Similar results were seen with analysis of the 'protocol correct' group for study 0067 and there was a greater response in MPS across all 5 treatment arms [V1.189:81]. Statistically significant differences between the 4 active treatment groups and placebo were noted.

Of note, one of the investigators in study PJPR0039-Dr. Edwards (site PPJST0283) who was disqualified did not partake in study PJPR0067.

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 [V1.189:78]. The treatment-by-baseline TSS interaction (without treatment-by-site) was not found to be statistically significant (p=0.1080) [V1.189:79]. There was no statistical evidence of dependence of treatment effect on the investigative site (p=0.8491) [V1.189:79].

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, and comparable to the 120 mg bid and 240 mg bid dose, although numerically, the 240 mg bid dose appeared to decrease the primary efficacy endpoint the most. These results were overall consistent with those seen in CIU study PJPR0039. Hence, based of these clinical data, the 60 mg bid dose appears most appropriate 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 [V1.189:79]

	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=91)	**(n=86)**	**(n=89)**	**(n=83)**	**(n=90)**				
Baseline MPS	1.85 ± 0.098	1.98 ± 0.097	2.04 ± 0.090	1.81 ± 0.081	1.92 ± 0.091				
Double-blind Treatment Period MPS	1.00 ± 0.072	0.86 ± 0.076	0.88 ± 0.072	0.69 ± 0.065	1.43 ± 0.083				
Change from baseline in MPS	-0.88 ± 0.068	-1.07 ± 0.070	-1.07 ± 0.069	-1.18 ± 0.071	-0.47 ± 0.068	**0.0001**	**0.0001**	**0.0001**	**0.0001**
Mean Difference ± SE						-.41±.10	-.60±.11	-.60±.10	-.71±.10

[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 [V1.189:107], age [V1.189:106, V1.197:268], race [V1.189:108], weight [V1.189:109], and study site [V1.189:102-105, V1.197:261-266]. 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 of age (i.e. ≤ 16 years, 16- <40 years of age, and ≥ 40 years of age) was performed [V1.189:106]. The statistical model used for this analysis was ANCOVA with a significance level of 0.1 [V1.189:102].

Based on these subgroup analyses, no statistical significance was noted for the study site by treatment interaction (p=0.9889) or main effect of site for mean change from baseline in MPS (p=0.4832); indicating that the treatment effects were consistent across investigative sites [V1.189:105]. Furthermore, no statistical significance was noted for the treatment-by-age interaction for mean change from baseline in MPS (p=0.7947). The main effect of age was also not statistically significant (p=0.0673). No statistically significant difference was noted in the gender by treatment interaction (p=0.2604) or main effect of gender (p=0.9757) for the change in the mean reflective MPS over the double-blind period [V1.189:107], no statistical significance was noted for weight by treatment (p=0.7254) or main effect of weight (p=0.4831) for the change in the mean reflective MPS [V1.170:112-113], along with no statistical significance noted for

race by treatment interaction (p=0.6014) or main effect of race (p=0.7437) [V1.189:108-109]; 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 PJPR0067 (as in PJPR0039). Review of numerical trends generally showed a greater decrease in symptoms with active treatment for the fexofenadine 120 mg and 240 mg bid groups, very closely followed by the fexofenadine 60 mg bid group for most of the secondary endpoints [V1.189:82, 85-102]. 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 [V1.189: 82, 85-102, V1.197:246-254].

Specifically with regard to analysis of the week 1 vs. week 2 vs. week 3, vs. week 4 change in mean reflective MPS, all 4 active treatment groups in this study (including the fexofenadine 20 mg group showed a statistically significantly greater decrease compared to placebo treatment for all 4 weeks of treatment, in contrast to study PJPR0039 where only the fexofenadine 60 mg group showed a consistent significantly lower decrement in MPS [V1.189:87-88]. Similar results were also seen for the weekly analysis of the mean average MNW (mean # of wheals) scores where the fexofenadine 60 mg, 120 mg, and 240 mg bid groups demonstrated a consistent statistically significant decrease in MNW during all 4 weeks of the study [V1.189:90-91].

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 the closest 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, none of the 4 active treatment groups demonstrated a statistically significant decrease in CIU symptoms compared to placebo treatment [V1.189:101-102] (in contrast to study PJPR0039 where 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])). Numerically, compared to the patient-self rated 7 a.m. and 7 p.m. 12 hour reflective MNW scores for the double-blind period, the physician-

rated differences in these scores were somewhat smaller, despite different numerical scales [V1.170:189:95-96, 101]. Why the overall difference noted between patient-rated and physician-rated is difficult to explain, it is possible that a large placebo response was seen in the physician-rated responses, which is the likely explanation for this finding in study PJPR0067. Based on review of the secondary efficacy endpoints for PJPR0067, 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 PJPR0067 (nor PJPR0039).

Reviewer's Note: Review of the secondary efficacy endpoints for CIU study 0067 indicates that fexofenadine 60 mg bid dose is the most appropriate dose for treatment of CIU in patients ≥ 12 years of age since the numerical differences between the 60 mg bid dose and the higher fexofenadine doses (120 mg bid and 240 mg bid) were small. 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 0067: Fexofenadine HCl 20 mg, Fexofenadine HCl 60 mg, Fexofenadine HCl 120 mg, Fexofenadine HCl 240 mg, vs. Placebo [V1.189:82, 85-102, V1.197:246-254]
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=0.0238)	Yes (p=0.0002)	Yes (p=0.0001)	Yes (p=0.0001)
2. Δ from baseline in patient self-rated average MTSS over the 4 week double-blind period	Yes (p=0.0010)	Yes (p=0.0001)	Yes (p=0.0001)	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=0.0276)	Yes (p=0.0007)	Yes (p=0.0001)	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=0.0001)	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=0.0012)	Yes (p=0.0001)	Yes (p=0.0001)	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=0.0541)	Yes (p=0.0009)	Yes (p=0.0001)	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=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)	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=0.0030)	Yes (p=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)
9. Weekly Δs from baseline in patient's MPS:				
Week 1	Yes (p=0.0003)	Yes (p=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)
Week 2	Yes (p=0.0016)	Yes (p=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)
Week 3	Yes (p=0.0023)	Yes (p=0.0001)	Yes (p=0.0003)	Yes (p=0.0001)
Week 4	Yes (p=0.0002)	Yes (p=0.0001)	Yes (p=0.0005)	Yes (p=0.0001)

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 0067
Fexofenadine HCl 20 mg, Fexofenadine HCl 60 mg, Fexofenadine HCl 120 mg, Fexofenadine HCl 240 mg, vs. Placebo [V1.189:82, 85-102, V1.197:246-254]

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=0.0126)	Yes (p=0.0001)	Yes (p=0.0001)	Yes (p=0.0001)
Week 2	No (p=0.1368)	Yes (p=0.0043)	Yes (p=0.0002)	Yes (p=0.0004)
Week 3	No (p=0.1428)	Yes (p=0.0196)	Yes (p=0.0017)	Yes (p=0.0111)
Week 4	Yes (p=0.0331)	Yes (p=0.0028)	Yes (p=0.0006)	Yes (p=0.0003)
11. Δ from baseline in patient self-rated average interference of wheals with sleep over the 4 week double-blind period	Yes (p=0.0003)	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=0.0001)	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=0.3362)	No (p=0.6113)	No (p=0.6850)	No (p=0.1350)
14. Δ from baseline in the average investigator's assessment of the size of wheals at Visit 2 and the final visit.	No (p=0.4488)	No (p=0.2915)	No (p=0.5179)	No (p=0.0432)
15. Δ from baseline in the average investigator's assessment of intensity of erythema at Visit 2 and the final visit.	No (p=0.3051)	No (p=0.3090)	No (p=0.4021)	No (p=0.0407)
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=0.2315)	No (p=0.1285)	No (p=0.1316)	No (p=0.0077)

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

8.4.4.2.1. Quality of Life (QOL) Analysis

The sponsor's evaluation of the health outcome parameters in CIU study PJPR0067 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 423 patients that constituted the QOL ITT population ($p \leq 0.0085$) [V1.221:42]. Treatment comparisons (active treatment-placebo) for average change from baseline in overall DLQI were –2.021 units in the fexofenadine 20 mg bid group, -3.192 units in the fexofenadine 60 mg bid group, -3.220 units in the fexofenadine 120 mg bid group, and –3.415 units in the fexofenadine 240 mg bid group [V1.221:42].

