut-off because of the large # of AEs > 1% noted in the AE database for study 0039), is presented in Table VIII.

Table VIII. Adverse Event (AE) Frequency:
AE's ≥ 3% for ALLEGRA (Fexofenadine 20 mg, 60 mg, 120 mg bid, 120 mg bid vs. Placebo), by Organ System and Preferred Term; Safety Evaluable Population
[V1.170:115-120]

BODY SYSTEM	Preferred Term	Fexo 20 mg (n=92) n (%)	Fexo 60 mg (n=97) n (%)	Fexo 120 mg (n=79) n (%)	Fexo 240 mg (n=84) n (%)	Placebo (n=85) n (%)
All Systems	Any AE	57 (62.0%)	57 (58.8%)	48 (60.8%)	52 (61.9%)	44 (51.8%)
Neurologic	**Headache**	**26 (28.3%)**	**22 (22.7%)**	**21 (25.3%)**	**24 (23.8%)**	**17 (20.0%)**
Respiratory	URI	**7 (7.6%)**	**8 (8.2%)**	**6 (7.6%)**	**8 (9.5%)**	**8 (9.4%)**
	Pharyngitis	**3 (3.3%)**	**4 (4.1%)**	**3 (3.8%)**	**5 (6.0%)**	**3 (3.5%)**
	Rhinitis	**2 (2.2%)**	**2 (2.1%)**	**4 (5.1%)**	**2 (2.4%)**	**3 (3.5%)**
	Upper respiratory congestion	2 (2.2%)	4 (4.1%)	1 (1.3%)	3 (3.6%)	3 (3.5%)
	Sinusitis	2 (2.2%)	2 (2.1%)	3 (3.8%)	2 (2.4%)	0 (0.0%)
	Bronchitis	0 (0.0%)	0 (0.0%)	3 (3.8%)	0 (0.0%)	0 (0.0%)
Body as a Whole-General	Pain	**4 (4.3%)**	**6 (6.2%)**	**2 (2.5%)**	**2 (2.4%)**	**3 (3.5%)**
	Abdominal Pain	**7 (7.6%)**	**2 (2.1%)**	**1 (1.3%)**	**2 (2.4%)**	**3 (3.5%)**
	Back Pain	1 (1.1%)	3 (3.1%)	3 (3.8%)	3 (3.6%)	1 (1.2%)
GI	Dyspepsia	**3 (3.3%)**	**9 (9.3%)**	**1 (1.3%)**	**4 (4.8%)**	**4 (4.7%)**
	Nausea	**5 (5.4%)**	**4 (4.1%)**	**3 (3.8%)**	**5 (6.0%)**	**3 (3.5%)**
	Diarrhea	2 (2.2%)	3 (3.1%)	1 (1.3%)	4 (4.8%)	1 (1.2%)
	Gastroenteritis	1 (1.1%)	0 (0.0%)	2 (2.5%)	4 (4.8%)	1 (1.2%)
Musculo-skeletal	Myalgia	2 (2.2%)	1 (1.0%)	3 (3.8%)	4 (4.8%)	4 (4.7%)
	Arthalgia	3 (3.3%)	2 (2.1%)	1 (1.3%)	3 (3.6%)	0 (0.0%)
Infectious Disease	Influenza	3 (3.3%)	1 (1.0%)	1 (1.3%)	0 (0.0%)	1 (1.2%)
Reproductive	Dysmenorrhea	1 (1.1%)	1 (1.0%)	3 (3.8%)	4 (4.8%)	1 (1.2%)

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

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 5 treatment groups, with a slightly higher preponderance of 'severe' AEs in the placebo group [V1.170:124].

8.3.4.4.2. Cardiac Adverse Events

Cardiovascular adverse events were only specifically recorded under the 'cardiovascular' category for the 1 clinical endpoint of tachycardia (0.0-1.1% incidence across all 4 fexofenadine doses, 0.0% for the placebo group); however the additional adverse events of: dizziness (0.0-2.1% incidence across all 4 fexofenadine doses, 0.0% for the placebo group) and chest pain (0.0% across all 4 fexofenadine doses, 1.2% for the placebo group) were added to the list of cardiovascular adverse events by the medical reviewer [V1.170:115, 116, 119]. As noted, the frequency of these potential cardiovascular AEs were low for all treatment groups.

Aside from these AE recordings, no additional cardiovascular monitoring (i.e. ECGs) was performed in this study.

8.3.4.5. Adverse Event Stratification by Duration of Treatment

Adverse event stratification by duration of treatment was not performed by the sponsor, given the study's entire duration of 4 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. Similar to the SAR trials, many of the adverse events described in the safety database for study 0039 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).

