CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-064

MEDICAL REVIEW(S)

Medical Team Leader Memorandum

Date: April 19, 2007

To: NDA 22-064

From: Lydia I. Gilbert-McClain, MD, FCCP
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Product: Zyzal® (Levocetirizine dihydrochloride) 5 mg tablets

Applicant: UCB Inc.

Background/Administrative
NDA 22-064 was submitted by UCB, Inc. on July 24, 2006, under 505(b)(2) of the Federal Food, Drug and Cosmetics Act for approval to market levocetirizine dihydrochloride 5 mg oral tablets as a prescription product for the symptomatic treatment of seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in adults and children 6 years of age and older. The application is submitted in electronic format in the structure of a Common Technical Document (CTD) hybrid. Levocetirizine, a histamine H_1 receptor competitive antagonist is the R-enantiomer of the racemate cetirizine and is purported to be solely responsible for the therapeutic antihistaminic activity of the racemate cetirizine.

For their 505(b)(2) NDA, the Applicant references the approved prescription drug Zyrtec® (cetirizine hydrochloride) approved under the following NDAs: 19-835 (5 mg and 10 mg tablets), NDA 20-346 (oral syrup, 5mg/ml) and NDA 21-621 (chewable tablets, 5 mg and 10 mg).

The development program for levocetirizine was conducted entirely outside the US and none of the clinical studies were conducted under an IND. The Applicant had a pre-IND meeting with the Division on June 14, 2005. Although this was called a pre-IND meeting, this was in essence a pre-NDA meeting because the development program was (for the most part) already completed and the questions and discussion focused on the general plan to submit the NDA under the 505 (b)(2) pathway and UCB's intent to seek marketing status for levocetirizine as a prescription product ———— There was also a follow up teleconference on October 28, 2005 with the Division in which UCB, Inc. provided the division with their rationale for why their product should be marketed as a prescription product ———— During the Pre-IND meeting the Division pointed out that UCB will need to conduct a study comparing levocetirizine (LCTZ) and cetirizine (CTZ) using multiple doses to support their argument that LCTZ at half the dose of CTZ has the same effect.

During the 45-day filing review, it was noted that the NDA did not contain an integrated summary of efficacy. The applicant was contacted regarding this omission and they indicated that they did not submit an integrated summary of efficacy (ISE) with their application. The Division initially took a Refuse to File action for this Application but later rescinded that action and filed the application following an explanatory correspondence from the Applicant. UCB agreed to submit the ISE in a timely manner which they did.

Chemistry Manufacturing and Controls and Establishment Evaluation

Levocetirizine is the R-enantiomer of the racemate cetirizine responsible for the therapeutic antihistamine activity of cetirizine. The product is formulated as 5 mg immediate release tablets for oral administration. The tablets are white; film-coated oval-shaped and scored to allow breaking into 2 equal parts each part delivering 2.5 mg. There are no novel inactive ingredients in the tablets. During the CMC review the impurity ——— was noted to be present in the tablet. The preclinical team was consulted and they determined that ——— was acceptable up to ——— maximum daily dose and a limit of ——— in the drug product. For additional details on CMC see Art Shaw's primary review.

OVERVIEW OF CLINICAL PROGRAM

Of the multiple studies submitted in the application, a total of 14 studies make up the clinical program to support the proposed indications. Of these studies, 6 are efficacy and safety studies in adult and adolescent patients with seasonal and perennial allergic rhinitis, 2 are efficacy and safety studies in adult patients with chronic idiopathic urticaria, 2 are efficacy and safety studies in pediatric patients 6 to 12 years of age with seasonal and perennial allergic rhinitis, 2 are environmental exposure unit studies, and 2 are long term safety studies. Of the 6 efficacy and safety studies in adults and adolescents with seasonal and perennial allergic rhinitis, 5 studies are adequately designed for efficacy evaluation, and one study is not suitable for efficacy evaluation because the study duration (1 week) is too short however, this study can be used in the safety data base for the short term studies. The studies that make up the clinical program are displayed in the table below.

Table 1: Clinical Program

Study /Population	Design/objective LCTZ dose	Age range (years)	Treatment Duration	Number Exposed to study treatment	Number of Males/Females
Allergic Rhinitis Studies – Adults and Adolescents 12 years of age and older					
A217/SAR	Dose ranging 2.5, 5, 10 mg	17-72	2 weeks	470	235/235
A219/PAR	Dose-ranging 2.5, 5, 10 mg	12-66	4 weeks	421	205/216
*A222/SAR	Efficacy 5 mg	12-66	1 week	797	398/399
A265/PAR	Dose ranging 2.5, 5, 10 mg	12-74	2 weeks	519	206/313
A266/PAR	Efficacy 5 mg	12-71	6 weeks	294	126/168
A268/SAR	Efficacy 5 mg	12-71	2 weeks	236	89/147
Chronic Idiopathic Urticaria Studies – Adults 18 years of age and older					
A269/CIU	Efficacy 5 mg	18-79	4 weeks	166	68/98
A270/CIU	Dose-ranging 2.5, 5, 10 mg	18-85	4 weeks	257	71/186
Allergic Rhinitis Studies – Pediatric Patients 6 to 12 years of age					
A303/SAR	Efficacy 5 mg	6 -12	6 weeks	177	117/60
A304/PAR	Efficacy 5 mg	6-12	4 weeks	306	186/120
Long term Safety studies Adults and adolescents 12 years of age and older					
A264/PAR		18-70	6 months	551	241/310
**A306/SAR		12-68	16 weeks	459	203/256
Environmental Exposure Unit studies					
A379/SAR		16-69	Single dose	570	233/337
A412/SAR		16 -71	Single dose	551	239/312

*Study A222 is only used for the safety database because the study duration is too short for confirmatory efficacy. This study included a cetirizine arm (n = 318), placebo (n =160) and LCTZ 5 mg (n = 319). Of 319 patients on LCTZ there were 168 males and 151 females.

** In Study A306 one study arm had 153 patients treated for the first 8 weeks with placebo followed by treatment with LCTZ 5mg for the last 8 weeks. Therefore, these 153 patients are excluded from the safety analysis.

FFICACY (Adults and adolescents 12 years of age and older)

Allergic rhinitis

Efficacy is assessed from 5 placebo-controlled clinical studies. Of these, 3 are dose-ranging studies and 2 are confirmatory efficacy studies.

Dose-ranging studies

The three dose-ranging studies were identical in design except that study A217 was conducted in patients with seasonal allergic rhinitis and the other two studies (A265 and A219) were conducted in patients with perennial allergic rhinitis.

All three studies A217, A219, and A265 evaluated three doses of LTCZ: 2.5, 5, and 10 mg compared to placebo for the treatment of the symptoms of SAR (study A217) and PAR (studies A219 and A265).

A total of 470 patients 18 - 72 years of age with SAR were enrolled in study A217 whereas, 521[1] PAR subjects were randomized in A265, and 421 PAR patients were randomized in study A219. SAR patients had a positive skin test or RAST to grass and/or weed pollen and had a history of SAR for at least 2 years. Patients with PAR had at least a 2-year history of PAR due to house dust mites and a positive skin test or RAST to house dust mites.

Following a screening period of approximately 7 days, patients were randomized to treatment with LTCZ 2.5, 5, or 10 mg or placebo once daily in the evening for 14 days (study A217) or 4 weeks (study A265, A219). Patients recorded the severity of four symptoms (runny nose, itchy nose, sneezing, and ocular pruritus) once daily in a diary based on a severity scale of 0 to 3 [0 = none, 1 = mild, 2= moderate, 3 = severe] to reflect how they felt over the entire 24 hour treatment period and recorded that score in their diary just before taking the next dose of study medication (reflective score). Instantaneous scores were not recorded in these studies. The primary efficacy variables were the change from baseline in the average of the reflective total symptom score (T4SS over the first week and over the entire treatment period. The baseline score was the mean of the daily reflective T4SS (assessed in the evening) over the 7-day screening period (period from the day of the initial visit to the day preceding the randomization visit). The results were analyzed using an analysis of covariance (ANCOVA) with the inclusion of baseline as a covariate in the model.

The efficacy results for the dose-ranging studies are shown in Table 2. There was evidence of a dose-ordering effect in studies A217 and A265 but not in study A219 where the 5 mg dose did not reach statistical significance however, the change from baseline in symptom score was numerically better than placebo. A clear dose-ordering effect was seen in study A217 across all three doses. In study A265 all three doses had a statistically significantly greater improvement compared to placebo, but the effect size with the 10 mg dose was smaller than with the 2 lower doses.

Table 2: Dose-ranging studies A217 and A265 –mean T4SS over the entire treatment Period

Treatment	N	Baseline mean (SD)	Adjusted mean change from baseline (SE)	Difference vs. placebo (98% CI)	p-value
Study a 217 (SAR – 2 week treatment period)					
Placebo	118	7.94 (2.06)	5.18 (0.19)		
LTCZ 2.5mg	116	7.83 (2.14)	4.27 (0.19)	0.91 [0.27, 1.55]	0.001
LTCZ 5mg	115	7.45(2.07)	4.06 (0.20)	1.11[0.47, 1.75]	<0.001
LTCZ 10mg	118	7.15(2.08)	3.57(0.19)	1.61[0.96, 2.25]	<0.001
Study a 265 (PAR – 4-week treatment period)					
Placebo	128	7.22 (1.75)	5.29 (0.17)		
LTCZ 2.5mg	133	7.14(1.64)	4.12 (0.17)	1.17 (0.71; 1.63)	< 0.001
LTCZ 5mg	127	7.18 (1.68)	4.07 (0.17)	1.22(0.76; 1.69)	<0.001
LTCZ 10mg	129	7.58 (1.79)	4.19 (0.17)	1.10 (0.64; 1.57)	<0.001
Study A219 (PAR – 4 week treatment period)					

[1] Two patients did not received study medication and 519 patients make up the ITT and the safety population for study A265.

Placebo	104	6.77 (1.62)	4.84		
LTCZ 2.5mg	105	6.64 (1.59)	4.03	0.81 (0.18; 1.45)	0.003
LTCZ 5mg	103	7.00 (1.75)	4.28	0.56 (-0.07;1.20)	0.041
LTCZ 10mg	109	6.82 (1.56)	3.64	1.21 (0.58; 1.84)	<0.001

Data source: Mean change from baseline data for study A217 taken from Biostatistics reviewer Dr. Jim Gebert's review. Data essentially identical to Applicant's data expect that Applicant's data table (Table 10 page 46/5599 of study report) did not include SE. Data for study A265 taken in its entirety from Applicant's data table.

- **Confirmatory Efficacy studies**

Allergic Rhinitis- Study a268 and a266

Two randomized double-blind placebo-controlled studies – A268 [SAR patients] and A266 [PAR patients] comparing the efficacy and safety of LTCZ 5 mcg to placebo were conducted in adult and adolescents 12 years of age and older. In study A268, patients who had a history of SAR for at least 2 years and a positive allergen skin test to grass or weed pollen were randomized to study treatment for 2 weeks. Patients in study A266 had a history of PAR to house dust mites for at least 2 years. Study A268 was conducted at 20 different sites in South Africa in adolescent and adult patients 12 to 71(mean 30) years of age. In addition to the usual exclusion criteria in clinical trials, patients were excluded if they had nasal polyps or nasal malformations, vasomotor rhinitis, dermatitis or urticaria requiring antihistamine or corticosteroid therapy (oral or topical),clinically significant disease, ear, nose, or throat infection within 2 weeks of screening, or had active asthma. Patients were prohibited from medications such as corticosteroids, other intranasal medications, and immunosuppressive therapies, short and long-acting antihistamines during the study, and needed to have discontinued these medications for a pre-defined period prior to study enrollment to allow for an adequate washout.

A total of 237 patients were randomized to study treatment of which 232 (94%) completed the study. The majority of patients (62%) were female, 71% were Caucasian 14% Asia/Pacific Islander, 4% Black and 11% were of other racial backgrounds. One subject in the placebo group did not take any study medication. Therefore, the ITT population was made up of 236 patients.