Analyses of changes in the 6 individual DLQI domains (symptoms/feelings, daily activities, leisure, work/school, personal relations, and treatment) were

performed to explore the extent of the differences observed in the overall DLQI score and showed improvement in approximately half (3 out of 6) domains, (excluding the leisure, treatment, and personal relations domain) for all 4 fexofenadine groups compared to placebo, with the exception of the fexofenadine 20 mg bid group ($p \leq 0.0169$ for the symptoms/feelings domain, $p \leq 0.0096$ for the daily activities domain, and $p \leq 0.0099$ for the work/school domain [V1.221:120]. Aside from the fexofenadine 60 mg group, there were no statistically significant differences among treatments with respect to the treatment domain. The fexofenadine 60 mg and 120 mg bid groups had significantly greater improvement than placebo in the personal relations domain ($p \leq 0.0046$). The domain which appeared to contribute the most to the determination of the overall DLQI score (the primary endpoint) for each of the 4 fexofenadine treatment groups consisted of the symptoms/feelings domain. These results are summarized in Table 8 of Volume 221 of NDA 20-872 [V1.221:46] and are presented below in Table VII.

With respect to the change from baseline in the Work Productivity and Activity Impairment (WPAI) assessment, all fexofenadine doses were statistically significantly superior to placebo with respect to average change from baseline in percent work productivity ($p \leq 0.0138$) [V1.221:50]. These results are summarized in Table 9 of Volume 221 of NDA 20-872 [V1.221:50]. 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) [V1.221:52-53]. Similar results were likewise seen in CIU study PJPR0039. 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 that were statistically significantly greater than placebo treatment ($p \leq 0.0152$) [V1.221:56]. Results for this domain are summarized in Table 11 of Volume 221 of NDA 20-872 [V1.221:56].

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 10-17) per treatment group, the comparison may have been sufficiently underpowered to detect a statistical difference [V1.221:57-58]. Again, similar findings to those noted above were shown in CIU study PJPR0039. 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 [V1.221:60-61]. 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 ($p \leq 0.0112$) [V1.221:63]. These results are presented in Table 17 of Volume 221 of NDA 20-872 [V1.221:63].

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], conclusions that can be reached from these studies are limited.

Table VII: DLQI SUMMARY: [1]Average Change from Baseline [V1.221:46]

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
9. Overall DLQI Score (Planned Primary Analysis)	-2.021 ± .7625 (p=0.0085)	-3.192 ± .7962 (p=0.0001)	-3.220 ± .7693 (p=0.0001)	-3.415 ± .7913 (p=0.0001)
2. Symptoms/Feelings Domain	-0.779 ± .2016 (p=0.0001)	-0.945 ± .2127 (p=0.0001)	-1.007 ± .2043 (p=0.0169)	-1.406 ± .2099 (p=0.0001)
3. Daily Activities Domain	-0.323 ± .1801 (p=.0743)	-0.492 ± .1886 (p=0.0096)	-0.753 ± .1820 (p=0.0001)	-0.556 ± .1869 (p=0.0032)
4. Leisure Domain	-0.391 ± .2191 (p=0.0754)	-0.342 ± .2297 (p=0.1377)	-0.339 ± .2221 (p=0.1286)	-0.505 ± .2284 (p=0.0278)
5. Work/School Domain	-0.145 ± .1082 (p=0.1815)	-0.345 ± .1140 (p=0.0028)	-0.287 ± .1103 (p=0.0099)	-0.374 ± .1132 (p=0.0011)
6. Personal Relations Domain	-0.407 ± .2125 (p=0.0565)	-0.830 ± .2221 (p=0.0002)	-0.618 ± .2159 (p=0.0046)	-0.413 ± .2225 (p=0.0645)
7. Treatment Domain	-0.166 ± .0967 (p=0.0876)	-0.335 ± .1010 (p=0.0010)	-0.163 ± .0978 (p=0.0959)	-0.154 ± .1005 (p=0.1266)

[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).

8.4.4.3. Safety Analysis

Safety analysis for study PJPR0067 was essentially the same as that conducted for other fexofenadine trials (adult CIU study PJPR0039, 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 five (95) patients comprised the fexofenadine HCl 20 mg, 89 patients comprised the fexofenadine HCl 60 mg, 93 patients comprised the fexofenadine HCl 120 mg, 85 patients comprised the fexofenadine HCl 240 mg, and 93 patients

comprised the placebo group safety evaluable populations (i.e. exposed to double-blind medication with at least 1 postbaseline AE assessment) [V1.189:110]. In this trial, the safety evaluable population (n=455) was somewhat higher than the ITT population (patients with baseline and postbaseline 12 hour reflective MPS assessments; n=439 patients total) [V1.189:63].

8.4.4.3.1. 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 [V1.189:69]. In summary, all 5 treatment groups were similar in baseline characteristics.

8.4.4.3.2. 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 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.

8.4.4.4. 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 drug groups and ranged from ~ 50-67% for all AEs combined [V1.189:111-114]. As previously noted for other clinical indications, the most frequent adverse event for all 5 treatment groups consisted of headache (with an incidence of 26.3% in the fexofenadine HCl 20 mg group, an incidence of 13.7% in the fexofenadine HCl 60 mg group, an incidence of 20.4% in the fexofenadine HCl 120 mg group, an incidence of 15.3% in the fexofenadine HCl 240 mg group, and an incidence of 18.3% in the placebo group), followed by upper respiratory tract infection (an incidence of 5.3% in the fexofenadine HCl 20 mg group, an incidence of 5.6% in the fexofenadine HCl 60 mg group, an incidence of 17.2% in the fexofenadine HCl 120 mg group, an incidence of 8.2% in the fexofenadine HCl 240 mg group, and an incidence of 7.5% in the placebo group) [V1.189:111]. 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, but similar in frequency to that noted in pivotal CIU study PJPR0039. With the minor exception of a progressively slightly higher incidence of abdominal pain across the 3 active treatment groups, starting with fexofenadine 60 mg po bid, no dose response for AE frequency was noted across

treatment groups [V1.189:112]. Of note, the incidence of somnolence was very low for all 4 treatment groups (fexofenadine 20 mg: 1.1%, 60 mg: 1.1%, 120 mg: 3.2%, 240 mg: 1.2%, and placebo: 0.0%) [V1.189:111].

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 0067 ≥ 3% (chosen as a cut-off because of the large # of AEs > 1% noted in the AE database for study 0067), 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 [V1.189:111-114, V1.201:46-51]

BODY SYSTEM	Preferred Term	Fexo 20 mg (n=95) n (%)	Fexo 60 mg (n=89) n (%)	Fexo 120 mg (n=93) n (%)	Fexo 240 mg (n=85) n (%)	Placebo (n=93) n (%)
All Systems	Any AE	67 (70.5%)	51 (57.3%)	60 (64.5%)	50 (58.8%)	61 (65.6%)
Neurologic	**Headache**	**25 (26.3%)**	**12 (13.5%)**	**19 (20.4%)**	**13 (15.3%)**	**17 (18.3%)**
	Dizziness	2 (2.4%)	2 (2.2%)	4 (4.3%)	2 (2.4%)	1 (1.1%)
Respiratory	URI	**5 (5.3%)**	**5 (5.6%)**	**16 (17.2%)**	**7 (8.2%)**	**7 (7.5%)**
	Pharyngitis	**8 (8.4%)**	**4 (4.5%)**	**2 (2.2%)**	**6 (7.1%)**	**7 (7.5%)**
	Rhinitis	**6 (6.3%)**	**4 (4.5%)**	**1 (1.1%)**	**2 (2.4%)**	**6 (6.5%)**
	Upper respiratory congestion	0 (0.0%)	2 (2.2%)	1 (1.1%)	3 (3.5%)	3 (3.2%)
	Sinusitis	3 (3.2%)	2 (2.2%)	3 (3.2%)	1 (1.2%)	2 (2.2%)
Body as a Whole-General	Pain	**3 (3.2%)**	**3 (3.4%)**	**3 (3.2%)**	**3 (3.5%)**	**8 (8.6%)**
	Abdominal Pain	1 (1.1%)	1 (1.1%)	2 (2.2%)	3 (3.5%)	3 (3.2%)
	Back Pain	3 (3.2%)	1 (1.1%)	0 (0.0%)	2 (2.4%)	1 (1.1%)
	Fever	2 (2.1%)	0 (0.0%)	4 (4.3%)	0 (0.0%)	2 (3.2%)
	Fatigue	0 (0.0%)	0 (0.0%)	2 (2.2%)	0 (0.0%)	3 (3.2%)
GI	Dyspepsia	**6 (6.3%)**	**0 (0.0%)**	**6 (6.5%)**	**3 (3.5%)**	**5 (5.4%)**
	Nausea	**6 (6.3%)**	**1 (1.1%)**	**5 (5.4%)**	**6 (7.1%)**	**4 (4.3%)**
	Diarrhea	3 (3.2%)	3 (3.4%)	1 (1.1%)	1 (1.2%)	5 (5.4%)
	Vomiting	0 (0.0%)	1 (1.1%)	2 (2.2%)	1 (1.2%)	3 (3.2%)
Infectious Disease	Influenza	**6 (6.3%)**	**4 (4.5%)**	**5 (5.4%)**	**6 (7.1%)**	**4 (4.3%)**
Musculo-skeletal	Myalgia	**5 (5.3%)**	**3 (3.4%)**	**1 (1.1%)**	**3 (3.5%)**	**1 (1.1%)**
	Arthalgia	4 (4.2%)	0 (0.0%)	1 (1.1%)	1 (1.2%)	3 (3.2%)
Psychiatric	Insomnia	3 (3.2%)	1 (1.1%)	2 (2.2%)	3 (3.5%)	1 (1.1%)
Reproductive	Dysmenorrhea	3 (3.2%)	1 (1.1%)	2 (2.2%)	1 (1.2%)	2 (2.2%)

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 [V1.189:117].