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

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

8.3.4.7. Patient Discontinuation due to Adverse Events

A total of 16 patients randomized to double-blind study medication discontinued treatment due to AEs: 14 patients with either of the 4 doses of fexofenadine HCl (4 fexofenadine 20 mg patients, 5 fexofenadine 60 mg patients, 4 fexofenadine 120 mg patients, and 1 fexofenadine 240 mg patient) and 2 patients treated with placebo discontinued treatment prematurely due to adverse events [V1.170:126-127]. On review of the adverse event summaries by the medical reviewer, 2 patients (1 taking fexofenadine 60 mg bid (patient # 318-002) and 1 taking fexofenadine 240 mg bid (patient # 298-009) discontinued treatment due to somnolence which may have been related to study medication [V1.170:127]. The other reasons for patient discontinuation for the fexofenadine groups were similar to those noted in other trials with fexofenadine (e.g. headache, asthma, bronchitis) and not dissimilar for the reasons leading to discontinuation in the placebo group patients (i.e. asthma and URI) [V1.170:127].

8.3.4.8. Serious Adverse Events and Death

No deaths were reported during this CIU trial for any of the 5 treatment groups. One case of cancer (breast cancer in a 51 yo female randomized to the

fexofenadine 60 mg bid arm ~ 1 month after treatment, patient PJST0282-0008) and 1 pregnancy (patient # PJST0315-0007, fexofenadine 20 mg bid arm; unknown follow-up) were reported [V1.170:125, 128].

The sponsor's definition of [3]serious treatment emergent adverse events was modified somewhat in this study (similar to that specified in study 3081 and pediatric SAR trials 0066/0077) 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 [V1.170:124].

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 [V1.170:128, V1.182:259-298]. 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 placebo group and 6 patients in the fexofenadine groups [V1.170:125].

8.3.4.9. Laboratory Test Results

Laboratory tests performed during visit 1/1a (pre-randomization) and visit 4 (completion of treatment) 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) and did not reveal any unexpected abnormalities in fexofenadine HCl or placebo treated patients, although by the sponsor's analysis a 'statistically' significant (though clinically insignificant) correlation between dose of fexofenadine and change from baseline in total protein and RBC was noted [V1.170:128, 129]. This change tended to be greater in placebo group patients than in the active medication arms. The effects of the 5 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 [V1.170:129-146]. 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 [V1.170:142-

[3] 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.

143, V1.183:7-30]. These criteria were the same as those for evaluation of laboratory outliers in the adult SAR trials [V1.225:123-125, 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) [V1.170:129-135]. Likewise shift tables were performed in this study as a mean of presenting laboratory data [V1.170:136-140].

No clinically meaningful change from baseline values in any laboratory parameter was noted, with the exception of the statistically significant change seen for total protein and RBC. Furthermore, no dose response was seen for these 2 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 5 treatment arms [V1.170:136-140].

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 [V1.170:142-143]) for each laboratory test showed no significant numerical difference in the number of patients with outliers between the 5 treatment groups, nor any obvious dose-related trends for laboratory outlier trends. These data are summarized in Table 53 of the study report of CIU study 0039 and Appendix K2, Summary 1 [V1.170:144-146, V1.183:33-35]. A slightly greater number of 'low' outliers was noted all 5 treatment arms for the hemoglobin and serum glucose parameters (seen in more than 1 fexofenadine treatment group) [V1.170:114, 146] and conversely, a slightly greater number of 'high' outliers was noted across all 5 treatment arms for the laboratory parameters of WBC, neutrophil count and triglycerides [V1.170:145, 146].

8.3.4.10. Vital Signs and Weight

Vital signs (blood pressure (systolic and diastolic), and heart rate were monitored in this study at baseline (Visit 1/1a) 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 5 treatment groups [V1.170:146-148]. These data are summarized in Tables 54-56 of the study report for CIU study 0039 [V1.170:146-148].

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, or vital sign that differed from those seen at the other study sites for study 0039. 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].

8.3.4.11. Pharmacokinetic Studies

Population pharmacokinetic studies of fexofenadine HCl in adult and adolescent patients age ≥ 12 years of age with CIU utilizing patients from protocols PJPR0039 and PJPR0067 combined (study PJPR0067 was identical in study design to PJPR0039) 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 2 (week 2) and at the final study visit (week 4). Plasma fexofenadine levels were analyzed for fexofenadine (MDL 16,455) using with an assay sensitivity of ng/mL [V1.63:322].

A total of 1200 fexofenadine plasma samples were collected from 660 patients (from the 4 fexofenadine treatment groups) all of whom were included in the population PK analysis. The potential covariates examined in the population PK model were: age, weight, height, gender, race, dose, country, and concomitant medications. Based upon population PK modeling results, the PK of fexofenadine in pediatric SAR patients appeared to be affected by patient demographics [V1.63:324]. The population PK model best describing the data was a 2-compartment oral model with oral clearance increasing with both patient age and height [V1.63:324].

No covariates were established for the volume of distribution, as inter-individual variability for this parameter could not be established for the model. The coefficient of variation on the population estimate of fexofenadine oral clearance was 49.4%. The coefficient of variation for the estimate plasma fexofenadine concentration was 68%. The estimated values for clearance across the height range (130-199 cm) and age range (12-68 years) for this population would be 32 L/h (at the minima) to 74 L/h (at the maxima) [V1.63:323]. Conclusions reached regarding this model were that application of the model outside this data set might not be warranted due to the unusually high residual variability in the base model (CV_{base}=72%) which was not substantially reduced by the addition of the covariates (CV_{final}=68%). Neither the base nor final population models reliably predicted the highest fexofenadine concentrations (>1000 ng/mL) [V1.63:324]. Despite these limitations, model predicted clearance values for the CIU population were within the range normally observed for fexofenadine.