Study A266 was also conducted in South Africa in patients 12 -71 years (mean 29 years) of age. A total of 294 patients at 26 centers in South Africa were randomized to study treatment with LTCZ 5 mg or placebo. A total of 276 (94%) patients completed the study. The demographic characteristics were similar to the population in study A268: The majority was female (57%) and Caucasian (68%). Both studies were designed with a screening period of approximately 7 days (range 3- 9 days) during which, patients eligible for enrollment recorded the severity of four symptoms (runny nose, itchy nose, sneezing, and ocular pruritus) once daily in the evening in a diary based on a categorical severity scale of 0 to 3 [0 = none, 1 – mild, 2= moderate, 3 = severe]. The total score of these symptoms make up the Total symptom Score (T4SS) [maximum score = 12]. At the end of the screening period, patients with a reflective mean score of at least 6 during the screening period as well as on the day before the randomization visit were randomized. During the randomization period, patients recorded reflective symptom scores once daily in the evening before the patients took their study medication. Patients in study A268 were randomized to 2 weeks of treatment, whereas, patients in study A266 were treated

for 6 weeks. Compliance to treatment was assessed by the patient's diary data and by pill counts.

The primary efficacy variable was the mean change from baseline (the average reflective T4SS over the screening period) in the average of the reflective T4SS. The applicant evaluated this efficacy variable over 2 time points as co-primary efficacy endpoints:
(1) Over the first week AND
(2) Over the 2 –week treatment period (study A268) or the first 4 weeks (study A266).

In study A268, the patients also recorded their symptoms over the last hour of the treatment period (instantaneous) as a secondary endpoint. This is the only allergic rhinitis study that provides an assessment of the end-of-dosing interval efficacy.
In both studies, LTCZ 5 mg was statistically superior to placebo for the T4SS and for the T3SS [Total symptoms minus ocular pruritus) over Week 1 and over the entire treatment period. The results for the entire treatment period are displayed in the table.

Table 3: Primary Efficacy Results Study A268 and A266
Mean T4SS and T3SS over the entire treatment period

Treatment	N	Baseline (SD)	*Mean Change from Baseline (SE)	Difference from Placebo		
				Estimate	95% CI	P-value
Seasonal Allergic Rhinitis (StudyA268) r-T4SS						
LTCZ 5mg	118	8.40 (1.66)	5.20 (0.222)	0.89	(0.30, 1.47)	0.001
Placebo	117	8.50 (1.68)	6.09 (0.221)			
Seasonal Allergic Rhinitis (StudyA268) r-T3SS						
LTCZ 5 mg	118	6.53(1.37)	4.19 (1.98)	0.69	(0.23, 1.15)	0.003
Placebo	117	6.47(1.29)	4.86 (1.94)			
Seasonal Allergic Rhinitis (StudyA268) i-T3SS						
LTCZ 5mg	118	5.54(1.79)	3.56 (0.163)	0.58	(0.15, 1.01)	0.008
Placebo	117	5.60 (1.73)	4.14 (0.163)			
Perennial Allergic Rhinitis (Study A266) r-T4SS						
LTCZ 5mg	150	7.69 (1.82)	4.17 (0.176)	1.22	(0.76; 1.69)	<0.001
Placebo	142	7.44(1.80)	5.39 (0.183)			
Perennial Allergic Rhinitis (Study A266) r-T3SS						
LTCZ 5mg	150	5.98 (1.38)	3.29 (0.132)	0.99	(0.64; 1.34)	<0.001
Placebo	142	5.79 (1.41)	4.28 (0.137)			

Data Source: Applicant's data and Biostatistics review. The results in the Biostatistics review are essentially identical to that of the Applicant. The T4SS is the sum of the scores for sneezing, rhinnorrhea, nasal pruritus and ocular pruritus. The T3SS is the sum of the scores excluding ocular pruritus.
**From an ANCOVA model with baseline score as a covariate and pooled center and treatments as factors. Baseline symptom scores = mean of scores from the day of the initial visit to the day preceding the randomization visit.*

Chronic Idiopathic Urticaria

Two studies (A00270) and (A00269) conducted in France and Germany and Switzerland respectively provide support for the chronic idiopathic urticaria (CIU) indication. Study A00270 was a dose-ranging study and A00269 was a confirmatory efficacy study conducted in adult patients 18 to 70 years of age with symptoms of chronic idiopathic urticaria. Both studies were identical in design expect that study A00270 included doses

of 2.5 and 10 mg whereas, study A269 only studied the 5 mg dose. A total of 424 patients were randomized in these 2 studies (n=258 study A00270 and n = 166 study A269). In study A270 one patient did not take medication and was excluded from the ITT population. There were 148 patients who received placebo and 275 patients who received LTCZ. The demographic characteristics were similar to the patients in the allergic rhinitis studies with the majority of the patients (93%) being Caucasian, and 65% being female. The mean age was 41 years. The primary efficacy variable was the pruritus severity score and the primary efficacy endpoints were the mean pruritus severity score over 24 hours (reflective) averaged over the entire 4-week treatment period and over the first week. The severity of pruritus score was graded on a severity scale where 0 = absent, 1 = mild, 2 =moderate (disturbing but not hampering daytime activities or sleep), 3 = severe (hampering daytime activities and/or sleep). In these studies the severity of pruritus was also assessed in an instantaneous manner ("how is your itching now?") and provided support for end of dosing interval efficacy.

The week prior to randomization was used to obtain baseline scores. After being screened for the usual inclusion and exclusion criteria, patients who satisfied screening requirements were entered in the study if they had a severity of pruritus score of ≥ 2 and a number of wheals score of ≥ 1 over the 24-hour period for at least 3 distinct days during the baseline period. Other endpoints assessed (as secondary endpoints) were the duration of pruritus and the number and size of wheals. Wheal size and number were evaluated using a scoring system of 0 – 3 [number of wheals: 0 = none; 1= up to 6 wheals; 2 = 7 – 12 wheals; and 3 = > 12 wheals; for size of wheals 0 = no wheal; 1 = </= 1.5 cm; 2 = > 1.5 < 3 cm; 3 = more than 3 cm]. Both studies demonstrated that LTCZ 5 mg significantly reduced the severity of pruritus in patients with CIU. A significant reduction in pruritus was also observed with LTCZ 2.5 and 10 mg in study A270. The results of the two CIU studies are shown in the table below as the mean pruritus severity evaluated as reflective and instantaneous scores over the total treatment period.

Table 4: Mean pruritus severity over 4 weeks

Treatment	N	Baseline (SD)	Adjusted mean change from baseline (SE)	Difference from Placebo	
				Estimate (98% CI)	P-value
Study A270 Reflective pruritus severity score					
LTCZ 2.5mg	69	2.08(0.53)	1.02 (0.08)	0.82 (0.53, 1.11)	<0.001
LTCZ 5mg	62	2.07 (0.50)	0.92 (0.09)	0.91(0.62, 1.21)	<0.001
LTCZ 10mg	55	2.04(0.57)	0. 73 (0.09)	1.11 (0.81, 1.41)	<0.001
Placebo	60	2.25 (0.50)	1.84 (0.09)	-	-
Study A270 Instantaneous (at the moment) pruritus severity					
LTCZ 2.5mg	69	2.01(0.62)	0.99 (0.08)	0.80 (0.52, 1.09)	<0.001
LTCZ 5mg	64	1.97 (0.51)	0.91 (0.09)	0.88 (0.59, 1.17)	<0.001
LTCZ 10mg	57	1.99 (0.58)	0.75 (0.09)	1.05 (0.75,1.35)	<0.001
Placebo	61	2.18 (0.62)	1.79 (0.09)	-	-
StudyA269 Reflective pruritus severity score					

LCTZ 5 mg	80	2.07 (0.61)	0.94 (0.09)	0.62(0.38, 0.86)	<0.001
Placebo	82	2.06 (0.57)	1.56(0.09)	-	
Study A269 Instantaneous (at the moment) pruritus severity Score					
LCTZ 5mg	80	2.01 (0.61)	0.91 (0.09)	0.63 (0.39, 0.88)	<0.001
Placebo	82	2.00 (0.59)	1.55 (0.09)		

ONSET OF ACTION

Onset of action was evaluated in two environmental exposure unit (EEU) studies A00379 and A00412. Both studies were conducted in Kingston, Ontario Canada. Both were double-blind placebo and active-controlled studies in patients with SAR. Cetirizine 10 mg tablets were used in study A00379 and cetirizine 5mg (oral drops10 mg/ml) and 10 mg tablets were used in A00412 as active controls. LCTZ 5 mg was used in study A00379 whereas LCTZ 2.5 (oral drops 5 mg/ml) and 5 mg (tablet) were used in study A00412. Study A00412 was conducted with the primary objective to serve as a PD link to LCTZ and cetirizine to provide data in support of the Applicant's assertion that half the dose of LCTZ has equivalent efficacy to 2x the dose of cetirizine. The assertion is based on the acknowledgement that cetirizine is a racemic mixture of R and S enantiomers and that only the R enantiomer (LCTZ) is active therefore, the efficacious dose of LCTZ should be half that of cetirizine.

The primary objective of the study was therefore to compare the efficacy of LCTZ 2.5 mg, and LCTZ 5mg, CTZ 5mg and CTZ 10 mg vs. placebo however; the design of the study also allows it to be used to support an onset an duration of action claim. Except for the active doses of study medication the study designs were the same. Male and female patients age 16 years of age and older with a history of SAR to ragweed pollen confirmed by positive skin prick testing performed at screening or within 12 months prior to screening were enrolled in these 2 EEU studies. Subjects eligible for enrollment (identified at screening - study phase I) underwent priming exposure to ragweed pollen (study phase II), followed by double-blind treatment and pollen challenge (study phase III). There were two visits with pollen challenge in the EEU after single drug intake. The study phase III was divided into 2 study periods – Period 1 (day 1) five hours after the drug intake and Period 2 (day 2) from 21 hours to 29 hours after the drug intake. Study subjects were exposed in the EEU for 2 hours before Period 1 in order to obtain baseline symptom scores. Symptoms were recorded every 30 minutes during the 2 study periods. A complex of symptoms called the major symptom complex (MSC) was used as the primary efficacy variable. The MSC (Major symptom complex) consisted of 6 individual symptoms – runny nose, itchy nose, sniffles, nose blows, sneezes, and watery eyes. Four additional symptoms (itchy eyes and ears, itchy throat, cough, and postnasal drip) were combined with the MSC to form the Total Symptom Complex (TSC). In terms of severity, the individual symptoms with the exception of nose blows and sneezes were scored on a scale of 0 – 5 (0 = none, 1 = a little, 2 = moderate, 3 = quite a bit, 4 – severe, 5 = very severe). Severity of nose blows and sneezes were scored 1 -8 based on the number where 8 represents > 15. The subjects also reported nasal congestion as a separate symptom using a separate severity score (0 -4).

For study A00479, The primary efficacy endpoint was the mean change from baseline of the MSC score over period 2, whereas for study A412 the mean change over Period 1 was

the primary efficacy endpoint. However, efficacy over both periods was assessed in the two studies. Another difference with study A379 is that for study A412 the assessment of symptoms was up to 25 hours whereas, for study A379 is was up to 29 hours. The mean MSC score over Period 2 was defined as the average of the 16 MSC scores measured at half hourly intervals during the 8-hour pollen exposure of the second day. The baseline MSC score was the average of the 4 pre-treatment MSC scores on Day 1. Secondary efficacy endpoints included the mean change from baseline in MSC score over Period 1, over each 2-hour interval of Period 2, and over the entire treatment period. The change from baseline in the TSC score was also assessed as a secondary endpoint.

The individual time point analyses showing the onset and duration of action for study A379 is depicted in the table below.

Table 5: Onset and Duration of action Study A00379

Time point Treatment	N	Baseline (SD)	Adj. mean Change from Baseline (SE)	Diff. vs. Placebo
				Adj Mean [95% CI]
00:30min				
PBO	95	16.68 (5.36)	1.25 (0.481)	
LCTZ 5 mg	240	15.36 (5.39)	-1.08 (0.355)	-2.33 (-3.52,-2.25)
CTZ 10 mg	235	16.00 (5.73)	-0.55 (0.329)	-1.80 (-2.9, -0.66)
01:00 hr				
PBO	95	16.68 (5.36)	-2.93 (0.557)	
LCTZ 5 mg	240	15.36 (5.39)	-5.24 (0.359)	-2.31 (-3.62, -1.01)
CTZ 10 mg	235	16.00 (5.73)	-5.34 (0.352)	-2.41 (-3.71, -1.11)
04:00 hr				
PBO	95	16.68 (5.36)	-5.01 (0.627)	
LCTZ 5 mg	240	15.36 (5.39)	-10.23 (0.314)	-5.22 (-6.60, -3.84)
CTZ 10 mg	235	16.00 (5.73)	-10.20 (0.334)	-5.20 (-6.60,-3.79)
24:00 hr				
PBO	93	16.76 (5.37)	-1.88 (0.608)	
LCTZ 5 mg	236	15.40(5.38)	-7.05 (0.386)	-5.17 (-6.59, -3.75)
CTZ 10 mg	233	15.96(5.74)	-7.09 (0.411)	-5.22 (-6.66, 3.77)
29:00 hr				
PBO	93	16.76 (5.37)	-3.49 (0.688)	
LCTZ 5 mg	236	15.40(5.38)	-7.30 (0.414)	-3.80 (-5.38, -2.22)
CTZ 10 mg	233	15.96(5.74)	-7.21 (0.449)	-3.72(-5.34, -2.10)
P < 0.001 except at 00:30min for CTZ where p < 0.002				

Study Results A412

Over period 1 all active treatments were statistically significantly superior to placebo but there was no dose response as shown in the table below.