8.4.4.4.2. Cardiac Adverse Events

Cardiovascular adverse events were only specifically recorded under the 'cardiovascular' category for the 3 clinical endpoints: palpitation (0.0-1.2% incidence across all 4 fexofenadine doses, 0.0% for the placebo group), hypertension (0.0-1.1 % incidence across all 4 fexofenadine doses, 0.0% for the placebo group) and syncope (0.0% incidence across all 4 fexofenadine doses, 1.1% for the placebo group); however the additional adverse events of: dizziness (2.1-4.3% incidence across all 4 fexofenadine doses, 1.1% for the placebo group) and chest pain (0.0-1.1% across all 4 fexofenadine doses, 1.1% for the placebo group) were added to the list of cardiovascular adverse events by the medical reviewer [V1.189:113]. 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.

8.4.4.5. 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 and CIU study PJPR0039, many of the adverse events described in the safety database for study PJPR0067 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).

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

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

8.4.4.7. Patient Discontinuation due to Adverse Events

A total of 17 patients randomized to double-blind study medication discontinued treatment due to AEs: 12 patients with either of the 4 doses of fexofenadine HCl (4 fexofenadine 20 mg patients, 4 fexofenadine 60 mg patients, 3 fexofenadine 120 mg patients, and 1 fexofenadine 240 mg patient) and 5 patients treated with placebo discontinued treatment prematurely due to adverse events [V1.189:120, V1.201:336-337]. On review of the adverse event summaries by the medical reviewer, 1 patient (taking fexofenadine 120 mg bid (patient # 628-007) discontinued treatment due to somnolence which may have been related to study medication [V1.189:120]. In addition, 1 patient receiving placebo discontinued treatment due to syncope (patient # 614-014) [V1.189:120]. The other reasons for patient discontinuation for the fexofenadine groups were similar to those noted in other trials with fexofenadine (e.g. headache, bronchitis) and not dissimilar for the reasons leading to discontinuation in the placebo group patients (i.e. asthma and URI) [V1.189:111, 120].

8.4.4.8. Serious Adverse Events and Death

No deaths were reported during this CIU trial for any of the 5 treatment groups [V1.189:111, 119]. One patient (# 600-010), a 28 year old Caucasian female was hospitalized for nausea and vomiting after 18 days of treatment with fexofenadine 60 mg po bid [V1.189:111, 119, V1.201:294]. An endoscopy performed on day 19 revealed a hiatal hernia and thus this event was felt by the investigator not to be related to study medication.

The sponsor's definition of [4]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 [V1.189:118].

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) [V1.189:118-119]. 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 7 patients in the placebo group and 14 patients in the fexofenadine groups [V1.189:118-119].

8.4.4.9. 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) 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 SGPT (ALT) was noted (p=0.0482) [V1.189:121]. This change tended to be greater in placebo and fexofenadine 20 mg group patients than in the other 3 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

[4] 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.

values, along with a tabulation of outlier values for individual patients in order to identify potentially clinically important changes [V1.189:122-128, 136-137]. 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 [V1.189:134-135]. 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 [V1.189:129-132].

No clinically meaningful change from baseline values in any laboratory parameter was noted, with the exception of a statistically significant change seen for SGPT (decrease in value noted in the placebo and fexofenadine 20 mg group). Furthermore, no dose response was seen for these 2 parameters with respect to mean values with increasing fexofenadine dose [V1.202:115-120].

Evaluation of shift tables (having both baseline and endstudy values) for each laboratory parameter failed to reveal any significant trends and results were overall unremarkable across the 5 treatment arms [V1.189:129-132, V1.202:35-113]. Minor trends were noted for a slight upward shift in triglyceride levels with increasing fexofenadine doses (doses ≥ 60 mg displayed a greater upward shift than fexofenadine 20 mg po bid) [V1.189:132]

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 [V1.189:134-135]) 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 0067 and Appendix K2, Summary 1 [V1.189:136-137, V1.202:33-34]. A slightly greater number 'high' outliers was noted across all 5 treatment arms for the laboratory parameters of neutrophil count and triglycerides [V1.189:137, V1.202:33-34].

8.4.4.10. 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 [V1.189:138-139, V1.206:159]. These data are summarized in Tables 54-56 of the study report for CIU study 0067 [V1.189:138-139].

8.4.5. 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 a decrease in CIU symptoms comparable to that seen with higher doses of fexofenadine (i.e. 120 or 240 mg po bid) and with a lower frequency of adverse events. Hence fexofenadine 60 mg bid 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.

The QOL analysis conducted by the sponsor was flawed by multiple problems (no proof of validity of the instrument for the CIU indication, no evidence of reproducibility of results of this instrument for the CIU indication, no statement of a clinically relevant effect size in the protocol, reliance on the same data set to show correlation between the HRQL analysis and clinical efficacy endpoints for CIU, and no adjustment for multiple comparisons). While active treatment appeared to improve several quality of life domains compared with placebo, conclusions that can be reached based on this HRQL analysis are problematic due to the reasons listed above and because of lack of a consistently significant improvement in domains for fexofenadine treated patients over placebo controls.

Overall, ALLEGRA was safe and well-tolerated given twice a day, at a dose of 20 mg, 60mg, 120 mg or 240 mg in 455 CIU 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 PJPR0067. 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 (discussed in CIU study PJPR0039) 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 PJPRO067: Table of Study Procedures

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.
† Or early termination
‡ Performed at visit 1 only if patient was qualified to continued with study procedures at that time.
§ Patient was randomized before results were available.

CHRONIC IDIOPATHIC URTICARIA IN ADULT PATIENTS (BID Dosing, Non-Pivotal Trial (0019):

8.5. Protocol No. PJPR0019: A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 4 dosage regimes of fexofenadine HCl (20 mg, 60 mg, 120 mg, and 240 mg qd) in the treatment of chronic idiopathic urticaria.

Principal Investigator: None, multi-center study.

Participating Centers: 52 European centers

8.5.1. Objective

The primary objective of this study was to investigate the safety and efficacy of fexofenadine HCl at 60 mg po qd, 120 mg po qd, 180 mg po qd, and 240 mg po qd, compared to placebo treatment given qd in patients ≥ 18 years of age for the treatment of symptoms of chronic idiopathic urticaria (CIU). This is in contrast to the 2 pivotal CIU studies which examined bid dosing of fexofenadine HCl. Hence, the dose of fexofenadine HCl evaluated in this study was sometimes half of that evaluated in the 2 pivotal CIU studies. Importantly, in this study fexofenadine capsules (and not tablets—the 'to-be-marketed' product) were evaluated, unlike the other pivotal clinical studies in this NDA.

8.5.2. Study Design

The basic study design for study PJPR0019 was very similar to that of the 2 pivotal CIU studies (PJPR0039 and PJPR0067), with differences between this study and the 2 pivotal studies delineated below. This was a phase III, multi-center, randomized, double-blind, parallel group, with a **14 day** unblinded lead-in (compared to a 24 hour single-blind placebo lead-in period for the 2 pivotal CIU studies), safety and efficacy study of the treatment of fexofenadine HCl 60 mg po qd, 120 mg po qd, 180 mg po qd, and 240 mg po qd; vs. placebo qd in at least 300 randomized adult CIU patients (468 actually randomized). The study consisted of 4 or 5 patient visits: 1 screening visit (visits 1, weeks 1 and 2), visit 2 (study entry/randomization visit) and 3 treatment visits (visits 3, 4, and 5; 2 weeks, 4 weeks, and 6 weeks, respectively post-treatment) such that patients received study medication for approximately 6 weeks (in contrast to the 4 weeks duration in the 2 pivotal CIU studies). A table of study procedures is provided in Appendix 1 [V1.207:61, 175].

8.5.3. Protocol

8.5.3.1.a. Population: Male or female adult patients, ≥ 18 years of age, with a diagnosis of CIU (made or confirmed by the

investigator and documented in the case report form) [V1.207:39, 155].