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

The results of this study support the safety of twice daily ALLEGRA in adult and adolescent patients age 12 years and older at either the fexofenadine HCl 60 mg, 120 mg, or 240 mg dose for the treatment of symptoms of CIU. The

fexofenadine 20 mg bid dose rarely provided statistically significantly greater improvement in CIU symptoms over placebo. Importantly, the 60 mg bid dose appeared to offer the greatest decrease in CIU symptoms with the lowest frequency of adverse events and hence appears to be the preferred dose for treatment of CIU symptoms (over either the 120 mg or 240 mg bid doses). A dose response with respect to efficacy or safety issues was not noted for the 4 doses of ALLEGRA. Onset of action and duration of effect analysis (the end-of-dosing interval) was not formally performed in this study and was not deemed critical for the evaluation of CIU.

Overall, ALLEGRA was safe and well-tolerated given twice a day, at a dose of 20 mg, 60 mg, 120 mg or 240 mg in 352 patients. No serious related adverse events occurred in patients treated with ALLEGRA, nor were any deaths reported. Similar to placebo treatment, headache was the most common adverse event, followed by upper respiratory tract infection, and pharyngitis (similar AE profile to other studies reviewed in this ALLEGRA NDA). Virtually no cardiac adverse events were reported, although this may be a virtue of the limited adverse event reporting classification categories employed in this study and due to a lack of performing serial ECGs throughout the study. Interpretation of laboratory testing indicated no abnormal trends or worrisome laboratory findings in study 0039. No significant changes in vital signs were noted at the final study visit in safety evaluable patients. In addition, population PK studies performed in fexofenadine treated patients were consistent with findings seen in previous fexofenadine PK studies and predicted clearance values for the CIU population which were within the range normally observed for fexofenadine.

Summary:
Based on the results of this CIU trial, ALLEGRA tablets 60 mg bid demonstrated adequate evidence of efficacy and safety compared with placebo, for the twice daily treatment of CIU symptoms in adults and adolescents 12 years of age and older.

APPENDIX I: Study Procedures for CIU Study PJPR0039

[1.170:49]

Table 4. Table of Study Procedures

Study Procedure	*Visit*			
	1	*A**	*2*	*Final/Early Termination*
Day	0		15 ± 2	30 ± 4†
Informed Consent	X			
Medical/Medication History	X	X		
Physical Examination	X**	X		X
Inclusion/Exclusion Criteria	X	X		
Concomitant Medication Check			X	X
Blood Sample Clinical Lab‡	X**	X		X
Urine Sample for Drugs of Abuse Screen‡	X**	X		
Quality of Life/Work Productivity Questionnaires	X**	X	X	X
Daily Diaries Issued	X**	X	X	
Daily Diaries Collected			X	X
Investigator Assessments of CIU	X	X	X	X
Treatment-Emergent Adverse Event Check			X	X
Urine Pregnancy Test (all females)	X**	X		X
Study Medication Dispensed	X**	X	X	
Study Medication Collected			X	X
Blood Sample for Fexofenadine Levels			X	X

* For patients who met all entrance criteria with the exception of symptom assessment criteria.
** Performed at visit 1 only if patient was qualified to continued with study procedures at that time.
† Or early termination.
‡ Patient was randomized before results were available.

CHRONIC IDIOPATHIC URTICARIA IN ADULT PATIENTS (BID Dosing, Pivotal Trial (0067):

8.4. Protocol No. PJPR0067: 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) for the treatment of chronic idiopathic urticaria.

Principal Investigator: None, multi-center study.

Participating Centers: 35 U.S. and Canadian centers

8.4.1. Objective

The objectives of this pivotal CIU study were the same as those for the other pivotal CIU study—PJPR0039. Namely, 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.

8.4.2. Study Design

The basic study design for study PJPR0067 was identical to that of the phase 3 adult CIU study PJPR0039 and will not be re-iterated in this document (refer to study PJPR0039 for complete details): adult and pediatric SAR trials, albeit with modifications in the study protocol for the CIU indication. A table of study procedures is provided in Appendix 1 [V1.189:49, 184].

8.4.3. Protocol

8.4.3.1.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) [V1.189:31, 167].

(I) Inclusion Criteria [V1.189:32, 167]:
Same as those listed in study PJPR0039.

(II) Exclusion Criteria [V1.189:32-33, 168-169]:
Same as those listed in study PJPR0039.

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

(III). Concurrent Medication Restrictions [V1.189:34, 170-171]: 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 were identical to those cited in CIU study PJPR0039.

8.4.3.1.b. Procedure

A description of study procedure will not be re-iterated here, given the identical study design of PJPR0067 to CIU study PJPR0039 (please refer to the 'Procedure' section of PJPR0039) [V1.189:35-50, 172-186]. Patient self-rated symptom scores were collected twice daily before dosing with study drug. The same formulations of fexofenadine and same blinding strategy and dosing schedule as in study PJPR0039 was employed in study PJPR0067.