Table 6: Change from Baseline in the MSC score over period I (first 5 hours)

Treatment	N	Baseline (SD)	Adjusted Mean change from Baseline (SE)
Placebo	78	15.94(5.8)	- 3.80 (0.5)
LCTZ 2.5 mg	116	15.95 (5.6)	-7.15 (0.4)

LCTZ 5mg	119	16.36 (6.2)	-7.05 (0.4)
CTZ 5mg	119	15.25 (5.2)	-7.93 (0.4)
CTZ10mg	119	16.14 (5.7)	-7.54 (0.4)
Diff vs. Placebo		Estimate (SE)	95% CI [ ]*
LCTZ 2.5 mg		-3.35 (0.6)	[-4.61; 2.09]
LCTZ 5 mg			
CTZ 5 mg		-3.25 (0.6)	[-4.50; -2.00]
CTZ 10 mg		-4.13 (0.6)	[-5.38; -2.88]
		-3.74 (0.6)	[-4.99; -2.49]

*p < 0.001

The Applicant has not provided specific time point comparisons between LCTZ and placebo but provided graphic presentation of the time point change in the MSC score compared to placebo for Period 1 and Period 2. The Applicant will need to provide specific end point data so that a replicate onset of action and duration of action can be determined for the EEU studies. In the clinical trials, statistical analysis of onset and duration of action was not done however; patients recorded their symptoms daily on diary cards. The Applicant should provide a statistical analysis of the T4SS (LCTZ vs. placebo) for each day of the first Week and the last week of the treatment period for the confirmatory efficacy allergic rhinitis trials (A268 and A266) so that the onset of action in the clinical trials can be evaluated.

SAFETY

The Applicant submitted an extensive safety database incorporating all clinical studies including clinical pharmacology and active controlled studies conducted world-wide. The Applicant pooled all these studies together to make up the ISS. That database includes over 6,500 patients of whom over 4000 were exposed to LCTZ. Although this is a very extensive database it is not the best suited for providing the best safety information about LCTZ. The database includes 25 clinical pharmacology studies, and several studies that were not placebo controlled as well as other studies in different patient populations.

This reviewer selected the placebo-controlled studies in patients with SAR, PAR, and CIU conducted in adults and adolescents and the two placebo-controlled studies conducted in pediatric patients with SAR and PAR and used those studies to assess the safety profile of LCTZ. Therefore, the safety data base for the adults and adolescents is derived from 10 [8 short term and 2 long term] placebo-controlled studies[2] in which a total of 3699 adults and adolescents were treated with LCTZ or placebo in studies ranging from 1 week to 6 months duration. The details of seven of these studies were previously discussed above in the efficacy section of the review. The other 3 studies that make up the safety data base are: a one-week study in SAR (A222), and two longer term studies of up to 6 months treatment duration (A306 and A264). The safety database for the pediatric population is comprised of two studies of 4 to 6 weeks treatment duration in patients 6 to 12 years of age with SAR or PAR. A total of 483 patients randomized to placebo or LCTZ 5mg once daily were evaluated in these studies. These 2 studies are discussed in greater detail in the pediatric section of the review ((*see Pediatric Considerations*). Table 7 below provides a

[2] The studies are A222, A217, A00268, A219, A265, A266, A264, A269, A270 and A306. Data are obtained from the actual study reports.

breakdown of the number of patients exposed to LCTZ or placebo in the studies that make up the safety database.

Table 7: Number of patients exposed to LCTZ or Placebo in the safety database

Short term studies (1 - 6 weeks treatment duration) Adults and Adolescents 12 years and older					
Study	Placebo	LCTZ 2.5 mg	LCTZ 5 mg	LCTZ 10 mg	Total
A217/SAR	119	117	116	118	470
A219/PAR	104	105	103	109	421
A222/SAR	160	---	319	---	479
A265/PAR	128	133	128	130	519
A266/PAR	144	----	150	---	294
A268/SAR	117	----	119	---	236
A269/CIU	85	----	81	----	166
A270/CIU	63	70	65	59	257
Total	920	425	1081	416	2842
Pediatric Patients 6 – 12 years of age (1 – 6 weeks treatment duration)					
A303/SAR	88	---	89	---	177
A304/PAR	152	----	154		306
Total	240		243		483
Long-Term Studies ((16 weeks – 6 months treatment duration)					
A264/SAR & PAR	273	----	278		551
A306/SAR & Asthma	156	----	150		306
Total	429		428		857

- Short-Term safety (1- 6 weeks treatment duration)

A total of 2165 patients were exposed to LCTZ in the short term studies. Of these patients, 1922 were adults and adolescents 12 years of age and older from 8 short-term studies, and 243 were pediatric patients 6 to 12 years of age.

Adults and Adolescents 12 years of age and older

Of the 1922 adults and adolescents exposed to LCTZ in the 8 short term studies (1 -6 weeks) 425 and 1081 patients were exposed to treatment with LCTZ 2.5 and 5 mg respectively.

There were no deaths in any of the studies. Serious adverse events were reported by 15 patients. However, none of these events was related to the study drug and only one event (a case of cholecystitis) led to study discontinuation. A total of 44 patients discontinued the study because of an adverse event. Of note somnolence/fatigue or tiredness was the cause of study discontinuation in 3% (n = 10) of patients treated with LCTZ compared to 2 (<1%) of patients in the placebo group. Apart from somnolence, headache, pharyngitis, dry mouth, and asthenia were reported more frequently in the LCTZ-treated patients (≥2%) compared to placebo. The adverse event profile was similar in the allergic rhinitis patients and the CIU patients and there does not appear to be a gender effect. Table xx below displays the most common adverse events seen in the short-term studies.

Table 8: Adverse events reported in ≥ 2%*of subjects and more frequently in Xyzal in 8 placebo-controlled studies (1 – 6 weeks duration) in patients aged 12 years and older

Adverse Reaction n (%)	XYZAL 2.5 mg (n=425)	XYZAL 5 mg (n =1081)	Placebo (n = 920)
Headache	41 (9.6%)	154(14%)	80 (9%)
Pharyngitis	30 (7%)	41 (4%)	33 (4%)
Somnolence	22 (5%)	65 (6%)	16 (2%)
Fatigue	4 (<1%)	37 (3%)	13 (1%)
Dry mouth	10 (2%)	15 (1%)	12 (1%)
Asthenia	12(2%)	10 (<1%)	7 (<1%)

**Rounded to the closet unit percentage.*
Data from studies A00268, A00219, A217, A00265, A00266, A00269, A00270, A222

Pediatric patients 6 to 12 years of age

A total of 243 pediatric patients were exposed to LCTZ 5 mg once daily in short-term studies of 4 to 6 weeks duration. In this population, the most common adverse events seen with greater frequency (≥ 2%) compared to placebo were pyrexia, cough, somnolence, and epistaxis and are shown in the table below.

Table 9: Adverse Reactions Pediatric patients 6 – 12 years of age with allergic rhinitis

Adverse Reaction N (%)	Xyzal 5 mg N = 243	Placebo N = 240
Pyrexia	10 (4%)	5 (2%)
Cough	8 (3%)	2 (<1%)
Somnolence	7 (3%)	1 (<1%)
Epistaxis	6(2%)	1 (<1%)

Data from studies A303 and A304

- Long-term safety

Long-term safety data are derived from studies A306 and A264. In these 2 studies a total of 857 patients (429 exposed to placebo and 428 exposed to LCTZ) were evaluated. In study A306, patients with a history of SAR and asthma with exacerbations during the grass pollen season were randomized to treatment with placebo or LCTZ for up to 16 weeks. The study was designed such that patients in one of the study arms(= 153) were treated with placebo for the first 8 weeks of randomization followed by 8 weeks of treatment with LCTZ, whereas, in the other 2 study arms, patients were treated with either placebo or LCTZ for the entire 16-week treatment period. The objective of the study was to assess whether early initiation of LCTZ therapy prior to the pollen season had a beneficial effect. Only the patients treated with LCTZ for 16 weeks (n = 150) will be counted in the safety analysis. In the other long-term study A264, patients with "persistent allergic rhinitis" (defined as allergic rhinitis symptoms during the pollen season and on house dust mite exposure) were randomized to treatment with placebo or LCTZ for 6 months.

In these long term studies, a total of 38 patients (4%) discontinued because of an adverse event 27 patients (5%) in the LCTZ group and 11 patients (3 %) in the placebo group. When somnolence, fatigue, and tiredness are grouped together they constitute the most common adverse reaction leading to discontinuation in the LTCZ group. There were no deaths or drug-related serious adverse reactions in the long term studies. The adverse event profile in adults and adolescents was similar in the short-term (1 – 6 weeks) and the long-term studies.

CLINICAL PHARMACOLOGY

The applicant conducted extensive pharmacokinetic studies (over 25) to support their application. The clinical pharmacology reviewer conducted a detailed review of 8 studies including one bioequivalence study and one pharmacodynamic (wheal and flare) study in healthy volunteers. [redacted] The applicant also conducted a thorough QT study [Study A419] using moxifloxcin (400 mg) as a positive control and up to 30 mg of LCTZ in healthy volunteers. The study showed that LCTZ did not cause QT prolongation compared to the positive control. A PK study in 5 patients with renal failure on dialysis and in patients with varying degrees of renal impairment showed that systemic exposure (AUC) increased 1.8, 3.2, 4.3, and 5.7 -fold, in mild, moderate, severe, and end-stage renal disease (dialysis dependent) patients. Since LCTZ is excreted by the kidney and the clearance of LCTZ correlates with creatinine clearance, dose adjustment is needed in patients with renal impairment and LCTZ should be contraindicated in patients with end-stage renal disease (creatinine clearance < 10 mg) since LCTZ cannot be cleared by hemodialysis.

There was no significant difference in the rate (c_{max}) and extent (AUC) of absorption of LCTZ following food intake, neither was there any appreciable effect of gender on the pharmacokinetics of LCTZ. The development program did not look at the effect of race on LCTZ however; cetirizine the racemate compound did not show race-related differences in kinetics. Geriatric patients (65 years and older) demonstrate reduced body clearance (~ 33%) compared to younger adults but this may be due primarily to the reduced renal function commonly seen in the patients over 65. Pharmacokinetics for pediatric patients under 12 years of age is discussed under "Pediatric Considerations." For further details on clinical pharmacology please refer to Dr. Pratha Roy's review.

NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

Most of the preclinical information is referenced from cetirizine.

PEDIATRIC CONSIDERATIONS

Two studies in pediatric patients 6 to 12 years of age study A303 in patients with seasonal allergic rhinitis and study A304 in patients with perennial allergic rhinitis were conducted. There were a total of 483 patients enrolled in these studies. The design was similar to that of the confirmatory adult studies. Study A303 was conducted in France study, whereas

study A304 was conducted in South Africa. In study A303, 88 patients were exposed to placebo and 89 to LCTZ, 65% of the patients were males, 87% were Caucasian and the mean age was 9.9 years. Only 25 patients between 6 -8 years of age were exposed to LCTZ. A total of 145 subjects (82%) completed the study and 27 (15%) discontinued.[3] In study A304, 152 subjects were randomized to placebo and 154 to LCTZ. A total of 297 (97%) subjects completed study A304. A total of 54 subjects aged 6-8 were exposed to LCTZ. The mean age was 9.8 years and males made up 60% of the study population. In this study, Caucasians made up 28% of the population and Other/mixed race made up 44%. Although this study was conducted in South Africa, blacks only made up 5% of the population.

The primary efficacy variable was the same as that of the adult allergic rhinitis studies (the T4SS). The primary efficacy endpoint was the mean change (adjusted) of the T4SS over the 24-hour treatment period over the first 2 weeks of treatment. Other secondary endpoints included assessment of efficacy over the entire 4-week treatment period for study A304 (PAR) and over the entire 6 week treatment period for study A303. Both studies showed that LCTZ 5 mg once daily in the evening reduced the T4SS significantly more than placebo.