(I) Inclusion Criteria [V1.207:48, 50, 162-163]:

1. History or urticarial wheals (hives) for at least 1 day/week for the 6 consecutive weeks prior to Visit 1 (in contrast to criteria of at least 3 days/week in the 2 pivotal CIU studies).
2. At Visit 2, urticarial lesions must have been recorded as pruritic on the patient screening diary card, with a pruritus symptom rating of 'moderate' or 'severe' on at least 1 occasion in the preceding 2 weeks.
3. If urticarial lesions were evident at Visit 1 ant the patient's assessment of pruritus was 'moderate' or 'severe', the patient could be randomized to the study at Visit 1.

(II) Exclusion Criteria [V1.207:49-51, 162-164]:

1. A diagnosis of the following as a primary diagnosis: physical urticaria (e.g. cold, heat, sun-induced, pressure or dermatographism), cholinergic urticaria, urticaria due to medications, insect bites, food, or other known etiology, serum sickness, hereditary angioedema or known C_1 immunodeficiency, urticaria associated with an underlying disease (e.g. neoplasm, Hodgkin's disease, vasculitis, hyperthyroidism, thyroiditis, rheumatoid arthritis, complement abnormalities, SLE, hepatitis, mast cell disease, mixed connective tissue syndrome, mononucleosis, or other acute or chronic infections).
2. In France only, patients with a QT_c interval > 440 msec on 12 lead ECG.
3. Concomitant treatment with any H_1 antagonist, other than study medication during the treatment period.

Reviewer's Note: The clinical criteria for inclusion/exclusion for this CIU trial were deemed appropriate by the medical officer but did not include the following exclusion criteria (see below) which were cited in the 2 pivotal CIU studies (0039 and 0067):

1. **Any disease state or surgery known to affect the GI absorption of drugs,**
4. **Known history or lack of a positive response to an antihistamine for urticaria.**
5. **Urine drug screen positive for recreational drugs: cocaine, phencyclidine hydrochloride, or cannabinoids.**

(III). Concurrent Medication Restrictions [V1.207:50-51, 164]: 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 (in addition to H_1 antihistamines):

Medication	Time Discontinued Prior to Visit 1
1. Parenteral corticosteroids (IM, Intra-articular)	≥ 90 days
2. Topical corticosteroids	≥ 3 days
3. Short-acting systemic corticosteroids (e.g. Solu-Cortef, Solumedrol)	≥ 14 days
4. Astemizole	≥ 90 days
5. Anxiolytics, ASA or NSAID Containing medication	≥ 3 days
6. Investigational new drug	≥ 1 month

Reviewer's Note: In this study, use of H_2 antagonists was allowed, in contrast to the 2 pivotal CIU studies and this is a major study design flaw that could make interpretation of clinical efficacy potentially difficult since H_2 antagonists may be beneficial in treating uricaria *(Leung DYM, Diaz LA, DeLeo V, and Soter NA, Allergic and Immunologic Skin Disorders, JAMA, 1997, 278:1914-1923).* The medical officer thus reviewed the line listings for all concomitant medications taken by patients in each of the 5 treatment arms in order to determine if 1 group demonstrated a particularly high incidence of use of H_2 antagonists, which could impact review of clinical efficacy.

H_1 antihistamines were to be discontinued 24 hours prior to study Visit 2 (but were allowed to take it during the 14 day lead-in period).

8.5.3.1.b. Procedure

(IV) Screening Visit (Visit 1) [V1.207:59, 171]:

The procedure for Visit 1 was similar to those performed in the 2 pivotal CIU studies in this NDA, with a complete medical history, physical examination (including vital signs), laboratory and urine evaluation, assessment of adverse events performed at the screening visit. 12-lead ECGs were only performed in this study at French study sites (Amendment 3) [V1.207:48]. Patients were instructed to discontinue any prophylactic medication taken for their CIU and not to take any antihistamine (H_1 antagonist) within 24 hours of their next visit (Visit 2). For this CIU study, confirmation of the patient's diagnosis of

CIU by the PI was also ascertained and documented. As per the inclusion criteria, patients demonstrating adequate severity of CIU symptoms could be randomized to study treatment at Visit 1.

Patients were required to have at least a moderate severity of pruritus (score of ≥ 2), along with presence of urticarial lesions.

(V) Visit 2 (Randomization Visit) [V1.207:59-60, 172-173]:

At Visit 2, patients had to satisfy the inclusion criteria of urticarial lesions having at least a moderate pruritus severity score (see below), and having been either present at this visit or having occurred within the screening period. In addition, urticarial lesions were evaluated by the investigator (see scoring system below) and given an overall assessment of severity of skin condition pertaining to the previous period of up 2 weeks. A score of moderate-severe was required for patients to be continued in the study. Patients with very severe urticaria requiring topical corticosteroids were excluded from continuation in the study. In some centers in the U.K., patients were required to complete QOL questionnaires (exploratory analysis only, a pilot for site-specific use only) [Amendment 2, V1.207:48, 59].

The total symptom score (TSS) was defined as a composite score of the number of wheals (0-4 scale) and the pruritus scale (scale 0-3), with equal weight being given to both endpoints. The **patient self-rated symptoms** and rating scale is listed below:

Wheal Rating Scale (reflective; i.e. over previous 24 hours) [V1.207:53, 168]:

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

Pruritus Rating Scale (reflective; i.e. over previous 24 hours) [V1.207:53, 168]:

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

In addition, at the screening visit and at each visit thereafter, patients were asked to assess the interference of their skin condition with sleep (24 hour reflective assessment, recorded at the time of taking study medication) and to assess the interference of their skin condition with normal activities (24 hour reflective

assessment, recorded at the time of taking study medication) [V1.207:53] using the following scales:

Interference of skin condition with sleep scale) [V1.207:53, 168]:
(reflective; i.e. over previous 24 hours)

Scale	Rating
0	None
1	Mild (didn't wake up properly)
2	Moderate (awake part of night)
3	Severe (awake most of night)

Interference of skin condition with normal daily activities scale [V1.207:53, 168]: (reflective; i.e. over previous 24 hours)

Scale	Rating
0	None
1	Mild (< 1 hour with wheals or hives)
2	Moderate (1-6 hours with wheals or hives)
3	Severe (> 6 hours with wheals or hives)

At all visits, including Visit 1, **the investigator** was also to assess patients':
(a) # of wheals using the following scale [V1.207:54, 169]:

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

(b) longest diameter of wheals, using the following scale [V1.207:54, 169]:

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)

(c) Intensity of erythema on average, using the following scale [V1.207:54, 169]:

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

(d) Extent of skin area involved, using the following scale [V1.207:54, 169]:

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: > 30% of body involved)

Physicians also assessed the overall severity of the skin condition during the last 2 weeks (between study visits) using the following subjective scale [V1.207:55, 169]:

Scale	Rating
0	Complete relief (symptoms are completely controlled)
1	Marked relief (symptoms are well controlled and although present, are scarcely troublesome)
2	Moderate relief (pruritus is present and may be troublesome but is significantly controlled)
3	Slight relief (symptoms are present and only minimal control has been obtained)
4	No relief (symptoms are uncontrolled)
5	Symptoms are worse

Both patients and physicians were asked to conclude the 'overall effectiveness of study medication' during the treatment period, using the following scale [V1.207:55, 170]:

Scale	Rating
0	Excellent
1	Very Good
2	Good
3	Slight
4	None

In addition, physicians assessed the degree of overall symptom control by study medication during the last 2 weeks between study visits (taking into consideration the frequency of episodes, duration, extent of body area involvement, severity of pruritus and erythema as well as physical examination findings) using the following arbitrary subjective scale [V1.207:55, 170]:

Scale	Rating
0	Absent
1	Mild
2	Moderate
3	Severe

Patients who met all study entrance criteria then underwent randomization to treatment with assignment of a treatment assignment number (TAN) and dispensation of study medication. After the 14 day lead-in period, the 4 treatments that patients were randomized to consisted of the following [V1.207:51, 165]:

Treatment	Dosing
Placebo po bid	4, 60 mg size placebo capsule
Fexofenadine 60 mg po qd	3, 60 mg size placebo capsules + **1, 60 mg size fexofenadine capsule**
Fexofenadine 120 mg po qd	2, 60 mg size placebo capsules + **2, 60 mg size fexofenadine capsules**
Fexofenadine 180 mg po qd	1, 60 mg size placebo capsule + **3, 60 mg size fexofenadine capsules**
Fexofenadine 240 mg po qd	**4, 60 mg size fexofenadine capsules**

A double dummy blinding method was instituted in this study, as all placebo tablets were identical in appearance to their respective active drug (fexofenadine 60 mg capsules). Hence, all patients were to take 4 capsules at each dosing, 1 hour before food ingestion, at intervals of 24 hours for 6 weeks, commencing within 24 hours of entry visit.