8.4.3.2. Clinical Endpoints

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

Primary Efficacy Variables [V1.189:57]:

(1) The change from baseline in the mean reflective pruritus score (MPS) over the 4 week double-blind treatment period.

Reviewer's Note: The range of scores that could be achieved for the primary efficacy endpoint ranged from 0-4 [V1.189:38].

Since single-blind placebo was administered the evening of Day 1 and the morning of Day 2, baseline symptom scores were defined using the 7:00 a.m. and 7:00 p.m. scores obtained on Day 2. Double-blind treatment scores were collected on Day 3 through the morning of the final visit (or early termination visit. The MPS (also MNW, MTSS; see below in 'Secondary Efficacy Variables' section for definition) was not computed on the day of the final visit since only a 7:00 a.m. score was recorded, hence the daily MPS was computed using the 7:00 a.m. and 7:00 p.m. 12 hour 'reflective' pruritus scores performed on each day of the study beginning on the day following Visit 1 or Visit 1a [V1.189:56]. Missing symptom scores were handled such that if any of the individual symptoms used in calculating the MPS, (also MTSS (sum of MPS and MNW), and MNW) were missing, missing data were not imputed and the MPS score was noted as missing (of note, this also excluded patients for secondary efficacy parameters in which MPS was used to calculate a symptom score, i.e. MTSS) [V1.189:56, 60, 188-190]. In general, collection of symptom scores and

determination of the primary efficacy endpoint was handled in the same manner as in study PJPR0039.

Secondary Efficacy Variables [V1.189:57-58, 190-191]:

(1) Change from baseline in the patient's reflective self-rated average mean number of wheals (MNW) score over the 4 week double-blind treatment period,
(2) Change from baseline in the patient's reflective self-rated average mean total symptom score (MTSS) over the 4 week double-blind treatment period,
(3) Change from baseline in the patient's self-rated average 7:00 a.m. 12 hour reflective mean number of wheals (MNW) score over the 4 week double-blind treatment period,
(4) Change from baseline in the patient's self-rated average 7:00 a.m. 12 hour reflective mean pruritus (MPS) score over the 4 week double-blind treatment period,
(5) Change from baseline in the patient's self-rated average 7:00 a.m. 12 hour MTSS score over the 4 week double-blind treatment period,
(6) Change from baseline in the patient's self-rated average 7:00 p.m. 12 hour reflective mean number of wheals (MNW) score over the 4 week double-blind treatment period,
(7) Change from baseline in the patient's self-rated average 7:00 p.m. 12 hour reflective mean pruritus (MPS) score over the 4 week double-blind treatment period,
(8) Change from baseline in the patient's self-rated average 7:00 a.m. 12 hour MTSS score over the 4 week double-blind treatment period,
(9) Weekly changes from baseline in the patient's MPS.
(10) Weekly changes from baseline in the patient's MNW.
(11) Change from baseline in patient self-rated average interference of wheals with sleep over the 4-week double-blind treatment period,
(12) Change from baseline in patient self-rated average interference of wheals with normal daily activities over the 4-week double-blind treatment period,
(13) Change from baseline in the average investigator's assessment of the number of wheals at Visit 2 and the final visit (or early termination),
(14) Change from baseline in the average investigator's assessment of the size of wheals at Visit 2 and the final visit (or early termination),
(15) Change from baseline in the average investigator's assessment of intensity of erythema at Visit 2 and the final visit (or early termination),
(16) Change from baseline in the average investigator's assessment of extent of skin area involved at Visit 2 and the final visit (or early termination),

All primary and secondary efficacy endpoints were analyzed using the 'intent-to-treat population', defined as 'patients with baseline and post-12 hour reflective MPS' [V1.189:54, 192], along with the evaluation of the primary efficacy endpoint and the secondary efficacy endpoint of patient self-rated

assessment of wheals using 'protocol correct' patients (= 'intent-to-treat' patients with no major protocol violations) [V1.189:54, 192].

Reviewer's Note: The secondary efficacy endpoints were identical to those evaluated in CIU study PJPR0039 and were deemed acceptable from the FDA standpoint. In addition, the QOL analysis was considered to be a secondary endpoint.

8.4.3.3. Statistical Analysis [V1.189:53, 187-195]

The statistical analysis employed in CIU study PJPR0067 was identical to that of CIU study PJPR0039 and was based on efficacy findings of the same once daily dosing CIU trial.

A sample size of 75 patients per treatment arm was calculated based on the primary efficacy endpoint of change in the MPS from baseline between placebo and a treatment to detect a treatment difference of at least 0.32 units in the average change of the MPS symptom score from baseline between placebo and treatment given a standard deviation of no larger than 0.68 units with 80% power, given a 2-sided test with type I α error=0.05. This power calculation was based on previous CIU trials of once daily dosing of fexofenadine HCl in which the difference in mean pruritus scores (average effect over 6 weeks) between fexofenadine HCl and placebo was 0.48 with a standard deviation of 0.68 [V1.189:53, 193].