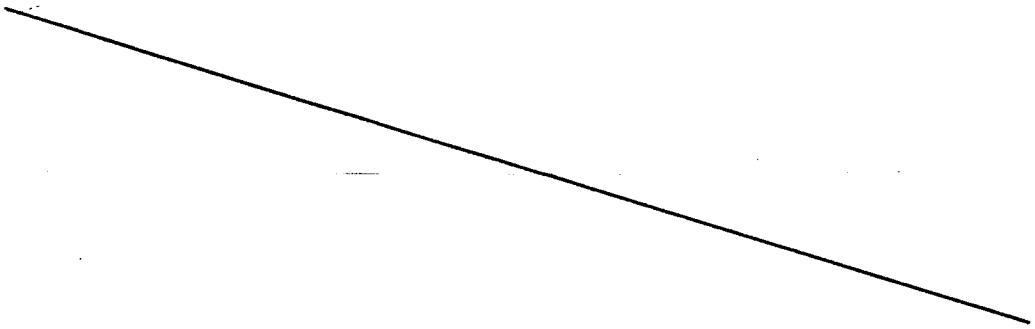
There were no deaths during the study, however one patient, a 9 year old boy died from accidental electrocution after the end of the study. Serious adverse events were not reported in these 2 studies. The most common reason for discontinuation was lack of efficacy and was reported for 10 (4%) patients in the placebo group compared to 6 (2%) patients in the LCTZ group. An adverse event was an infrequent reason for discontinuation occurring in only 5 patients (<1%) [3 in placebo and 2 in LCTZ]. None of the events leading to study discontinuation appear to be related to the study drug. The most common ($\geq$ 2% and > placebo) adverse reactions seen in the studies were pyrexia, cough, somnolence, and epistaxis (*see Table 9*).

The applicant did not submit pharmacokinetic studies in patients under 12 years of age however, they provided a reference[4] for a PK study conducted in children age 6 to 11 years of age with allergic rhinitis. In that study, the rate (C_{max} ng/ml)) and extent (AUC ng/ml/hr) of exposure following administration of a single 5 mg dose of LCTZ was 450 $\pm$ 37 and 3549 $\pm$ 342 respectively corresponding to approximately two times the exposure in healthy adults given the same dose from a cross study comparison (*See Clinical Pharmacology review*). Given that LCTZ displays linear pharmacokinetics, one can reasonably conclude that a dose of 2.5 mg in children 6 – 11 years of age would provide exposure comparable to the 5 mg dose in adults. The adult program for allergic rhinitis and CIU explored both the 2.5 mg and the 5 mg dose for efficacy in dose-ranging studies and the 5 mg dose in confirmatory efficacy studies. Given that the pathophysiology of the diseases and the effect of LCTZ is expected to be the same in adults and children it is reasonable to extrapolate the efficacy seen in the adults and older children (12 years and above) to the 6 to 11 year olds. Safety information to support approval is obtained from

[3] A total of 5 patients (2 placebos and 3 LCTZ) were reported as missing due to the death of the Investigator at the study site.

[4] Levocetirizine: Pharmacokinetics and pharmacodynamics in children age 6 to 11 years. J allergy clin Immunol 2005; 116:355-61

the 2 safety and efficacy studies described along with the safety data in adults and children 12 years of age and older. For the CIU indication, the applicant only conducted studies in adult patients 18 years of age and older; however for the same reasons efficacy of LCTZ for CIU in pediatric patients can be extrapolated from the adult studies.



ETHICS AND DATA INTEGRITY

All of the clinical studies were conducted outside of the United States. The Applicant affirms that the clinical studies were conducted in keeping with good clinical practice and in accordance with the appropriate regulations for human subjects' protection and review of the financial disclosure information submitted did not reveal any irregularities that could bias the study results. Because the NDA relied on data that was entirely non-U.S a Division of Scientific Investigation (DSI) audit was requested from 3 study sites in South Africa. These sites were chosen primarily because they enrolled a large number of patients but there were no data integrity signals that prompted the audit. The DSI audit has been completed and preliminary communications between the field inspector and the DIS Medical reviewer indicated that no irregularities were noted that would render the data from the study sites unsuitable for use in making regulatory determinations (*See Dr. Tejashri Purohit-Sheth's preliminary evaluation of clinical inspections*). Detailed review of the application did not reveal any irregularities in the data and the efficacy data are fairly consistent throughout.

NOMENCLATURE

The proposed trade name for the product is Xyzal ®. The name was previously submitted to the Agency for review and was found to be acceptable at the time. The Division of Medication Errors and Technical Support (DMETS) was re-consulted to address the acceptability of the proposed name, and they have concluded that the name is acceptable.

SUMMARY/CONCLUSIONS

The LCTZ development program for allergic rhinitis and chronic idiopathic urticaria is comprised of multiple dose ranging and confirmatory efficacy studies in adults and adolescents which demonstrate robust efficacy of LCTZ for the proposed indications. All three doses studied showed efficacy but the effect size was not consistent across all the studies. The Applicant proposes a recommended dose of 2.5 or 5 mg once daily for ——— adults ——— For the adults and adolescents the 5 mg dose had a greater effect size in 2 of the 3 dose ranging studies and this was the dose studied in the confirmatory

efficacy studies. In studies with the 10 mg dose somnolence was more frequently reported. For these reasons, the 5 mg dose should be the recommended dose in adults and adolescents. Given that the 2.5 mg dose also showed efficacy in the dose-ranging studies, for some patients, the 2.5 mg dose may be effective. Since the applicant did not conduct any comparative efficacy studies with the 2.5 and 5 mg dose the statement in the label that

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Rather, a general statement that "*some patients may be adequately controlled with 2.5 mg once daily in the evening*" would be more appropriate. Furthermore, since in all the studies the drug was administered in the evening, the qualifier "*once daily in the evening*" should be stated in the Dosing and Administration section. For children 6 to 11 years the recommended dose should be 2.5 mg since this is the dose most likely to have a similar exposure to the 5 mg dose in adults. With the robust efficacy, LCTZ was also associated with somnolence, and other adverse reactions that could be related to somnolence (i.e. fatigue, tiredness, and asthenia). This is remarkable given that the drug was given in the evening. Therefore, one can reasonable conclude that LCTZ is probably more sedating that the racemate cetirizine. For this reason, the recommended dosing administration would be once daily in the evening.

LABELING

The proposed package insert was submitted in the new labeling format of the Physician Labeling Rule (PLR). The label needs to be revised extensively to comply with the implementation guidances of the PLR. Furthermore, the content for several sections in particular the Clinical Pharmacology, Adverse Reactions, and Clinical Trials sections of the label needs to be extensively revised and in some cases re-written. The safety database described in the applicant's proposed label is not suitable for providing the best safety information about the drug because that database is comprised of all clinical pharmacology PK and PD studies, and other studies that were not placebo-controlled. The clinical studies section as proposed by the applicant was also not acceptable as it did not include important information needed to comply with the PLR Clinical Studies guidance. Furthermore, additional information reflecting the Division's current thinking on the Clinical Studies section of the label (e.g. inclusion of data tables for dose-ranging and efficacy studies) needed to be addressed. Therefore, this reviewer re-wrote the entire ADVERSE REACTIONS and the CLINICAL STUDIES section of the label. Labeling comments will be sent to the applicant. Furthermore, this reviewer added a new section "Patient Counseling Information" to the label to comply with the PLR since the applicant's proposed label did not have this section.

RECOMMENDATION

Depending upon the applicant's acceptance of the Division's labeling revisions; I recommend that levocetirizine be approved for treatment of the symptoms of allergic rhinitis (seasonal and perennial) in adults and children 6 years of age and older. The recommended dose for adults and adolescents 12 years of age and older is 5 mg to be administered once daily in the evening. For children 6 to 11 years of age a dose of 2.5 mg is recommended. The higher dose (5 mg) is not recommended because of the increased (~ 2-fold) systemic exposure seen with the 5 mg dose in this age group.

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/s/

Lydia McClain
4/19/2007 02:13:38 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: QT Study Review

IND or NDA	NDA22064
Brand Name	Xyzal
Generic Name	Levocetirizine dihydrochloride
Sponsor	UCB, Inc.
Indication	Seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU)
Dosage Form	tablet
Therapeutic Dose	2.5 mg or 5 mg once daily
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Not reported.
Application Submission Date	25 July 2006
Review Classification	Standard NDA
Date Consult Received	8 Dec 2006
Date Consult Due	10 Feb 2007
Clinical Division	Pulmonary (DPAP / HFD 570)
PDUFA Date	25 May 2007

1 SUMMARY

This is a negative Thorough QT study.

1.1 Overall Summary of Findings

We evaluated this study independently with the data provided. Our findings are consistent with those from the sponsor. The data suggest that both levocetirizine 5 mg and 30 mg do not seem to prolong QTc interval in a clinically meaningful way.

1.2 Responses to Questions posed by Review Division

There were no questions from the review division.

1.3 Reviewer Comments

The following comments should be conveyed to the sponsor:

1. Please submit case report forms and narratives for Subjects 100036, 100039, 100041, and 100043.

2 PROPOSED LABEL

The sponsor proposed the following labeling under Section 12.2, PHARMACODYNAMICS section of the label, and we have edited the label to reflect the findings of the thorough QT study. These recommendations are suggestions for labeling only and are open to modification pending further discussion with the review division. We defer all final labeling decisions to the review division.

3 BACKGROUND

3.1 INDICATION

Seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria

3.2 DRUG CLASS

Levocetirizine, the active enantiomer of cetirizine, is an anti-histamine; its principal effects are mediated via selective inhibition of peripheral H1 receptors.

3.3 MARKET APPROVAL STATUS

Levocetirizine is currently under review for approval in USA. Levocetirizine is marketed by UCB, Inc. under the brand names XYZAL® and XUSAL™ in the European Union for treatment of symptoms of seasonal and perennial allergic rhinitis, persistent allergic rhinitis, and chronic idiopathic urticaria (CIU, also known as hives of unknown cause) in adults and children ages 6 years and older.

3.4 PRECLINICAL INFORMATION

There were no preclinical reports included in this submission.

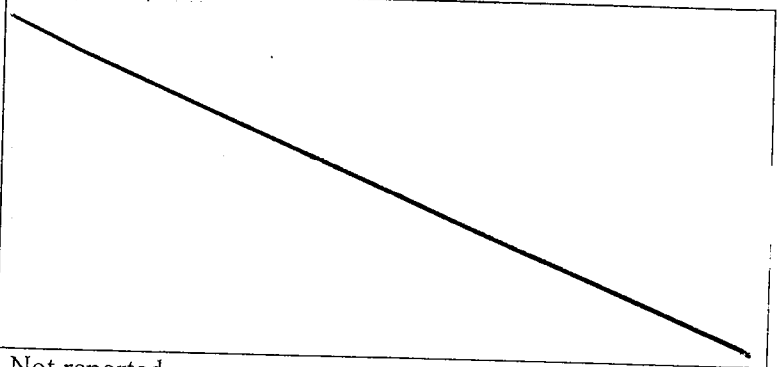
3.5 PREVIOUS CLINICAL EXPERIENCE

As of October 2006, a total of 4,067 subjects were exposed to levocetirizine at different daily dosages. Incidences of adverse events (AEs) reported by at least 1% of the subjects in any treatment groups and at least possibly related to the investigational product were somnolence, dry mouth, headache, and fatigue. Somnolence, dry mouth, and fatigue occurred more frequently in the levocetirizine-treated subjects than during placebo treatment.

3.6 CLINICAL PHARMACOLOGY

Table 1 summarizes the key features of levocetirizine's clinical pharmacology.