Patients completed diaries where urticaria symptoms were rated and 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.

(VI) Visit 3 and 4 (2 and 4 weeks after Visit 2) [V1.207:52, 60, 173]:

Procedures for Visit 3 and 4 consisted of a physical exam of skin lesions by the investigator and rating of the overall severity of the skin condition, assessment of the degree of overall symptom control by study medication, and the # of days with wheals since the previous visit was recorded. Again, plasma fexofenadine levels were measured (timing of specimen not specified in protocol or study report) in order to assess patient compliance, however results of these data were not reported in the sponsor's study report submission or supportive documentation for study 0019. Compliance with study medication was evaluated and patients whose compliance with study medication was not between 80-120% for the study visit during the double-blind in period were requested to follow the protocol (no further questioning for possible discontinuation from the study discussed in the study report or protocol as seen in the 2 pivotal CIU studies [V1.207:52]).

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

(V) Visit 5 (Final study visit) [V1.207:60, 173-174]:

At the final study visit, many of the same procedures as performed during visit 3 and 4 were repeated (see above). Assessment by both the investigator and patient of the overall effectiveness of treatment was performed. At the French study sites, a 12 lead ECG was performed.

8.5.3.2. Clinical Endpoints

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

Primary Efficacy Variables [V1.207:69, 177]:

(1) The change from baseline in the mean daily reflective total symptom score (TSS) over the 6 week double-blind treatment period. The mean was calculated over all study days with data available, from Day 2 of Diary Card 2 (the 1st on-treatment day).

Reviewer's Note: The range of scores that could be achieved for the primary efficacy endpoint (a composite score of the mean pruritus score (scored 0-3) and the # of wheals score (scored 0-4), ranged from 0-7 [V1.207:69].

Secondary Efficacy Variables [V1.207:69-71, 177]:

(1) Patient self-rated mean daily pruritus score over the double-blind treatment period,
(2) Patient self-rated mean daily number of wheals score over the double-blind treatment period,
(3) Patient self-rated mean daily interference of skin condition with sleep score over the double-blind treatment period,
(4) Patient self-rated mean daily interference of skin condition with normal daily activities score over the double-blind treatment period,
(5) Patient self-rated weekly mean daily total symptom score over the double-blind treatment period,
(6) Patient self-rated weekly mean daily pruritus score over the double-blind treatment period,
(7) Patient self-rated weekly mean daily number of wheals score over the double-blind treatment period,
(8) Last observation carried forward (i.e. the latest available weekly mean score to replace any missing weekly mean score) weekly patient self-rated mean daily total symptom score,
(9) Last observation carried forward weekly patient self-rated mean daily total symptom score,
(10) Last observation carried forward weekly patient self-rated mean number of wheals score,
(11) Visit 5 patient assessment of the overall effectiveness of study medication during the double-blind treatment period (0-4 scale),
(12) Visit 5 physician assessment of the overall effectiveness of study medication during the double-blind treatment period,
(13) Visit 5 physician assessment of the overall severity of skin condition during the last 2 weeks (of the double-blind treatment period) (0-3 scale),
(14) Visit 5 physician assessment of the overall severity of skin condition during Visit 5 (0-3 scale),
(15) Visit 5 physician assessment of the # of lesions during Visit 5 (0-4 scale).

(16) Visit 5 physician assessment of the intensity of erythema during Visit 5 (0-3 scale),
(17) Visit 5 physician assessment of the size of lesions during Visit 5 (0-4 scale),
(18) Visit 5 physician assessment of skin area involvement during Visit 5, and
(19) The physician's assessment of the degree of overall symptom control (0-5 scale).

All primary and secondary efficacy endpoints were analyzed using the 'intent-to-treat population', defined as 'patients with baseline and at least 1 day on-treatment diary data total symptom scores [V1.207:67]. A 'protocol correct' patient population was constructed by removing patients with protocol violations 'highly likely' to seriously compromise the evaluation of the primary efficacy endpoint from the ITT dataset (= 'intent-to-treat' patients with no major protocol violations) [V1.207:67].

Reviewer's Note: The secondary efficacy endpoints were somewhat different from those evaluated for the pivotal CIU studies but were nonetheless acceptable from the FDA standpoint. In addition, the QOL analysis performed in the U.K. was not considered to be secondary endpoint.

8.5.3.3. Statistical Analysis [V1.207:66-67, 71-75, 177-179]

The estimated sample size for this study was based on results from terfenadine report 048-139, where the analyses were performed with the 'last observation carried forward'. The sample size was based on 2 of the primary efficacy endpoints: (1) the patient self-rated pruritus score and (2) the patient self-rated number of wheals score. For the pruritus score, the difference in mean scores between terfenadine and placebo was 1.1 (terfenadine mean=1.2, placebo mean=2.3, and SEM=0.2 for both treatments). For the number of wheals score, the difference in mean scores between terfenadine and placebo was 1.0 (terfenadine mean=0.7, placebo mean=1.7, and SEM=0.1 for both treatments).

The sample size of 60 'protocol correct patients per treatment arm was calculated based on these 2 primary efficacy endpoints, based on a power of 80% to detect a difference at the 5% significance level. Assuming a difference in scores between fexofenadine HCl and placebo of 1.0 with a standard deviation for the difference in the pruritus score of 1.5, a sample size of 36 evaluable patients per treatment group was required. For the number of wheals score, assuming a difference of 1.1, with standard deviation of 2.0, the required sample size was 52 evaluable patients per treatment group. Thus, a sample size of 60 protocol correct patients per treatment arm was chosen which would ensure that both primary efficacy endpoints would have sufficient power to detect the required differences.

Importantly, the sample size was subsequently revised by the sponsor following a re-analysis of the data from the terfenadine report (048-139) which showed variability to much less than that used in the power calculation of the study. In addition, blinded data from a group of 87 patients entered into the study

(by 11/17/95) were reviewed to check the assumptions used to calculate the sample size [V1.207:66]. Analysis of this blinded data showed the variability to be consistent with the re-analysis of the terfenadine data. Hence, the number of patients needed for the study was reduced from 300 randomized patients (60 patients per arm) to 200 randomized patients (40 patients per arm).

ANCOVA was used to compare the effects of fexofenadine HCl 60 mg po qd, 120 mg po qd, 180 mg po qd, 240 mg po qd, and placebo for the primary efficacy variable, which included terms for investigative sites, treatment groups, and baseline TSS values (as covariate adjustment). The mean baseline TSS was computed as the mean of all available diary TSS prior to randomization. If all pre-randomization baseline assessments were missing, then the 1st post-randomization assessment was used, if non-missing.

The treatment-by investigative site interaction and treatment-by-baseline TSS 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 10 ITT patients were pooled to form 'pseudo-sites' prior to analysis after unblinding of the final database.

Pairwise comparisons were based on a closed procedure in which the following comparisons were made sequentially, if the previous higher dose was significant: fexofenadine HCl 240 mg po qd vs. placebo, fexofenadine HCl 180 mg po qd vs. placebo, fexofenadine HCl 120 mg po qd vs. placebo, and fexofenadine HCl 60 mg po qd vs. placebo. All tests were 2-sided and used the 5% significance level. In addition to the hypothesis tests, 95% confidence intervals (2 sided) were calculated for each pairwise comparison.

Analysis of some secondary endpoints was performed with the same ANCOVA model used in the primary efficacy analysis, but endpoints which examined the patient's assessment of overall effectiveness were analyzed categorically using a Mantel-Haenzel test, adjusted for investigative site. The number of patients dropping out of the study before 6 weeks, by visit and overall, was compared between treatments using a chi-square test. If the assumptions for the validitiy of the chi-square test were not met (i.e. >80% of cells with expected frequency < 5), a Fisher's exact test was used instead [V1.207:74].

Treatment effect was characterized in subgroups of patients defined by investigative site, age, gender, race, and country. Age was only categorized as < 40 years of age, 40-64 years of age, and ≥ 65 years of age. Race was categorized as Caucasian and non-Caucasian [V1.207:74]. Country was categorized as: U.K., Germany, and France.

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 by 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 [V1.207:75]. In addition, potentially clinically significant outliers were identified.

8.5.4. Results

8.5.4.1. Patient Demographics and Accounting [V1.207:76-88, V1.213:15]
(A) A total of 224 patients were randomized into the study, though 2 patients (#0117-17 and #0210-07) discontinued the study following randomization but prior to receiving double-blind medication. The remaining 222 patients were exposed to double-blind treatment, and 146 (only 65% or 146/222) of these patients completed the study.