This sample size likewise provided at least 80% power for the secondary analysis of change from baseline in the number of wheals score if the difference between fexofenadine HCl and placebo was at least 0.42 units and the population standard deviation was no greater than 0.90 units.

Based on these calculations and taking into account patient discontinuation, the target sample size was 400 randomized patients, which was expected to yield at least 375 ITT patients.

ANCOVA was used to compare the effects of fexofenadine HCl 20 mg po bid, 60 mg po bid, 120 mg po bid doses, 240 mg po bid doses and placebo for the primary efficacy variable, which included terms for investigative sites, treatment groups, and baseline MPS values (as covariate adjustment). The treatment-by investigative site interaction and treatment-by-baseline interaction were assessed separately for inclusion in the model and were included in the final model if significant at the α=0.10 level.

Of note, sites with fewer than 1 ITT patient/dose group were pooled to form 'pseudo-sites' prior to analysis after unblinding of the final database (and did not exceed the largest site in number of patients).

A supportive analysis was performed using ANCOVA of the rank transformed data without testing for normality. The rank analysis was performed on pooled data and pairwise comparisons to placebo were based on a step-down procedure so as to protect the overall type I error. In particular, the following comparisons were made sequentially: fexofenadine HCl 240 mg po bid vs.

placebo, fexofenadine HCl 120 mg po bid vs. placebo, fexofenadine HCl 60 mg po bid vs. placebo, and fexofenadine HCl 30 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 5 treatment groups was performed to further characterize the dose response relationship.

The same ANCOVA model used in the primary efficacy analysis was used to analyze all secondary efficacy variables.

Treatment effect was characterized in subgroups of patients defined by investigative site, age, gender, weight, and race. Age was only categorized as < 16 years of age, 16-40 years of age, and ≥ 40 years of age. Race was categorized as Caucasian and other. Weight was also categorized as: < 60 kg, 60-90 kg, and ≥ 90 kg [V1.189:60].

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 [V1.189:61, 195]. In addition, potentially clinically significant outliers were identified.

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

8.4.3.3.1. Pharmacokinetic Analysis [V1.170:204, 189:196]

Pharmacokinetic analysis and collection of plasma for measuring fexofenadine levels in CIU study PJPR0067 was identical to the procedure employed in CIU study PJPR0039.

8.4.3.3.2. Dermatology Quality of Life (DLQI) and Work Productivity and Impairment (WPAI) Questionnaire Evaluation

For study PJPR0067, impact of urticaria on patients' quality of life and work/classroom productivity was also evaluated using the same self-administered questionnaire employed in study PJPR0039—the Dermatology Life Quality Index (DLQI) and Work Productivity and Activity Impairment (WPAI) Questionnaire--completed by each patient at the end of each visit (Visit 1/1a, Visit 2, and the final/early termination visit) [V1.221:14]. A data set which provided evidence of a correlation between the HRQL endpoints and traditional endpoints for CIU (e.g. a patient self-rated assessment of pruritus) which were separate (i.e. 2 different data sets) was not provided by the sponsor. Methods employed for evaluation of QOL and work productivity in study PJPR0067 were the same as those utilized in CIU study PJPR0039 and are thus (in addition to the above stated deficiency)

affected by the same inadequacies as previously discussed for the QOL analysis of PJPR0039.

Despite, the deficiencies of the sponsor's QOL analysis, the overall procedure and plan for study interpretation is presented below.

The primary objective of this evaluation was to assess the impact of treatment on patients with CIU, as measured by the following endpoints: the average change from baseline in the overall DLQI score (a composite score of 6 domains delineated as (1)-(6) below), the average change from baseline % of work/classroom productivity, and the average change from baseline % of work/classroom time missed. A definition of a clinically relevant change (effect size) was not provided in the sponsor's submission of this QOL study. Nor does the sponsor state why the DLQI score is a preferred instrument for the CIU indication. Nonetheless, the sponsor's plan was to measure the average change from baseline using the average of data from Visit 2 and the final/early termination visit. Of note, work and classroom endpoints were calculated on different patients (employees and students, respectively).

Secondary objectives included an assessment of the following secondary endpoints: (1) DLQI symptoms/feeling domain, (2) DLQI daily activities domain, (3) DLQI leisure domain, (4) DLQI work/school domain, (5) DLQI personal relations domain, (6) DLQI treatment domain, (7) overall work/classroom productivity, and (8) regular activity [V1.221:15]. Secondary endpoints were defined as the average change from baseline in each of the 6 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 average change from baseline to Visit 2 and from baseline to the 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 [V1.221:16].

A sample case report form for the DLQI questionnaire and sample form of the WPAI questionnaire is presented on pages 138-143 and pages 185-244, respectively of Volume 221 of NDA 20-872. For the DLQI questionnaire, items were generally rated as either: very much, a lot, a little, not at all, or not relevant (pertaining to skin condition) [V1.221:139-140]. For the WPAI questionnaire, work, productivity, and resource utilization were generally rated on a scale of 1-10 [V1.221:142-143]. The specific scoring method for each of the domains was calculated using an equation, which is discussed on page 26 of Volume 221. In these computations, the higher the score, the greater the impairment of quality of life.