Table 1 Highlights of Clinical Pharmacology

Therapeutic dose		
Maximum tolerated dose	Not reported.	
Principal adverse events	Somnolence, dry mouth, headache, and fatigue	
Maximum dose tested	Single Dose	30 mg
	Multiple Dose	5 mg once daily
Exposures Achieved at Maximum Tested Dose	Single Dose	Cmax: 1256 ng/mL
	Multiple Dose	Cmax: 308 ng/mL
Range of linear PK	Linear over doses studied	
Accumulation at steady state	Not reported	
Metabolites	The extent of metabolism of levocetirizine in humans is less than 14% of the dose	
Absorption	Absolute/Relative Bioavailability	Not reported
	Tmax	0.9 hour
Distribution	Vd/F or Vd	0.4 L/kg
	% bound	The mean plasma protein binding of levocetirizine in vitro ranged from 91 to 95%, independent of concentration in the range of 25-1000 ng/mL
Elimination	Route	The major route of excretion of levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose.
	Terminal t½	8 hours
	CL/F	0.63 mL/kg/min

Intrinsic Factors	Age	No pharmacokinetic studies were conducted with levocetirizine in children ages 6 to 12 years. Pharmacokinetic profiles of levocetirizine are available in 9 elderly patients (65-74 years of age). Following repeat administration for 6 days, the apparent total body clearance was 0.41 mL/kg/min, which represents a reduction of approximately 33% when compared to adults.
	Sex	The half-life was slightly shorter in women (7.08 ± 1.72 hr) than in men (8.62 ± 1.84 hr); however, the body weight-adjusted clearance in women (0.67 ± 0.16 mL/min/kg) appears to be comparable to that in men (0.59 ± 0.12 mL/min/kg).
	Race	The effect of race on levocetirizine has not been studied.
	Hepatic & Renal Impairment	The apparent body clearance of levocetirizine is correlated to the creatinine clearance.
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Food had no effect on the extent of exposure (AUC) of the levocetirizine tablet, but Tmax was delayed by about 1.25 hours and Cmax was decreased by about 35% after administration with a high fat meal
Expected High Clinical Exposure Scenario	Moderate to Severe renal impairment.	

4 SPONSOR'S SUBMISSION

4.1 SUBMITTED MATERIALS

The sponsor submitted a thorough QT study as part of 120-day safety for review.

4.2 QT STUDY

4.2.1 Title

Four-Way Crossover, Randomized, Placebo- and Moxifloxacin Controlled Study of the Effect of Levocetirizine on Cardiac Repolarization in 52 Healthy Male and Female Subjects

4.2.2 NDA Number

NDA 22064

4.2.3 Objectives

Primary Objective:

To determine whether levocetirizine has a threshold pharmacologic effect on cardiac repolarization, as detected by QTc prolongation.

Secondary Objectives:

1. To determine the pharmacologic effect of levocetirizine on the following electrocardiogram (ECG) parameters:
   - Time-matched baseline-subtracted QTcF interval.
   - Time-matched baseline-subtracted QTcSS at tmax.
   - Non baseline-subtracted QTc, QT, RR, PR, and QRS.
2. To determine the incidence of outliers with new abnormalities or new supra-threshold values of ECG (QT, QTc) and/or of change from baseline (QTc, PR, QRS, Heart Rate [HR]).
3. To perform time-averaged analysis for the ECG interval (QTc, QT, HR, PR, QRS) data.
4. To assess the pharmacokinetics of single oral doses of 5 mg and 30 mg levocetirizine.
5. To explore QTc/ pharmacokinetics relationships.
6. To assess the safety of single oral doses of 5 mg and 30 mg levocetirizine

4.2.4 Design

4.2.4.1 Description

This was a single center, Phase I, randomized, single dose, 4-way crossover study in healthy male and female subjects. Subjects were randomly assigned to receive the 4 treatments according a random sequence of administration: 3 double-blind treatments; 5 mg levocetirizine, 30 mg levocetirizine, placebo, or an open label treatment of 400 mg moxifloxacin. Each of the 4 periods were 3 days in duration (4 days for the first period) and separated by a 7-day washout period.

The subjects entered the clinical center for the treatment period in the afternoon (around 16:00) prior to dosing (except for Period 1 where subjects reported to the clinical center 2 days prior to dosing). A standard meal was provided in the evening of the check-in day of each period (Day -2 for the Period 1). The subjects were confined in the clinical center for 3 days each period (4 days for Period 1) or longer if necessary and during which all the study procedures (cardiac safety, pharmacokinetics and safety) were performed.

Withdrawn subjects were not to be replaced.

4.2.4.2 Sponsor's Justification for Design

A single dose crossover design was selected because levocetirizine exhibits linear pharmacokinetics, with a rapid absorption (t_{max} within 0.9 h) and a relatively rapid elimination ($T_{1/2}$ ca. 8 hours), suggesting limited accumulation at steady-state.

Moxifloxacin also exhibits a relatively rapid absorption (Tmax = 0.5 to 4 h) with a rapid elimination (T1/2 =11.5 to 15.6 h). As a result, a 7-day washout period was considered appropriate. The crossover design minimized the influence of variability between subjects and minimized the number of subjects required since each subject served as his own control.

4.2.4.3 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.4.4 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.5 Study Subjects

The study enrolled 52 healthy males or females, eighteen (18) to forty five (45) years of age, with a normal 12-lead ECG.

4.2.6 Dosing Regimens

4.2.6.1 Treatment Arms

Single doses of 5 mg levocetirizine, 30 mg levocetirizine, 400 mg moxifloxacin and placebo

4.2.6.2 Sponsor's Justification for Doses

Levocetirizine tablets are approved in a number of countries worldwide for the treatment of SAR, PAR and CIU in adults and children 6 years of age and above, at the dose of 5 mg once daily. The dose of 5 mg levocetirizine was chosen as representative of the therapeutic dose. The supra-therapeutic dose was set at 30 mg, which corresponds to 6 times the therapeutic dose as it is the highest dose tested to date.

4.2.6.3 Instructions with regard to meals

Subjects had to take the study medication under fasting conditions. The subjects fasted from 22:00 the day before and continued to fast until 4 hours post-dose. All medications were to be taken in an upright sitting position with 240 mL of tap water at room temperature.

4.2.6.4 Study Assessments

Table 2. Highlights of Schedule of Interventions

Study Day	-1	1	2-7
Intervention	No treatment	Single dose	No treatment (Washout)
12-Lead ECGs	Record ECGs[###] (Baseline)	Record ECGs[###]	None recorded
PK Samples for drug	None collected	Collected[###]	None collected
Meal Instructions	None specified	To be dosed without food	None specified

[###]0,0.5,1,1.5,2,4,6,8,9,12,24 hours postdose

4.2.6.5 Sponsor's justification for sampling schedule

The sponsor did not provide justification for sampling times

4.2.6.6 Baseline

Time-matched baseline at day -1 was used.

4.2.7 ECG Collection

Continuous Holter monitoring was recorded at baseline from -24 h pre-dose up to pre-dose, and from pre-dose up to 24 h post-dose at subsequent treatment periods using the Mortara Holter Device. Each subject was assigned 1 Holter device throughout the study and used the same device at each treatment period. Arrhythmia evaluation for each Holter session was conducted by the central ECG reader at the specified periods. Subjects remained resting in a supine position in a controlled, calm environment for 15 minutes prior to the pharmacokinetics sampling time, i.e., pre-dose and at each post-dose time-point.

The ECG central reading was performed by [redacted]

Standard 12-lead ECGs after 10 min supine rest were recorded at screening; pre-dose, 1.5 h, 4 h, and 24 h post-dose of each period; and at discharge. ECGs had to be appropriately collected, i.e., at a speed of 25 mm/sec, with a calibration of 1 cm/mV and of good quality. Each original ECG had to be reviewed, signed and dated by the principal Investigator or sub-Investigator. Two copies of each ECG had to be made: 1 for retrieval with the Sponsor's CRF copy and 1 to remain with the Investigator's CRF copy.

4.2.8 Endpoints

4.2.8.1 Primary Endpoint

The primary variable was the largest time-matched baseline-subtracted mean difference of QTcSS between drug and placebo. QTcSS is the QT interval with gender-specific and study-specific correction exponent determined by non-linear (log/log) regression of QT versus RR.

4.2.8.2 Safety assessments

Please see Appendix 6 for a Table of safety assessments.

4.2.9 Sponsor's Results

4.2.9.1 Study Subjects

4.2.9.1.1 Disposition

Of the 75 screened subjects, 23 were not randomized, including 8 males (of whom 4 were stand-by subjects) and 15 females (of whom 6 were stand-by subjects).

A total of 52 subjects, including 28 men and 24 women, were enrolled in this 4-way crossover study. All 52 randomized subjects received double-blind treatments of 5 mg

levocetirizine, 30 mg levocetirizine, and placebo and open-label treatment of 400 mg moxifloxacin.

The disposition of subjects by gender is provided in Table 3 below. There were 52 subjects in the Intent-to-Treat (ITT) and Safety Populations and 51 in the Per Protocol (PP) Population. One subject (001/0016) had missing Holter recording during the first 6 hours after administration of Placebo (Period 3) and was excluded from the Per Protocol Population.

Table 3. Disposition of Subjects

	Male n (%)	Female n (%)	Overall n (%)
Screened Subjects	36	39	75
Randomized Subjects	28	24	52
ITT Population	28	24	52
Completed the Study	28 (100%)	24 (100%)	52 (100%)
PP Population	27 (96.4%)	24 (100%)	51 (98.1%)

Note: Each % is based on the ITT Population.
Source: Table 14.1.1:1 and Listing 16.2.1:2

(Reproduced from Sponsor, Table 10.1, page 66 of 4265)

4.2.9.1.2 Demographics

Demographics for the ITT Population are displayed in Table 4.

Table 4. Demographics (ITT Population)

Characteristic		Male (N=28)	Female (N=24)	Overall (N=52)
Age (year) [a]	Mean (SD) Min-Max	31.47 (6.13) 21.7-43.3	31.64 (7.75) 18.4-46.0	31.55 (6.85) 18.4-46.0
Weight (kg)	Mean (SD) Min-Max	76.2 (10.1) 56-96	63.7(8.7) 46-78	70.4 (11.3) 46-96
Height (cm)	Mean (SD) Min-Max	178.3 (6.6) 169-192	166.3 (6.8) 155-179	172.8 (9.0) 155-192
BMI (kg/m^2) [b]	Mean (SD) Min-Max	23.94 (2.55) 19.1-28.6	23.04 (3.05) 19.1-27.9	23.52 (2.80) 19.1-28.6
Race (n [%])	Caucasian Black Asian/Pacific Islander	28 (100%)	22 (92%) 1 (4%) 1 (4%)	50 (96%) 1 (2%) 1 (2%)

Note: Each % is based on ITT Population.
[a] Age (years) at the randomization visit
[b] BMI = weight(kg)/[height(m)]^2
Source: Table 14.1.2:1

(Reproduced from Sponsor, Table 11.1, page 69 of 4265)

4.2.9.2 Statistical Analyses

Data Sets Analyzed

The Intent-to-Treat Population (ITT) consisted of all randomized subjects who received at least 1 dose of any treatment.

The Per-Protocol Population (PP) was a subset of the ITT Population, consisting of those subjects who had no major protocol deviations affecting the primary variable, as confirmed during the pre-analysis review of the data prior to unblinding of the data.

The analysis was performed on all subjects with available ECG data at baseline and who received at least 1 treatment.

Demographic and other baseline characteristic analyses were performed on the ITT Population.

4.2.9.2.1 Primary Analysis

The primary variable was defined as the QT interval corrected using a gender-specific, study-specific correction: $QTcSS = QT/(RR/1000)^a$. For each subject, a non-linear (log/log) regression of QT versus RR was run. Natural logarithms were used for log transformation. Each model was fitted using the 60 values corresponding to the individual ECGs from the baseline (Day -1) and the placebo treatment day (2 periods x10 time-points x 3 ECGs per time-point). The correction factor, a, was derived as the mean of the regression coefficients for all subjects of the same gender. The correction was applied to each of the 3 single QT measurements for each time-point. The QTcSS (QTcF) values used for subsequent analyses were computed as the mean of the 3 QTcSS (QTcF) values for each time-point. The adequacy of the correction was assessed by plotting QTcSS versus RR values. A slope close to zero indicates a low correlation and that the correction was valuable.

The primary analysis was performed on the time-matched, baseline-subtracted QTcSS (QTcSS) using a mixed model Analysis of Variance (ANOVA) with repeated measurements. The model included treatment, period, gender, post-dose time as fixed effects, the subject as random effect nested under gender, the pre-dose value as covariate, and the treatment-by-time and period-by-time interactions. Model-adjusted means were derived for each treatment at each post-dose time as well as 2-sided 90% confidence intervals (CIs) (equivalent to a 95% one-sided CI) of the differences between each active treatment and placebo at each post-dose time (QTcSS). The largest of all time-point differences (maximum QTcSS) was the primary endpoint. Only subjects with both baseline and treatment sets of ECGs were used. Absence of effects of levocetirizine on cardiac repolarization were concluded if the upper limit of the 95% one-sided CI for maximum QTcSS between levocetirizine and placebo was less than 10 ms and if the lower limit of the 95% one-sided CI for maximum QTcSS between moxifloxacin and placebo was greater than 0 ms (sensitivity criterion). The same approach was adopted for the analysis of QTcF. The treatment-by-gender interaction was evaluated at the 0.05 significance level. If the effect was detected as statistically significant, separate analyses for males and females were presented.