Two hundred and twenty two (222) patients of the 224 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. Two hundred and eight (208) patients were included in the intent-to-treat (ITT) population (received at least 1 dose of double-blind medication, with baseline and at least 1 day on treatment diary data). Of the 208 ITT patients, 29 had major protocol violations and thus only 179 patients were classified as 'protocol correct' [V1.207:80].

Table II. Patient Disposition [V1.207:80]

	Fexofenadine 60 mg qd	Fexofenadine 120 mg qd	Fexofenadine 180 mg qd	Fexofenadine 240 mg qd	Placebo	TOTAL
Randomized	45	38	50	39	52	224
Intent-to-Treat	40	36	47	39	46	208
Safety Evaluable	44	38	50	39	51	222
Protocol Correct	34	34	41	33	37	179

A total of 76 patients exposed to double-blind medication discontinued the study prior to scheduled completion [V1.207:80, V1.212:333-339]. The majority of patient withdrawals came from the placebo group (30 patients withdrew) and the most common reason for early discontinuation was treatment failure. Treatment withdrawals in the 4 active treatment groups were 14, 8, 16, and 8 patients, respectively, who withdrew from the study in the fexofenadine 60 mg, 120 mg, 180 mg, and 240 mg qd groups, respectively. This data is summarized in Table 11 of the study report for protocol 16455PR0019. [V1.207:81].

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 group (59% withdrawal rate) and fexofenadine 20 mg and 180 mg qd groups (32% withdrawal rate for both), with no dose response with respect to the

withdrawal rate noted amongst the 4 fexofenadine treatments. The predominant reason for patient discontinuation was treatment failure/lack of therapeutic effect (13% of total), followed by adverse event (7% of total, most commonly due to headache, acute urticaria, nausea and vomiting), and patient request (6% of total).

Pooled demographic data with regard to patient characteristics in the intent-to-treat population which are summarized in Table 12 of the study report for protocol 16455PR0019 [V1.207:82-83] revealed no statistically significant differences amongst the treatment groups with respect to gender, age, weight, height, years since 1st episode of urticaria occurred, and duration of the current episode of urticaria or # of days that wheals were present [V1.207:82-83]. The majority of patients enrolled in the study were Caucasian (≥ 89% across all treatment groups), with a somewhat greater proportion of female:male patients.

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 [V1.207:84-86] and no statistically significant difference was noted between the 5 ITT treatment groups for any of these parameters, including the primary efficacy endpoint—the patient self-rated total symptom score (TSS; p=0.8018). The range of the TSS score for the baseline period ranged from 0-7 with a mean TSS of 3.8 (std. dev.=1.9) for the placebo group, 0-7 for the fexofenadine 60 mg group with a mean TSS of 3.8 (std. dev.=2.0), 2-7 for the fexofenadine 120 mg group with a mean TSS of 4.3 (std. dev.=1.6), 0-7 for the fexofenadine 180 mg group with a mean TSS of 3.9 (std. dev.=1.5), and 1-7 for the fexofenadine 240 mg group with a mean TSS of 4.1 (std. dev.=1.9). In summary, these ranges in TSS were similar between the 5 treatment arms.

Forty three patients (or 19.4% of all exposed patients, 43/222) (13 treated with fexofenadine HCl 60 mg, 4 treated with fexofenadine HCl 120 mg, 9 treated with fexofenadine HCl 180 mg, 6 treated with fexofenadine HCl 240 mg, and 14 treated with placebo) valid for efficacy had a 'major' protocol violation [V1.2112:321-322]. The most common 'major' protocol violations consisted of the following: at the time of randomization into the study, rating of pruritus as 'mild' during the baseline period (7% of total patients), followed by 'no baseline or on-treatment diary data (6% of total patients), then 'use of medication that would severely jeopardize interpretation of the primary efficacy variable' (5% of total patients) [V1.207:80]. The % of patients with a violation tended to be higher for the placebo group for all categories of 'major protocol violation', closely followed by the fexofenadine 60 mg qd group.

With respect to use of prohibited medications (as per the study protocol), 4 patients (9%) in the placebo group, 3 patients (8%) in the fexofenadine HCl 60 mg group, 1 patient (3%) in the fexofenadine HCl 120 mg group, 1 patient (2%) in the fexofenadine HCl 180 mg group, and 2 patients (5%) in the fexofenadine HCl 240 mg group used a prohibited medication that consisted of an H_1

antagonist [V1.207:88]. No patients in any of the 5 treatment groups used a parenteral corticosteroid during the trial.

Hence, use of prohibited medications was slightly higher in the placebo and fexofenadine 60 mg qd groups.

With respect to H_2 antagonists, which were deemed permissible by the sponsor but nonetheless have been used to treat urticaria, a comparison of the frequency of H_2 antihistamine use was compared amongst treatment groups using line listings by the medical officer [V1.213:53-82]. Based on this analysis, 3 patients in the placebo group, 2 patients each in the fexofenadine 60 mg, 120 mg, and 180 mg groups, respectively, and 3 patients in the fexofenadine 240 mg group took an H_2 blocker during the study.

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.

The mean duration of double-blind exposure to study treatment for the safety population was 32.9 days (± 14.6 days) for all 5 treatment groups [V1.207:87]. The mean/range of duration of exposure was 25.7 days/1-49 days for the placebo group (n=51 patients), 34.4/1-49 days for the fexofenadine HCl 60 mg group (n=44), 35.9/1-50 days for the fexofenadine HCl 120 mg group (n=38), 34.2/1-55 days for the fexofenadine HCl 180 mg group (n=50), and 36.0/1-47 days for the fexofenadine HCl 240 mg group (n=39). Duration of exposure was calculated using the Visit 2 date as the date of the 1st dose of medication and the minimum of the last date of patient symptom assessment and the date of the final visit as the last dose date.

Assessment of patient compliance with double-blind medication was evaluated by the sponsor by dividing the total # of capsules taken during the double-blind dosing period (i.e. the total # of capsules dispensed – the total # of capsules returned) by the total # of capsules that should have been taken based on the duration of the double-blind period). Average compliance was found to be 103.1% for the placebo group, 97.4% for the fexofenadine HCl 60 mg group, 99.0% for the fexofenadine HCl 120 mg group, 96.0% for the fexofenadine HCl 180 mg group, and 96.9% for the fexofenadine HCl 240 mg group [V1.207:88]. Three patients had compliance < 80% and 3 patients had compliance above 120%. Based on these measurements, compliance was noted to be acceptable according to the sponsor's original protocol (compliance was to be between 80-120%) [V1.207:87].

8.5.4.2. Efficacy Endpoint Outcomes

(1) Primary Efficacy Variables:

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=40 for fexofenadine HCl 60 mg group, n=36 for fexofenadine HCl 120 mg group, n=47 for fexofenadine HCl 180 mg group, n=39 for fexofenadine HCl 240 mg group, and n=46 for placebo) for the primary efficacy variable of the change from baseline in the CIU total symptom score (TSS); where the primary comparison of interest was the response of the 4 fexofenadine doses vs. placebo. Choice of a reflective TSS as the primary efficacy endpoint did not provide information about the end-of-dosing interval efficacy (or duration of drug effect) but rather was chosen in order to give information about patients' response in decreasing pruritus symptoms over the preceding 24 hours.

Results of the primary efficacy analysis for CIU study 0019 are summarized in Table I. A statistically significant decrease in the primary efficacy endpoint was demonstrable only for the 180 mg and 240 mg qd dose, with the greatest numerical decrease in TSS over the 4 week double-blind period noted for the fexofenadine 180 mg qd group (change of -1.06 units), closely followed by the fexofenadine 240 mg bid group (change of -0.96 units).

Treatment-by-investigative site and treatment-by-baseline mean reflective TSS interactions were assessed using ANCOVA with the baseline reflective TSS, treatment, investigative site, treatment-by-investigative site and treatment-by-baseline reflective TSS at a significance level of 0.1 [V1.207:90]. There was no statistical evidence of dependence of treatment effect on the investigative site (p=0.1463) or baseline by treatment interaction (p=0.7576) [V1.207:90].

Separation of analysis of the TSS into the mean pruritus score and the # of wheals score was performed by the sponsor and results of these analyses indicate that for the pruritus score, there was a statistically significant difference amongst the 4 active treatments vs. placebo using the linear trend test (p=0.0167, p=0.0120, p=0.0001, and p=0.0001 for the fexofenadine 60 mg, 120 mg, 180 mg, and 240 mg doses vs. placebo, respectively) [V1.207:93]. A slight dose response was noted in this analysis, with the greatest numerical decrement in pruritus score noted for the fexofenadine 240 mg dose, closely followed by the fexofenadine 180 mg dose [V1.207:94]. For the # of wheals score, only the fexofenadine 180 mg dose demonstrated a statistically significantly greater difference compared to placebo (p=0.0064) [V1.207:96]. A dose response for the # of wheals score was not seen across fexofenadine doses. Of note, these 2 endpoints were defined by the sponsor as secondary efficacy endpoints.