The DLQI was designed to be a short and simple measure of the impact of various skin diseases on patients. This specialty-specific focus is created in the DLQI by asking patients to attribute the causes of their negative life experiences to the skin disease rather than to adverse experiences caused by other health and non-health-related factors. The random error or reliability of the DLQI has been assessed using a test-retest procedure, with responses found to be highly correlated. Information provided by the sponsor regarding the DLQI's internal

consistency, reliability, and validity are summarized as follows: The internal consistency of the DLQI items was assessed by examining the bivariate inter-correlations among all items. The correlations ranged from a low of 0.23 to a high of 0.70; none were negative. This correlation matrix was supposed to provide evidence in support of the scale's internal consistency. Scores on the DLQI were compared to a control group to test known groups validity and all individual questions showed significantly higher scores on the clinical group than the control group. The responsiveness of the DLQI to clinical change has been examined in 3 published studies, where it was shown that the change scores paralleled the measure of clinical severity in all studies [V1.221:248-271]. 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 DLQI and WPAI is presented on pages 24-30 of Volume 221, however in summary, sample size for these QOL study was dependent on the sample size of the CIU study (375 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 [V1.221:25].

ANCOVA was used for the analysis of primary outcomes variables (with terms for treatment, investigative site, and baseline values as covariate adjustment). 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 life and work/classroom productivity observations [V1.221:28]. No discussion of adjustment for multiple comparisons is addressed in the DLQI protocol.

8.4.4. Results

8.4.4.1. Patient Demographics [V1.189:62-69, V1.197:94-95]

(A) A total of 476 patients were randomized into the study, though 15 patients discontinued the study following randomization but prior to receiving double-blind medication. The remaining 461 were exposed to double-blind treatment, and 373 of these patients completed the study.

Four hundred and fifty five (455) patients of the 476 randomized 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. Fifteen (15) patients discontinued the study before receiving double-blind medication and 6 patients had no post-baseline AE assessment [V1.189:63]. For the 6 patients excluded from the safety analysis who received double-blind

study medication, no record of possible AEs experienced was provided by the sponsor since as the sponsor states, no post-baseline AE assessment was performed [V1.189:66]. Whether any of these 6 patients may have experienced an AE is not addressed in the sponsor's submission.

Four hundred and thirty nine (439) patients were identified as 'intent-to-treat' patients (=exposed patients with baseline and post-12 hour reflective MPS scores [V1.189:63]) and were used in the 'intent-to-treat' analysis (22 patients from the safety evaluable population were excluded for ITT because they had no baseline or post-baseline 12 hour reflective MPS assessments [V1.189:63]). Of the 439 ITT patients, only 309 had no major protocol violations and were classified as 'protocol correct' [V1.170:63] (i.e. a large number of patients in this study had protocol violations, similar to CIU study PJPR0039). A distribution of the patient population is summarized in Table II. below:

Table II. Patient Disposition [V1.189:65]

	Fexofenadine 20 mg bid	Fexofenadine 60 mg bid	Fexofenadine 120 mg bid	Fexofenadine 240 mg bid	Placebo	TOTAL
Randomized	99	95	95	92	95	476
Intent-to-Treat	90	91	86	89	83	439
Safety Evaluable	93	95	89	93	85	455
Protocol Correct	57	62	64	67	59	309

(B) A total of 103 patients exposed to double-blind medication discontinued the study prior to scheduled completion [V1.189:67]. Similar to study PJPR0039, the most common reason for early discontinuation was treatment failure (44/476 total patients or 9.2% of patients in all 5 treatment groups). Of the 44 treatment failures, 18 were from the placebo group and 11 were from the 20 mg treatment group—indicating that not all patients responded adequately in the 20 mg treatment group. The frequencies of discontinuation for the fexofenadine HCl 60 mg (5.3%), 120 mg (5.3%), and 240 mg groups (5.4%) were comparable. This data is summarized in Table III. [V1.189:67].

Table III. Number and Percentage (%) of Randomized Patients for CIU 0067 Who Discontinued the Study with Reasons for Discontinuation, ITT Population [V1.189:67]

	Fexo 20 mg (n=99)[1]	Fexo 60 mg (n=95)[1]	Fexo 120 mg (n=95)	Fexo 240 mg (n=92)	Placebo (n=95)	TOTAL (n=476)
Number (%) Completed	73 (73.7%)	75 (78.9%)	82 (86.3%)	76 (82.6%)	67 (70.5%)	373 (78.4%)
Reasons for Discontinuation						
Adverse event	5 (5.1%)	5 (5.3%)	3 (3.2%)	1 (1.1%)	5 (5.3%)	19 (4.0%)
Treatment Failure	11 (11.1%)	5 (5.3%)	5 (5.3%)	5 (5.4%)	18 (18.9%)	44 (9.2%)
Lost to follow-up	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	3 (0.6 %)
Patient elected to discontinue after exposure	2 (2.0%)	1 (1.1%)	2 (2.1%)	5 (5.4%)	1 (1.1%)	11 (2.3%)
Use of prohibited medication(s)	0 (0.0%)	3 (3.2%)	2 (2.1%)	1 (1.1%)	1 (1.1%)	7 (1.5%)
Other	8 (8.1%)	5 (5.3%)	1 (1.1%)	3 (3.3%)	7 (7.5%)	19 (4.0%)
ALL REASONS	26 (26.3%)	20 (21.1%)	13 (13.7%)	16 (17.4%)	28 (29.5%)	103 (21.6%)