The time-matched difference from baseline for QTcSS at subject-specific Tmax (SSTmax) was also analyzed using a mixed model ANOVA by study drug (5 and 30 mg levocetirizine, and 400 mg moxifloxacin), with the treatment (active treatment and placebo) and the gender as fixed effects, the treatment-by-gender interaction, and the subject as random effect nested under the gender. A 95% one-sided CI of the mean difference between each active treatment and placebo was derived, as displayed in Table 5 and Table 6.

Table 5. Sponsor's Analysis: Summary Statistics of the Largest Time-Matched Difference Between Active Treatment and Placebo: Maximum ΔΔQTcSS - PP and ITT Populations

Population	Treatment	Post-dose Time	Estimate	Two-Sided 90% Confidence Interval[a]	
PP (N=51)	5 mg LCTZ	24 h	2.86	0.02	5.70
	30 mg LCTZ	24 h	1.06	-1.78	3.90
	400 mg MOX	4 h	13.37	10.53	16.21
ITT (N=52)	5 mg LCTZ	4 h	2.78	-0.07	5.63
	30 mg LCTZ	24 h	0.96	-1.89	3.81
	400 mg MOX	4 h	13.32	10.47	16.17

[a] Equivalent to one-sided 95% Confidence Limit (in bold: the upper limit for LCTZ and the lower limit for MOX)
Source: Table 14.2.2:2

(Reproduced from Sponsor, Table 11.2, page 74 of 4265)

Table 6. Sponsor's Analysis: Summary Statistics of the Largest Time-Matched Difference between Active Treatment and Placebo: Maximum ΔΔQTcF - PP and ITT Populations

Population	Treatment	Post-dose Time	Estimate	Two-Sided 90% Confidence Interval[a]	
PP (N=51)	5 mg LCTZ	4 h	2.51	-0.50	5.52
	30 mg LCTZ	0.5 h	-0.44	-3.45	2.57
	400 mg MOX	4 h	13.64	10.63	16.65
ITT (N=52)	5 mg LCTZ	4 h	2.47	-0.55	5.49
	30 mg LCTZ	0.5 h	-0.21	-3.23	2.81
	400 mg MOX	4 h	13.61	10.60	16.63

[a] Equivalent to one-sided 95% Confidence Limit (in bold: the upper limit for LCTZ and the lower limit for MOX)
Source: Table 14.2.2:6

(Reproduced from Sponsor, Table 11.3, page 74 of 4265)

The one-sided 95% lower limit of the largest ΔΔQTcSS of the positive control treatment 400 moxifloxacin was noticeably higher than 0 ms (10.5 ms) and the mean estimate was higher than 5 ms (13.4 ms). Moreover, the moxifloxacin effect appeared as soon as 0.5 h after administration and was maintained until 24 post-dose.

4.2.9.2.2 Categorical Analysis

Results of categorical analyses are displayed in Table 7 for the PP Population.

Table 7. Sponsor's Analysis: Categorical Analysis of QT and QTc Intervals - PP Population

PP Population (N=51)	Maximum change[a] from baseline		New[b] Maximum Post-dose QT Interval		
Parameters	> 30 ms n%	> 60 ms n%	> 450 ms n%	> 480 ms n%	> 500 ms n%
QT					
LCTZ 5 mg			3 (5.9%)	0	0
LCTZ 30 mg			4 (7.8%)	0	0
MOX 400 mg			5 (9.8%)	1 (2.0%)	0
Placebo			2 (3.9%)	2 (3.9%)	0
QTcSS					
5 mg LCTZ	2 (3.9%)	0	2 (3.9%)	0	0
30 mg LCTZ	1 (2.0%)	0	0	0	0
400 mg MOX	10 (19.6%)	0	5 (9.8%)	0	0
Placebo	4 (7.8%)	0	3 (5.9%)	0	0
QTcF					
5 mg LCTZ	2 (3.9%)	0	0	0	0
30 mg LCTZ	1 (2.0%)	0	0	0	0
400 mg MOX	8 (15.7%)	0	2 (3.9%)	0	0
Placebo	3 (5.9%)	0	2 (3.9%)	0	0
QTcB					
5 mg LCTZ	6 (11.8%)	0	2 (3.9%)	1 (2.0%)	0
30 mg LCTZ	2 (3.9%)	0	1 (2.0%)	0	0
400 mg MOX	10 (19.6%)	0	6 (11.8%)	1 (2.0%)	0
Placebo	5 (9.8%)	0	3 (5.9%)	1 (2.0%)	0

(a)Change from the average 24-h baseline value
(b) Not present during the 24-h baseline period
Source: Table 14.2.2:13 and Table 14.2.2:14
(Reproduced from Sponsor, Table 11.7, page 78 of 4265)

QTcSS increase from baseline higher than 30 ms was observed in two subjects after 5 mg levocetirizine, and in one subject (two in the ITT Population) after 30 mg levocetirizine, compared to four subjects after placebo and 10 subjects after 400 mg moxifloxacin. The number of subjects with QTcF change higher than 30 ms was similar with 2, 1, 3, and 8 subjects, respectively, in the LCTZ 5 mg, LCTZ 30 mg, placebo, and moxifloxacin 400 mg treatment groups. There was no change higher than 60 ms for either QTcSS or QTcF in any treatment period.

Only one subject (001/0016), excluded from the PP Population, showed a QT interval value greater than 500 ms during the 30 mg levocetirizine period, from pre-dose through 4 hours post-dose (see Listing 16.2.6:1, page 3052 of 4265). Predose QT was 516-525 ms. QT interval ranged from 513 to 531 ms through 4 hours post-dosing. The maximum QTcF achieved during that time frame was 488

ms at 1.5 hours. No QTcF or QTcB values ever exceeded 500 ms. Since this patient never had a prolonged QT during any other predose period, a carryover effect for this patient cannot be excluded, although the washout period of 7-days would seem to be adequate.

In all other subjects (the whole PP Population), there was no case of QT or QTcB higher than 500 ms and no case of QTcSS or QTcF higher than 480 ms in any treatment period.

Only one subject (001/0001) had a single episode of tachycardia during the 5 mg levocetirizine treatment period at 9 hours post-dose (mean HR of the triplicate ECG: 113 bpm, with minimum HR of 94 and maximum HR of 125). HR was below 70 bpm at all other time-points (see Listing 16.2.6:1, page 2902 of 4265 for details).

Four cases were identified as bradycardic outliers: Subject 001/0017 during the 30 mg levocetirizine treatment period (at 2 h and 4 h, mean HR of the triplicate ECG: 47 bpm in both), Subject 001/0011 during the 400 mg moxifloxacin treatment period (at 1 h, mean HR of the triplicate ECG: 48 bpm), and subjects 001/0031 and 001/0044 during the placebo treatment period (at 0.5 h and 1.5 h, mean HR of the triplicate ECG: 49 bpm and 46 bpm, respectively).

Another subject (001/0047) exhibited an increased PR (> 200 ms) during both levocetirizine treatment periods (5 mg LCTZ: maximum PR 244 ms at 1.5 hours post-dosing; 30 mg LCTZ: maximum PR 250 ms at 1.5 hours after dosing).

Outlier Analysis

Outlier analyses were conducted by computing the number and the percentage of subjects in each treatment group that meet the following criteria:

- New QT values > 500 ms
- New QTc values > 450 ms, 480 ms and 500 ms
- Change from baseline in QTc of 30-60 ms and > 60 ms
- Change from baseline in PR: > 25% increase when PR > 200 ms
- Change from baseline in QRS: > 25% increase when QRS > 100 ms
- Change from baseline in HR: > 25% increase when HR > 100 beats per minute (bpm) or <25% decrease when HR <50 bpm.

If a subject experienced more than 1 episode of a particular event, the subject was counted only once for that event. "New" was defined as "not present on any baseline ECG but present on any treatment ECG". The outliers were defined on the basis of the maximum values presented at baseline and at each on-treatment period. Change from baseline was defined with respect to time-averaged baseline (i.e., the mean value on Day -1).

Outlier results using QTcSS and QTcF are displayed in Table 8 and Table 9.

Table 8. Sponsor's Analysis: Classification of QTc and QT Intervals (New Onset) by Treatment - PP Population: QTcSS

Treatment	>450 ms n (%)	>480 ms n (%)	>500 ms n (%)
Levocetirizine 5 mg (N = 51)	2 (3.9%)	0	0
Levocetirizine 30 mg (N = 51)	0	0	0
Moxifloxacin 400 mg (N = 51)	5 (9.8%)	0	0
Placebo (N = 51)	3 (5.9%)	0	0

(Reproduced from Sponsor, Table 14.2.2.13, page 1084 of 4265)

Table 9. Sponsor's Analysis: Classification of QTc and QT Intervals (New Onset) by Treatment – PP Population: QTcF

Treatment	>450 ms n (%)	>460 ms n (%)	>500 ms n (%)
Levocetirizine 5 mg (N = 51)	0	0	0
Levocetirizine 30 mg (N = 51)	0	0	0
Moxifloxacin 400 mg (N = 51)	2 (3.9%)	0	0
Placebo (N = 51)	2 (3.9%)	0	0

(Reproduced from Sponsor, Table 14.2.2.13, page 1086 of 4265)

4.2.9.2.3 Additional Analyses

A Secondary Endpoint

The time-matched QTcSS change from baseline at subject-specific Tmax was not higher after administration of either dose of LCTZ than after placebo. The drug minus placebo difference was even lower than 0 for both doses. However, the time-matched QTcSS change from baseline at moxifloxacin Tmax was statistically higher than the corresponding change observed after placebo; the mean difference was approximately 9 ms and the 90% CI was 5 to 12 ms.

Table 10. Sponsor's Analysis: Treatment Comparison of Time-Matched Difference from Baseline for QTcSS at Subject-Specific Tmax (SSTmax) - PP and ITT Populations

Population	Treatment	Δ_{tmax} (ms) Mean[a] (95% CI)		Active Drug – Placebo Difference (ms)
		Active Drug	Placebo	Point estimate (90% CI)
PP N=51	5 mg LCTZ	4.9 (1.9; 7.9)	7.1 (4.0;10.1)	-2.2 (-5.4; 1.0)
	30 mg LCTZ	3.5 (0.3; 6.7)	5.7 (2.5; 8.9)	-2.2 (-5.3; 1.0)
	400 mg MOX	14.3 (11.1; 17.4)	5.8 (2.6; 8.9)	8.5 (5.3; 11.6)
ITT N=52	5 mg LCTZ	4.6 (1.6; 7.6)	7.0 (4.0;10.0)	-2.4 (-5.6; 0.8)
	30 mg LCTZ	4.3 (0.9; 7.7)	6.0 (2.6; 9.4)	-1.7 (-5.0; 1.6)
	400 mg MOX	14.5 (11.4; 17.7)	5.9 (2.7; 9.0)	8.7 (5.5; 11.8)

[a] Values are Least-squares means derived from the analysis of variance
Source: Table 14.2.2:7 and Table 14.2.2:8

(Reproduced from Sponsor, Table 11.4, page 75 of 4265)

4.2.9.3 Clinical Pharmacology

4.2.9.3.1 Pharmacokinetic Analysis

Pharmacokinetic parameters of levocetirizine are presented in Table 11.

Table 11. FDA Analysis: Pharmacokinetic Parameters of Levocetirizine

Dose	Parameter	Cmax	AUC(0-t)	tmax
5 mg		[ng/mL]	[h*ng/mL]	[h]
	N	52	52	52
	Geometric mean	217	1660	1.29
	Arithmetic mean	228	1660	1.29
	SD	97.2	340	1.26
	CV(%)	42.7	20.5	97.9
	Minimum	123	1088	0.500
	Median	210	1596	1.00
	Maximum	852	2910	9.00
30 mg				
	N	52	52	52
	Geometric mean	1256	9760	1.09
	Arithmetic mean	1302	9987	1.35
	SD	372	2341	1.33
	CV(%) (c)	28.6	23.4	98.8
	Minimum	671	7201	0.500
	Median	1245	9415	1.00
	Maximum	2530	17433	9.00

4.2.9.3.2 Exposure-Response Analysis

The sponsor investigated the relationship between levocetirizine plasma concentration and QTcSS change from baseline (ΔQTcSS). The regression linear model (Figure 1): $\Delta QTcSS = \alpha + \beta Cp$, gave the following estimates of intercept and slope for levocetirizine: 1.47 ms (95% CI: -0.45; 3.40) and 0.002 ms/(ng/mL) (95% CI: -0.001; 0.006). Both coefficients were not statistically different from zero. The predicted ΔQTcSS at the average measured C_{max} is 1.9 ms and 4.1 ms for the therapeutic (5 mg) and the supra-therapeutic (30 mg) doses of levocetirizine which are below the threshold value of 5 ms.