A separation of the primary efficacy variable on a weekly basis (weekly analysis at weeks 1-6) using the last observation carried forward principle revealed a statistically significant dose response for both the fexofenadine 180 mg and 240 mg qd doses for all 6 weeks. The fexofenadine 120 mg qd dose demonstrated a statistically significantly greater response than placebo at weeks 1,2 and 5, and for the fexofenadine 60 mg qd dose, only a statistically significant difference was seen compared to placebo at week 4

[V1.207:97-98]. This efficacy endpoint was defined by the sponsor as a secondary efficacy endpoint.

Reviewer's Note: Based on evaluation of the primary efficacy endpoint in this CIU, the fexofenadine 180 mg qd dose offered a clinical response greater than any of the other fexofenadine doses. Hence, based of these clinical data, the 180 mg qd dose appears most appropriate for the treatment of CIU in adults patients age 12 years and older.

Table I.
Efficacy of Fexofenadine HCl 60 mg, 120 mg, 180 mg, and 240 mg qd, vs. Placebo
Primary Efficacy Variable: Intent-to-Treat (ITT) Population [V1.207:89]

	TREATMENT GROUP								
Primary Efficacy Variable	**(A) Fexo 60 mg qd**	**(B) Fexo 120 mg qd**	**(C) Fexo 180 mg qd**	**(D) Fexo 240 mg qd**	**(E) Placebo**	**P-value[1] A-E**	**B-E**	**C-E**	**D-E**
Change from Baseline in the Mean Total Symptom Score (MTSS, Mean ± Standard Error)									
	(n=40)	**(n=36)**	**(n=47)**	**(n=39)**	**(n=46)**				
Baseline TSS	3.93 ± 0.31	4.32 ± 0.26	3.91 ± 0.22	4.08 ± 0.30	3.80 ± 0.28				
Double-blind Treatment Period TSS	3.06 ± 0.27	3.17 ± 0.29	2.40 ± 0.25	2.70 ± 0.30	3.45 ± 0.28	0.1005	0.0670	0.0008	0.0041
Mean Difference ± SE						-.53±.32	-.62±.34	-1.06±.31	-.96±.33

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

A subgroup analysis of the primary efficacy variable to examine treatment interactions was performed by the sponsor on the basis of age, gender, race, country, and study site [V1.207:112-115]. No statistically significant subgroup by treatment interactions were noted ($p > 0.146$ for all interactions), and only the site main effect was statistically significant ($p=0.0123$) [V1.207:112]. Thus, these results suggest that the treatment effect among these subgroups of patients is not significantly different.

Review of onset of action for daily change from baseline change from baseline in the mean reflective TSS for the double-blind treatment period (the primary efficacy variable) for the intent-to-treat population was not performed by the sponsor for study 0019 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.

(II). Secondary Efficacy Variables:

A summary of analysis of the secondary efficacy variables for the ITT population is provided in Table II. Below, excluding those secondary efficacy

endpoints that comprised sub-analyses of the primary efficacy endpoint and were already discussed in Section (I) 'Primary Efficacy Variables' above. For fewer than half of the secondary efficacy endpoints, a statistically significant difference in symptom scores was not seen for the 4 fexofenadine doses compared to placebo in study 0019. Review of numerical trends generally failed to show a consistent dose response or trend of decrease in symptoms with increasing fexofenadine dose. Only the fexofenadine 60 mg qd and fexofenadine 180 mg qd groups showed a reasonable number of statistically significant secondary endpoints compared with placebo treatment.

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 end-study of: (1) skin condition, (2) the extent of skin area involved, (3) the # of wheals, (4) the size of wheals, and (5) the intensity of erythema, represent the closest 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 qd group demonstrated the most consistent statistically significant difference compared to placebo (for only 1 out of the 5 endpoints, with marginal efficacy seen in 2 additional endpoints out of the 5) [V1.207:104-109]. The next most efficacious dose numerically, was the fexofenadine 180 mg qd dose, however statistical significance was not achieved for any of these 5 endpoints.

Reviewer's Note: Review of the secondary efficacy endpoints for CIU study 0019 would support the fexofenadine 60 mg qd dose as the most appropriate dose for treatment of CIU in patients ≥ 12 years of age, however these data were overall marginal at best for all 4 active treatments, since fewer than half of the endpoints demonstrated greater efficacy in the active treatments than placebo.

Table II: Secondary Efficacy Variables for the ITT Population for CIU Study 0019: Fexofenadine HCl 60 mg, Fexofenadine HCl 120 mg, Fexofenadine HCl 180 mg, Fexofenadine HCl 240 mg qd, vs. Placebo [V1.207:100-111]

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No			
	Fexo 60 mg qd	Fexo 120 mg qd	Fexo 180 mg qd	Fexo 240 mg qd
Secondary Efficacy Variables				
1. Interference of skin condition with sleep	Yes (p=0.0001)	Yes (p=0.0106)	Yes (p=0.0005)	Yes (p=0.0001)
2. Interference of skin condition with normal daily activities	Yes (p=0.0110)	Yes (p=0.0458)	Yes (p=0.0024)	Yes (p=0.0006)
3. Patients assessment of overall effectiveness of study medication	Yes (p=0.0157)	No (p=0.3752)	Yes (p=0.0119)	No (p=0.1136)
4. Overall severity of skin condition during the last 2 weeks	No (p=0.1088)	No (p=0.1235)	Yes (p=0.0038)	No (p=0.1844)
5. Overall severity of skin condition at endstudy	Yes (p=0.0054)	No (p=0.1246)	No (p=0.0973)	No (p=0.4094)
6. Extent of skin involvement at endstudy	No (p=0.0625)	No (p=0.5729)	No (p=0.1320)	No (p=0.8436)
7. Number of lesions at endstudy	No (p=0.1496)	No (p=0.9001)	No (p=0.1161)	No (p=0.9337)
8. Intensity of erythema at endstudy	No (p=0.0582)	No (p=0.5429)	No (p=0.1490)	No (p=0.8401)
9. Size of lesions in general at endstudy	No (p=0.0559)	No (p=0.2738)	No (p=0.2104)	No (p=0.7600)
10. Degree of overall symptom control	Yes (p=0.0123)	No (p=0.0618)	Yes (p=0.0024)	Yes (p=0.0162)
11. Overall effectiveness of study medication	Yes (p=0.0538)	No (p=0.5024)	Yes (p=0.0327)	No (p=0.1658)

* Weekly analyses of the pruritus and # of wheals score (a secondary efficacy variable) was evaluated in the primary efficacy endpoint section as a sub-analysis of the primary efficacy variable (the total symptom score).

8.5.4.3. Safety Analysis

Safety analysis for study 0019 was essentially the same as that conducted for other fexofenadine trials (CIU studies 00039, 0067, adult qd SAR, pediatric SAR) and consisted of an evaluation of adverse events, standard laboratory tests, 12-lead ECGs (performed only at the French study sites), and vital signs pre- and post-treatment in patients randomized into the study and 'exposed' to study medication (the safety evaluable population).

Forty four (44) patients comprised the fexofenadine HCl 60 mg, 38 patients comprised the fexofenadine HCl 120 mg, 50 patients comprised the fexofenadine HCl 180 mg, 39 patients comprised the fexofenadine HCl 240 mg, and 51 patients comprised the placebo group safety evaluable populations (i.e. exposed to double-blind medication with at least 1 post-baseline AE assessment, total n=222) [V1.207:117].

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 somewhat lower incidence noted in the fexofenadine 180 mg qd group (56% incidence for all AEs) compared with a range of 68-79% for the other 3 active fexofenadine groups and placebo treatment [V1.207:117].