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

Reviewer's Note: Similar to CIU study PJPR0039, for all 5 treatment groups, the total % of patient discontinuation was significantly higher than that noted in any of the other trials in this NDA (>20%) and was higher than normally deemed acceptable in such a study (i.e. ≤ 10%), though CIU- perhaps being a more systemic illness than SAR, might in general be less responsive to antihistamine therapy. Compared with PJPR0039 however, somewhat fewer patients in this study discontinued treatment across the spectrum of reasons than in PJPR0039. The highest discontinuation rate was seen in the placebo and fexofenadine 20 mg bid group, with slightly lower rates at the medium to high doses of fexofenadine (60 mg, 120 mg and 240 mg bid). Similar to PJPR0039, the predominant reason for patient discontinuation was treatment failure.

(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 [V1.189:69, V1.197:94-95]:

Variable	Fexo 20 mg (n=91)	Fexo 60 mg (n=86)	Fexo 120 mg (n=89)	Fexo 240 mg (n=83)	Placebo (n=90)	P-Value
Gender: (n, (%))						
Male	25 (28%)	22 (26%)	17 (19%)	29 (35%)	20 (22%)	
Female	66 (73%)	64 (74%)	72 (81%)	54 (65%)	70 (78%)	.1677[1]
Race: (n, (%))						
Caucasian	84 (92%)	75 (87%)	80 (90%)	73 (88%)	83 (92%)	
Black	1 (1%)	5 (6%)	5 (6%)	3 (4%)	3 (3%)	
Asian	4 (4%)	4 (5%)	2 (2%)	6 (9%)	3 (1%)	
Multiracial	2 (2%)	2 (2%)	2 (2%)	1 (1%)	1 (1%)	.8399
Age: (yrs)						
Mean ± SD	37.58 ± 11.82	37.91 ± 13.14	38.25 ± 12.28	39.48 ± 13.26	39.22 ± 12.82	
Range	12-59	12-66	12-65	12-68	13-67	.8879
Age: (yrs, n%)						
<16	3 (3%)	2 (2%)	2 (2%)	3 (4%)	2 (2%)	
16-<40	46 (51%)	49 (57%)	44 (49%)	37 (45%)	42 (47%)	
≥ 40	42 (46%)	35 (41%)	43 (48%)	43 (52%)	46 (51%)	.8874
Weight: (kg)						
Mean ± SD	74.29 ± 19.98	76.15 ± 19.19	74.83 ± 20.17	76.02 ± 20.6	76.62 ± 18.62	
Range	32.7-126.1 kg	32.2-136.1 kg	33.6-130.2 kg	36.7-143.3 kg	46.9 –136.1 kg	.8281
Height: (in)						
Mean ± SD	66.11 ± 3.72	65.6 ± 3.73	64.96 ± 3.86	66.57 ± 3.87	65.40 ± 3.11	
Range	55.0-77.0	55.0-76.0	51.2-78.5	59.0-76.0	59-73	.0690

[1]P-value comparing the 5 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 5 treatment groups, with the majority of patients Caucasian and a greater proportion of female:male patients (generally > 2:1). No statistically significant differences or trends were noted between the treatment groups with regard to demographic factors, except for a marginal difference in height between the 5 treatment arms.

(D) Patient distribution by disease severity at baseline in the ITT population was provided by the sponsor for a number of patient and investigator-rated efficacy parameters [V1.189:71-74, 79] and no statistically significant difference was noted between the 5 ITT treatment groups for any of these parameters, including the primary efficacy endpoint—the MPS (p=0.2692), except for the interference with normal daily activities score (p=0.0319) and the amount of itching felt by patient score (12 hour reflective score, p=0.0358) [V1.189:72, 74]. This difference appeared to be primarily driven by the fexofenadine 20 mg group having fewer patients with severe itching and the fexofenadine 120 mg group having more patients with severe itching.

With regard to the primary efficacy variable, the range of the MPS score for the baseline period ranged from 0-4.0 (std. dev.=0.865) for the placebo group, 0-4.0 (std. dev.=0.938) for the fexofenadine 20 mg group, 0-4.0 (std. dev.=0.904) for the fexofenadine 60 mg group, 0-4.0 (std. dev.=0.850) for the fexofenadine 120 mg group, and 0-3.5 (std. dev.=0.736) for the fexofenadine 240 mg group. In summary, these ranges in MPS were similar between the 5 treatment arms.