The sponsor also investigated the relationship between moxifloxacin plasma concentration and ΔQTcSS. The same linear model for moxifloxacin

Figure 2Figure 2 gave intercept and slope estimates of 2.80 ms (95% CI: 0.31; 5.28) and 0.004 ms/(ng/mL) (95% CI: 0.003-0.005), respectively. The predicted ΔQTcSS at the average measured C_{max} is 15.6 ms which is clearly above the threshold value of 10 ms and close to the mean observed ΔQTcSS at t_{max} (14.5 ms).

Figure 1. FDA Analysis: Plot of Individual QTcSS Change from Baseline versus Plasma Concentrations at Corresponding Time Points for Levocetirizine

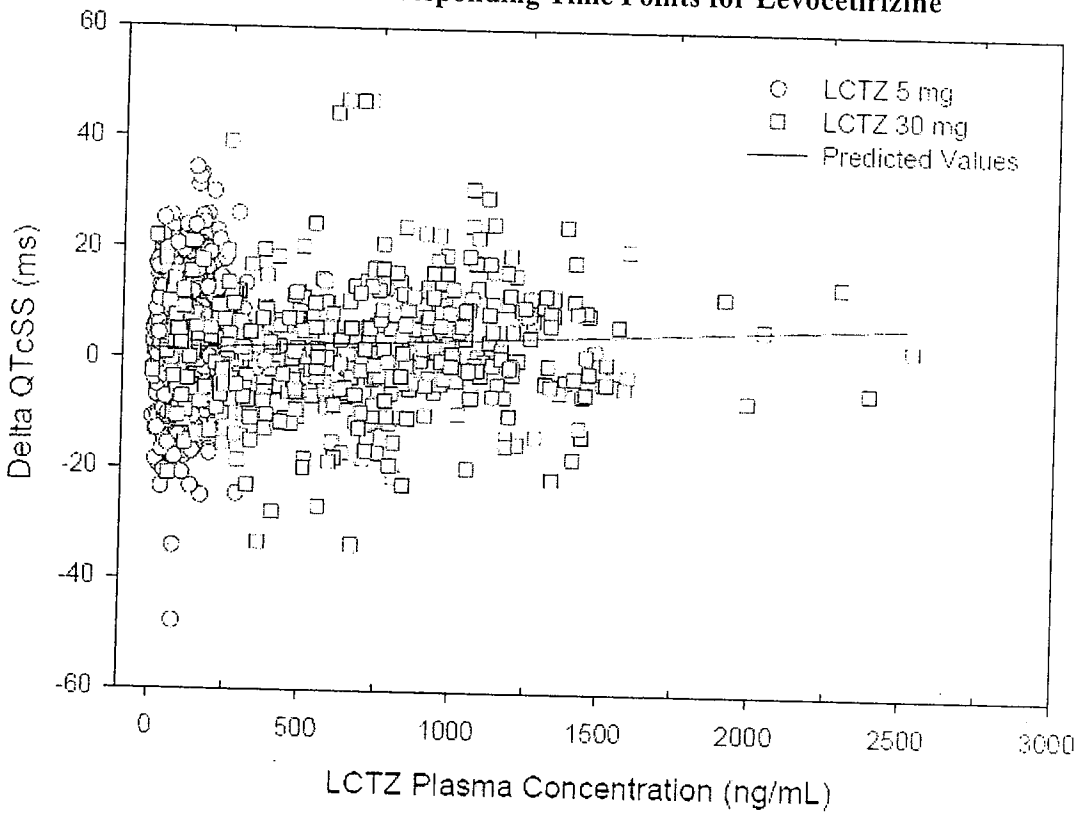


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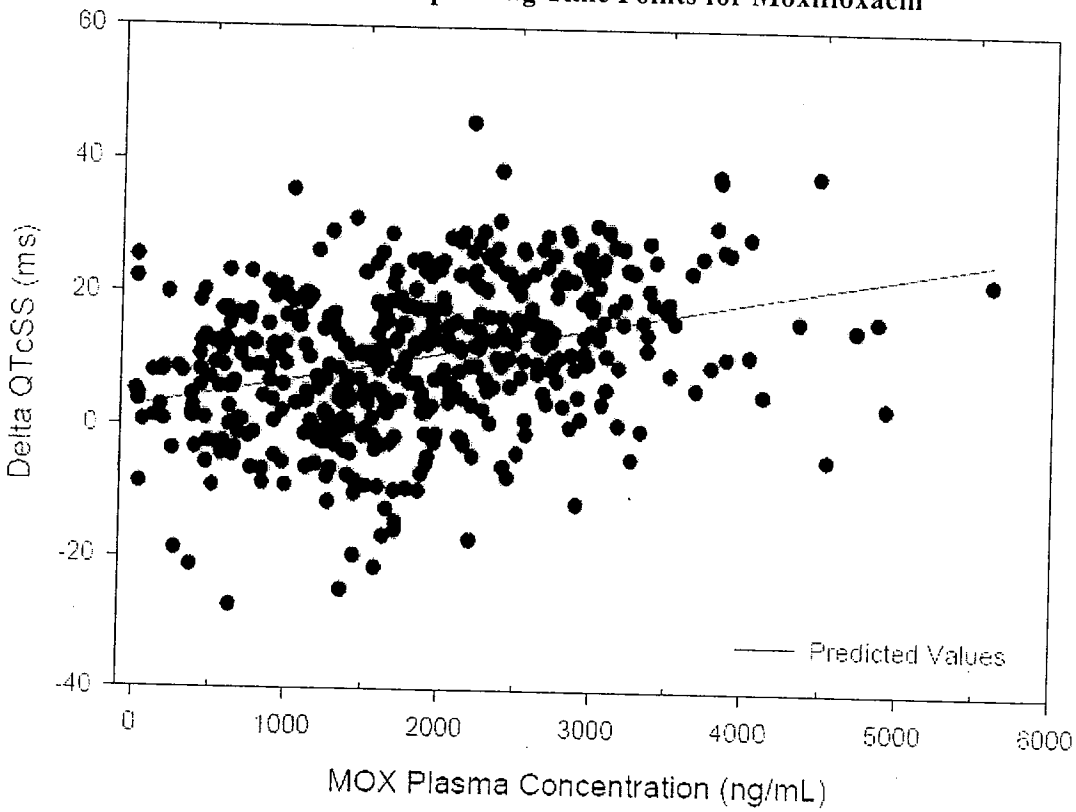
Figure 2. FDA Analysis: Plot of Individual QTcSS Change from Baseline versus Plasma Concentrations at Corresponding Time Points for Moxifloxacin



5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The mean differences of the drug and placebo as well as the moxifloxacin and placebo have been calculated after baseline adjustment. In this study, baseline was the average (the triplicate) of pre-dosing QTc measurement. Our analysis results are presented in Tables 12, 13, and 14.

Table 12. FDA Analysis: Mean difference of 5mg Levocetirizine and placebo after baseline adjustment as well as 90% CI (QTcF)

Hours	ΔΔMEAN Dif	90% Lower Bound	90% Upper Bound
0.5	-0.35294	-3.08843	2.38254
1.0	-0.22876	-3.24548	2.78796
1.5	2.05229	-0.75384	4.85841
2.0	1.59477	-1.21005	4.39959
4.0	3.33987	-0.15629	6.83602
6.0	2.05882	-0.94557	5.06322
9.0	0.89542	-2.32497	4.11582

Hours	ΔΔMEAN Dif	90% Lower Bound	90% Upper Bound
12.0	0.21569	-3.03700	3.46838
24.0	3.23529	-1.00055	7.47114

Table 13. FDA Analysis: Mean difference of 30mg Levocetirizine and placebo after baseline adjustment as well as 90% CI (QTcF)

Hours	ΔΔMEAN Dif	90% Lower Bound	90% Upper Bound
0.5	-1.24183	-4.04941	1.56575
1.0	-4.54902	-7.33813	-1.75990
1.5	-1.81046	-4.40411	0.78320
2.0	-2.05229	-5.33631	1.23174
4.0	-3.49020	-6.70208	-0.27831
6.0	-1.67974	-4.89180	1.53232
9.0	-3.85621	-7.70011	-0.01231
12.0	-1.62092	-5.00337	1.76154
24.0	-1.45752	-5.22622	2.31119

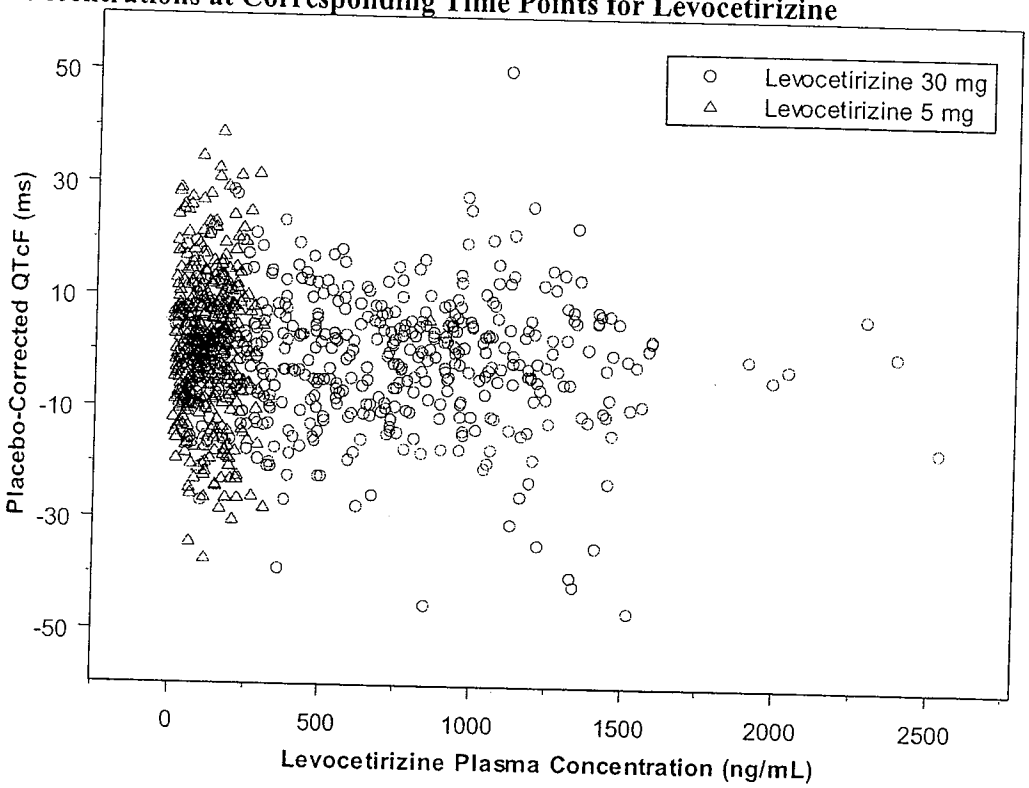
Table 14. Mean difference of Moxifloxacin and placebo after baseline adjustment as well as 90% CI (QTcF)

Hours	ΔΔMEAN Dif	90% Lower Bound	90% Upper Bound
0.5	4.3333	1.8793	6.7874
1.0	8.5752	5.5758	11.5745
1.5	12.1569	9.4275	14.8863
2.0	13.0458	10.6948	15.3967
4.0	14.4510	11.7846	17.1173
6.0	12.0719	9.6272	14.5166
9.0	6.7516	4.0345	9.4688
12.0	7.1699	4.4950	9.8449
24.0	7.0654	3.8218	10.3089

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The clinical pharmacology reviewer did not perform additional concentration-QTc analysis due to the negative findings using both ICH guidance approach and PK/PD approach. A plot of placebo-corrected QTcF vs concentration (Figure 3) further confirmed the negative results.

Figure 3. FDA Analysis: Plot of Individual Placebo-Corrected QTcF versus Plasma Concentrations at Corresponding Time Points for Levocetirizine



5.3 MEDICAL ASSESSMENTS

5.3.1 ADVERSE EVENTS

There were no deaths or serious adverse events. There were a total of 83 treatment emergent adverse events (TEAEs) reported by 37 of 52 subjects (71.2%). The increase in TEAEs was dose-related. There were no severe or serious TEAEs, and none of the subjects having TEAEs discontinued the study. The most frequently reported TEAEs for levocetirizine were somnolence, headache, and fatigue.