As previously noted for other clinical indications, the most frequent adverse event for all 5 treatment groups consisted of headache (with an incidence of 34% in the fexofenadine HCl 60 mg group, an incidence of 42% in the fexofenadine HCl 120 mg group, an incidence of 36% in the fexofenadine HCl 180 mg group, an incidence of 49% in the fexofenadine HCl 240 mg group, and an incidence of 31% in the placebo group), followed by viral infection (an incidence of 9% in the fexofenadine HCl 60 mg group, an incidence of 8% in the fexofenadine HCl 120 mg group, an incidence of 2% in the fexofenadine HCl 180 mg group, an incidence of 10% in the fexofenadine HCl 240 mg group, and an incidence of 8% in the placebo group) [V1.207:117-118]. In particular, for headache, the incidence of this AE was ~ twice as high as that noted in the SAR trials and higher than that noted in the other 2 CIU trials, with unclear reasons for this. Other more frequent AEs consisted of dizziness (with an incidence of 5% in the fexofenadine HCl 60 mg group, an incidence of 3% in the fexofenadine HCl 120 mg group, an incidence of 8% in the fexofenadine HCl 180 mg group, an incidence of 5% in the fexofenadine HCl 240 mg group, and an incidence of 6% in the placebo group), nausea (with an incidence of 7% in the fexofenadine HCl 60 mg group, an incidence of 8% in the fexofenadine HCl 120 mg group, an incidence of 8% in the fexofenadine HCl 180 mg group, an incidence of 8% in the fexofenadine HCl 240 mg group, and an incidence of 8% in the placebo group), fatigue (with an incidence of 0% in the fexofenadine HCl 60 mg group, an incidence of 8% in the fexofenadine HCl 120 mg group, an incidence of 6% in the fexofenadine HCl 180 mg group, an incidence of 8% in the fexofenadine HCl 240 mg group, and an incidence of 4% in the placebo group), and diarrhea (with an incidence of 5% in the fexofenadine HCl 60 mg group, an incidence of 5% in the fexofenadine HCl 120 mg group, an incidence of 4% in the fexofenadine HCl 180 mg group, an incidence of 10% in the fexofenadine HCl 240 mg group, and an incidence of 2% in the placebo group). With the minor exception of a progressively slightly higher incidence of diarrhea at the highest dose of fexofenadine evaluated in this study (240 mg qd), no dose response for AE frequency was noted across treatment groups. Of note, the incidence of drowsiness (termed 'somnolence' in other studies in this NDA) was very low-not detected in all 5 treatment groups (fexofenadine 60 mg: 0%, 120 mg: 0%, 180 mg: 0%, 240 mg: 0%, and placebo: 2%) [V1.207:117].

Cardiovascular adverse events were only specifically recorded under the 'cardiovascular' category for the 1 clinical endpoint of chest pain--precordial (0.0-1.1% incidence across all 4 fexofenadine doses, 0.0% for the placebo group); however the additional adverse events of: dizziness (0-2% incidence across all 4 fexofenadine doses, 0% for the placebo group) and chest pain (0-2% across all 4 fexofenadine doses, 0% for the placebo group) were added to the list of cardiovascular adverse events by the medical reviewer [V1.207:119]. As noted, the frequency of these potential cardiovascular AEs were low for all treatment groups.

12 lead ECGs performed at the French study sites before and after treatment with study drug failed to demonstrate a significant increase in QT_c interval [V1.216:282-285]. QT_c intervals were below 440 msec for all patients tested.

Adverse event stratification by duration of treatment was not performed by the sponsor, given the study's entire duration of 6 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 CIU trials, many of the adverse events described in the safety database for study 0019 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). Adverse event stratification by demographics was not performed in this study.

A total of 26 patients randomized to double-blind study medication discontinued treatment due to AEs: 13 patients with either of the 4 doses of fexofenadine HCl (3 fexofenadine 60 mg patients, 3 fexofenadine 120 mg patients, 4 fexofenadine 180 mg patients, and 3 fexofenadine 240 mg patients) and 13 patients treated with placebo discontinued treatment prematurely due to adverse events [V1.207:125-127]. On review of the adverse event summaries by the medical reviewer, the majority of these patients withdrew from study treatment due to headache, acute urticaria, or angioedema .

No deaths were reported during this CIU trial for any of the 5 treatment groups.

[5]Serious treatment emergent adverse events were reported in 2 placebo group patients (#0117-03 and # 1007-06). Patient 0117-03 was a 59 year old female who experienced angioedema of the face after 7 days of double-blind study treatment, which required hospitalization and treatment with I.V. prednisolone. The other patient, a 44 year old female discontinued treatment after 28 days, after a routine physical examination revealed uterine enlargement (due to an ovarian cyst) [V1.207:123-124]. Neither of these 2 events were deemed drug related.

Laboratory tests performed during baseline (pre-randomization) and visit 5 or end-study (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) 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) negative correlation between dose of fexofenadine and change from baseline in SGPT ($p=0.0355$, note that there was a decrease in SGPT for the fexofenadine groups, a slight increase in placebo group),

[5] 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.

bilirubin (p=0.0090) and creatinine (p=0.0219) [V1.207:128, 130-133]. The effects of the 5 treatments on laboratory parameters were analyzed using shift tables and tabulation of outlier values for individual patients in order to identify potentially clinically important changes [V1.207:133]. 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 [V1.207:137-139].

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 [V1.207:133-136].

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 [V1.207:137-139]) 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 50 of the study report of CIU study 0019 and Appendix K2, Summary 1 [V1.207:139-140]. No obvious trends for outlier values were noted in this analysis.

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

The results of this study, support the safety of once daily ALLEGRA capsules in adult and adolescent patients age 12 years and older at a dose of fexofenadine HCl of 180 mg or 240 mg qd for the treatment of symptoms of CIU, based on results of the primary efficacy variable and safety data. Fexofenadine capsules and not tablets (the 'to-be-marketed' formulation) were studied in trial 0039.

Again, similar to the other 2 CIU studies, 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 once a day, at a dose range of 60 mg to 240 mg in 222 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 viral infection, and nausea (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 at all study sites. Interpretation of laboratory testing indicated no abnormal trends or worrisome laboratory findings in study 0019.

Summary:

Based on the results of this CIU trial, ALLEGRA capsules 180 mg or 240 mg qd demonstrated reasonable evidence of efficacy and safety compared with placebo, for the once daily treatment of CIU symptoms in adults and children 12 years of age and older.

APPENDIX I: Study Procedure for Protocol 0019 [V1.207:61]

Table 6. Study Schema

VISIT	1 SCREENING	2 RANDOMISATION	3 TREATMENT	4 TREATMENT	5 END OF STUDY
DAY	0 to -14	0	14	28	42
Medical History	X				
Physical Examination	X				
12-lead ECG (France only)	X				X*
Informed Consent	X	confirm			
Physician Exam of Urticaria	X	X	X	X	X*
Physician Assessment of Urticaria	X	X	X	X	X*
Blood Sample Clin Chem/Haem	X				X*
Inclusion/Exclusion Criteria	X				
Patient Assessment of Urticaria	X	X	X	X	X*
Quality of life questionnaire (UK only)		X	X	X	X*
Pregnancy Test (if applicable)		X			X*
Study Medication Dispensed		X	X	X	
Adverse Event Check		X	X	X	X*
Blood for MDL 16,455 levels			X	X	X
Physician & Patient Conclusion of Effectiveness of Study Medication					X*
Final Evaluation					X*

* To be performed when the patient completed the study, or at any time the patient discontinued study medication.

NON-PIVOTAL CLINICAL STUDIES

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

8.6. Protocol PJPR0032: A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 2 dosage strengths of fexofenadine HCl (120 mg and 180 mg qd) in the treatment of seasonal allergic rhinitis (SAR).

Principal Investigator: None, multi-center study.

Participating Centers: 49 European, South African, and Australian centers.

8.6.1. Objective

The primary objective of this study was to investigate the safety and efficacy of fexofenadine HCl 120 mg po qd and fexofenadine HCl 180 mg po qd compared to placebo treatment and the active comparator, cetirizine 10 mg po qd in patients age 12-65 years for the treatment of symptoms of grass pollen-induced (indigenous to the region) seasonal allergic rhinitis (SAR).

Secondary objectives of the study were to determine onset of action and duration of action of fexofenadine over 24 hours, and to the evaluate potential for the 2 dosage strengths of fexofenadine and its active comparator, cetirizine, to cause sedation using a 'somnolence visual analogue' scale.

8.6.2. Study Design

The study was a phase 3, multi-center, randomized, double-blind, parallel group, with a 3-5 day single-blind placebo lead-in, safety and efficacy study of the treatment of fexofenadine HCl 120 mg po qd, vs. fexofenadine HCl 180 mg po qd, vs. cetirizine 10 mg po qd, and vs. placebo in 821 ITT grass pollen sensitive seasonal allergic patients. The overall study design was essentially the same as that utilized in the pivotal adult SAR trial 3081 and will only be briefly discussed here (for complete details of study design, refer to SAR Study 3081).

The study consisted of 4 subject visits: 2 screening/baseline visits (visits 1 and 2; weeks 1 and 2), and 2 treatment visits (visits 3 and 4; weeks 3 and 4) such that patients received study medication for approximately 2 weeks. Patients participated in the study for a total of 19 days [V1.83:29]. The inclusion/exclusion criteria and disallowed medications for study enrollment were essentially the same as those noted in study 3081 [V1.83:40-44]. The usual safety monitoring procedures (AE reporting, physical exam, lab testing) and assessment of compliance were performed throughout the trial [V1.83:47, 49, 51-57].

A total of approximately 800 patients were to be randomized to the 4 treatment groups, with approximately 33 study sites and approximately 18