(E) Patient Validity [V1.189:66-68, 76-77]

One hundred and fifty two (152) patients (or 33.0% of all exposed patients) (39 treated with fexofenadine HCl 20 mg, 29 treated with fexofenadine HCl 60 mg, 29 treated with fexofenadine HCl 120 mg, 20 treated with fexofenadine HCl 240 mg and 35 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 (23.2% of total patients), followed by missing efficacy data (10.4% of total patients). The % of patients with a violation generally tended to be higher for the placebo group and/or the fexofenadine 20 mg group for all categories of 'major protocol violation' with the exception of: 'failure to meet entrance criteria' which was highest in the fexofenadine 60 mg group, closely followed by the fexofenadine 20 mg group.

With respect to use of prohibited medications, 26 patients (27.7%) in the placebo group, 28 patients (29.2%) in the fexofenadine HCl 20 mg group, 20 patients (22.0%) in the fexofenadine HCl 60 mg group, 20 patients (21.5%) in the fexofenadine HCl 120 mg group, and 13 patients (14.9%) in the fexofenadine HCl 240 mg group used ≥ 1 prohibited medication [V1.189:66]. Unlike study PJPR0039, use of prohibited medications was not higher in the fexofenadine 60 mg and 120 mg groups, but rather slightly higher in the fexofenadine 60 mg and placebo group. The most commonly used prohibited medications consisted of aspirin, NSAIDs, and narcotic analgesics across all 5 groups, with a slightly higher incidence of use of other H_1 antagonists (e.g. loratadine, cetirizine, fexofenadine) in the placebo group or fexofenadine 20 mg group patients than either of the other 3 'higher dose' active treatment groups [V1.189:77]. A summary of invalidated patients and the reasons for invalidation are summarized in Table 11 of the study report for CIU study PJPR0067 [V1.189:66].

Reviewer's Note: Criteria for invalidation of patient data were comparable to those seen in the SAR trials and CIU trial PJP0039 and thus deemed reasonable by the medical reviewer, although the overall numbers of invalidated patients per exposed patients was significantly higher across all treatment arms. This finding was driven by the high incidence of prohibited medication use amongst CIU patients.

(F) Duration of Study Medication Exposure [V1.189:74-75]

The mean duration of double-blind exposure to study treatment for the safety population was 26.47 days (± 9 days) for all 5 treatment groups. The mean/range of duration of exposure was 24.39 days/3-35 days for the placebo group (n=93 patients), 25.98/3-73 days for the fexofenadine HCl 20 mg group (n=95), 26.21/3-33 days for the fexofenadine HCl 60 mg group (n=91), 28.01/2-43 days for the fexofenadine HCl 120 mg group (n=85), and 27.88/2-35 days for the fexofenadine HCl 240 mg group (n=85). Duration of exposure was calculated using days between randomization and last dosing day of the double-blind treatment period.

(G) Patient Compliance [V1.189:76]

Assessment of patient compliance with double-blind medication was performed in the same manner as in study PJPR0039; namely 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 from Visit 1/1a to the final study visit/early termination visit (the double-blind period). Average compliance was found to be 98.83% for the placebo group, 97.18% for the fexofenadine HCl 20 mg group, 99.05% for the fexofenadine HCl 60 mg group, 98.62% for the fexofenadine HCl 120 mg group, and 99.66% for the fexofenadine HCl 240 mg group [V1.170:75]. Five 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 (compliance was to be between 90-110%) [V1.189:49].

8.4.4.2. Efficacy Endpoint Outcomes

(1) Primary Efficacy Variables:

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=91 for fexofenadine HCl 20 mg group, n=86 for fexofenadine HCl 60 mg group, n=89 for fexofenadine HCl 120 mg group, n=83 for fexofenadine HCl 240 mg group, and n=90 for placebo) for the primary efficacy variable ~~of the change from~~ baseline in the mean pruritus score (MPS); where the primary comparison of interest was the response of the 4 fexofenadine doses vs. placebo. Choice of a reflective MPS 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 decreasing pruritus symptoms over the preceding 12 hours. The 4 comparisons of individual fexofenadine dose groups to placebo were performed using a step-down approach in order to control the overall error rate.

Results of the primary efficacy analysis for CIU study 0067 are summarized in Table V., and are overall similar to results seen in the other pivotal CIU study in this submission—PJPR0039; albeit with a slightly greater effect of treatment noted in all 5 treatment groups. A statistically significant decrease in the primary efficacy endpoint for all 4 fexofenadine doses compared to placebo was demonstrable, with the greatest numerical decrease in MPS over the 4 week double-blind period noted for the fexofenadine 240 mg bid group (change of -1.18 units), closely followed by the fexofenadine 60 mg and 120 mg bid groups (change of -1.07 units seen in both). In this study (similar to study PJPR0039), a progressive numerical trend for decrease in the MPS was seen with increased fexofenadine dose from 20 mg bid to 240 mg bid (even though the dose response from the 60 mg and 120 mg bid dose was relatively flat), with the greatest decrement in MPS noted going from the fexofenadine 20 mg dose to the fexofenadine 60 mg dose. The test for dose response (linear trend test) was significant (p=0.0001) [V1.189:78-79].