Table 15. Sponsor's Analysis: Overall Summary of Treatment-Emergent Adverse Events by Treatment Period-ITT Population

	5 mg LCTZ (N = 52) n (%)	30 mg LCTZ (N = 52) n (%)	Placebo (N = 52) n (%)	400 mg MOX (N = 52) n (%)	Overall (N = 52) n (%)
Total number of TEAEs	18	28	17	20	83
Subjects with at least 1 TEAE	13 (25.0%)	22 (42.3%)	12 (23.1%)	13 (25.0%)	37 (71.2%)
Subjects with drug-related TEAEs [a]	11 (21.2%)	19 (36.5%)	8 (15.4%)	7 (13.5%)	32 (61.5%)

Notes: Each % is based on the number of ITT subjects in the condition group; LCTZ= levocetirizine; MOX=moxifloxacin;
[a] Drug-related AEs are described by the Investigator as possibly, probably or highly probably related to study drug.
Source: Table 14.3.1.1

(Reproduced from Sponsor, Table 12.1, page 91 of 4265)

Two subjects experienced isolated episodes of nonsustained ventricular tachycardia (NSVT) during the Holter session. For both subjects, NSVT occurred after more than 12 hours during the first treatment period (Subject 001/0008 after 5 mg levocetirizine: 7 ventricular complexes; Subject 001/0010 after 30 mg levocetirizine: 9 ventricular complexes). There was no recurrence of NSVT on telemetry for either subject in the subsequent 3 treatment periods.

Subject 100041, an Asian female, received a single dose of moxifloxacin 400 mg at 08:15 on———— At 9:37 a.m., she was found to have a "long QTc" on an ECG. Maximum QTcF was 461 ms at 10:11. The long QTc resolved at 14:12.

Subject 100039, a caucasian female, received levocetirizine 30 mg at 08:09 on June 19, 2006. From 12:15 until 16:00, she experienced "orthostatic dizziness," which subsequently resolved.

Subject 100036, a caucasian female, received levocetirizine 30 mg at 08:36 on June 8, 2006. She experienced dizziness at 10:35, which resolved at 11:20.

Subject 100043, a caucasian female, received moxifloxacin 400 mg at 8:21 on June 12, 2006. She experienced intermittent dizziness from 9:28 to 9:33.

Case report forms and narratives for Subjects 100041, 100039, 100036, and 100043 were not included in the submission, but we have requested them from the sponsor.

5.3.2 ECG WAREHOUSE

I reviewed a random sampling of ECGs from the following subjects:

- Subject 0001
- Subject 0011
- Subject 0028
- Subject 0048

Although I saw some ST/T wave changes and u waves in subjects who received levocetirizine or moxifloxacin, there was no clinically important levocetirizine-associated QT prolongation. All measured QTcF values were within normal limits.

6 APPENDIX

6.1 TABLE OF STUDY ASSESSMENTS

Assessments/Events	Screening	Treatment Periods 1 to 4			Discharge
	Day -21 to -2	Day -2, 7, 14, 21	Baseline Day -1	Days 1-2, 8-9, 15-16, 22-23	Day 23 to30
Confinement		X	X	X	
Written Informed Consent	X				
Demographic Data	X				
Height and Weight	X				
Lifestyle	X				
Incl./Excl. Criteria	X	X			
Medical / Surgical History	X				
Vital Signs	X		X	X(a)	X
Physical Examination	X				X
Blood chemistry, hematology, and urinalysis	X				X
Immunology	X				
Safety ECG (12-Lead)	X			X(a)	X
Urine Drug Screen and alcohol breath test	X	X			
Pregnancy Test(b)	X	X			X
12-lead Holter(c)			X	X	
Study Drug Administration(d)				X	
Pharmacokinetics Plasma Sampling(e)				X	
Conc. Medications	X	X	X	X	X
Medical Procedures	X	X	X	X	X
Check-out assessments				X(f)	
Appointment for next visit	X			X(f)	
Subject card				X	
Recording of AEs	X	X	X	X	X
Final evaluation					X

(a) At pre-dose, 1.5 h, 4 h and 24 h post-dose.
(b) Only for females with childbearing potential, serum Beta Human Chorionic Gonadotrpin (βHCG) test at screening and discharge, urine pregnancy test on the days of entry for confinement.
(c) Continuous Holter monitoring from pre-dose up to 24 h post-dose (from -24 h pre-dose up to pre-dose on baseline Day -1)
(d) Only for Days 1, 8, 15, 22
(e) Plasma samples were taken at the following time-points: pre-dose, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 9 h, 12 h, 24 h after dosing.
(f) Only for Days 2, 9, 16 and 23.

(Reproduced from Sponsor, Table 9.1, Study Flow Chart, page 46 of 4265)

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/s/

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3/7/2007 03:16:47 PM
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Dr. Japobrata Choudhury is the primary statistical reviewer for this NDA.

Norman Stockbridge
3/8/2007 03:40:33 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Office/Division): IRT-QT
Division of Cardiovascular and Renal Products

FROM (Name, Office/Division, and Phone Number of Requestor):
Lori Garcia, RPh., Project Manager
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 8, 2006		NDA 22-064	SU	November 20, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
levocetirizine	standard		February 10, 2007

NAME OF FIRM: UCB, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DPAP requests that the IRT-QT group review the final report for the study A00419 (thorough QT/QTc study) which was submitted as part of 120-day safety update on Nov 20, 2006, to NDA 22-064. Relevant materials are available in the EDR at \\Cdsesub1\n22064\N_000\2006-11-20.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Lori A. Garcia	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
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Lori Garcia
12/8/2006 05:52:42 PM

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-064
Submission Code	
Letter Date	July 24, 2006
Stamp Date	July 25, 2006
PDUFA Goal Date	May 25, 2007
Reviewer Name	Robert M. Boucher, MD, MPH
Review Completion Date	March 25, 2007
Established Name	Levocetirizine dihydrochloride
(Proposed) Trade Name	Xyzal®
Therapeutic Class	Anti-histamine
Applicant	UCB, Inc.
Priority Designation	S
Formulation	5 mg oral tablet
Dosing Regimen	2.5 mg ——— once daily
Indication	SAR, PAR, CIU
Intended Population	Six years and older

Table of Contents

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under curve
BA	bioavailability
BE	bioequivalence
BP	blood pressure
CBC	complete blood count
CRF	case report form
CTZ	cetirizine hydrochloride
CIU	chronic idiopathic urticaria
DRC	daily record card
DSI	Division of Scientific Investigations
DB	double-blind
ECG	electrocardiogram
EEU	environmental exposure unit
ITT	intent-to-treat
IRB	institutional review board
ISE	integrated summary of efficacy
ISS	integrated summary of safety
IV	intravenous
LCTZ	levocetirizine dihydrochloride
LFT	liver function tests
OTC	over-the-counter
PAR	perennial allergic rhinitis
PD	pharmacodynamic
PK	pharmacokinetic
PC	placebo-controlled
RBC	red blood cell
RQLQ	Rhinitis Quality of Life Questionnaire
SAR	seasonal allergic rhinitis
SAE	serious adverse event
T4SS	total four symptom score (sneezing, rhinorrhea, nasal pruritus, ocular pruritus)
T3SS	same as above, except for ocular pruritus
TEAE	treatment-emergent adverse event
U.S.	United States
URI	upper respiratory infection

VS	vital signs
WBC	white blood cell

Executive Summary

1.1 Recommendation on Regulatory Action

Levocetirizine for patients 12 years and older:

The recommended regulatory action for levocetirizine 5 mg oral tablets is approval, from a clinical standpoint, for the treatment of seasonal and perennial allergic rhinitis, and chronic idiopathic urticaria, in patients 12 years of age and older.

Based on substantial evidence from replicate adequate and well-controlled clinical studies, levocetirizine is safe and effective for the label indications at a dose of 2.5 mg to 5 mg taken orally, once daily in the evening. In placebo-controlled studies of patients 12 years and older with seasonal and perennial allergic rhinitis, levocetirizine is effective in improving the total symptom score comprised of sneezing, rhinorrhea, nasal pruritus, and ocular pruritus. In placebo-controlled studies of patients 12 years and older with chronic idiopathic urticaria, levocetirizine is effective in improving the severity of pruritus, wheal number, and wheal size.

Levocetirizine for patients 6-11 years of age:

The recommended regulatory action is for approval of levocetirizine oral tablets from a clinical standpoint, at a dose of 2.5 mg, for the treatment of seasonal and perennial allergic rhinitis, and chronic idiopathic urticaria, in patients 6-11 years old.

While placebo-controlled trials in the pediatric development program using a dose of 5 mg once daily demonstrate that levocetirizine is effective in this age group, information from a literature reference cited in the application indicates that the systemic exposure (AUC) of levocetirizine 5 mg in pediatric patients 6 to 11 years of age is approximately twice that of adults, and supports LCTZ 2.5 mg as the appropriate dose.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The clinical review does not identify concerns for which postmarketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are sought for levocetirizine 5 mg tablets.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Levocetirizine dihydrochloride, the R-enantiomer of the racemate cetirizine, is an oral tablet H_1 receptor antagonist proposed for use in the symptomatic treatment of seasonal and perennial allergic rhinitis (SAR and PAR, respectively), and chronic idiopathic urticaria (CIU) in children and adults age 6 years and older. The proposed product label recommends once daily dosing of _____. The product development program began in 1992 and the drug is currently marketed in over 80 countries. The NDA, submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act, referencing cetirizine, contains 54 clinical studies, all conducted in foreign countries. The clinical review assesses six confirmatory efficacy trials in detail (two each for adult and pediatric SAR/PAR, and two for adult CIU), and summarizes six key supporting studies (two for dose-ranging, two for comparative efficacy [referencing cetirizine], one for inhibition of wheal and flare, and one for persistence-of-effect). The two pediatric clinical trials are submitted to support the allergic rhinitis indications in children 6-11 years; all other reviewed studies are in subjects age 12 years and older.

The six confirmatory efficacy trials randomized a total of 1,435 subjects (483 were 6-12 years old) and 1,276 (88.9%) completed the studies. The key supporting trials enrolled an additional 2,681 subjects (12 years and older) and 2,436 (90.1%) completed the studies. The safety database includes information from 44 pooled studies of 4,067 unique pediatric and adult subjects exposed to levocetirizine 5 mg (3,134 [77.1%]), 2.5 mg (484 [11.9%]), and 10 mg (438 [10.8%]). Additional safety information from 688 subjects who received levocetirizine is summarized in four non-pooled studies. Most subjects received levocetirizine for two to six weeks; a total of 154 subjects received 5 mg/day for more than 26 weeks.

Other sources of data for the review include the applicant's global post-marketing drug safety database of 747 cases, the 120-day Safety Update, which includes data from five studies completed since the NDA was filed, and a review of the pertinent literature.

1.3.2 Efficacy

Levocetirizine is significantly more effective than placebo for the treatment of symptoms of allergic rhinitis and chronic idiopathic urticaria. Four confirmatory efficacy trials for the allergic rhinitis indications were reviewed: studies A00268 and A00266 for adult SAR and PAR, respectively; studies A00303 and A00304 for pediatric SAR and PAR, respectively. All four studies were randomized, placebo-controlled, double-blind, multi-center trials of levocetirizine 5 mg tablets taken orally once daily in the evening. Treatment periods were two weeks (A00268), four weeks (A00266 and A00304), and six weeks (A00303).

The study designs and statistical and analytical plans for all four trials were similar. The primary endpoints were change from baseline in adjusted mean total nasal symptom score ("T4SS", the sum of the individual scores for sneezing, rhinorrhea, nasal pruritus, and ocular pruritus)

reflective over the previous 24 hours, for various treatment intervals appropriate for the indication (FDA guidance recommends at least two weeks of treatment for SAR, and four weeks of treatment for PAR, indications). The adult studies analyzed treatment results after levocetirizine exposure of one week (both studies), two weeks (A00268) and four weeks (A00266); both pediatric studies analyzed results after two weeks of exposure for the primary outcome. Key secondary endpoints included assessment of: instantaneous total symptom scores by treatment week and total treatment period (A00268); individual symptom scores [sneezing, rhinorrhea, nasal pruritus, ocular pruritus, nasal obstruction] over various treatment periods (A00268, A00303, and A00304); and reflective total symptom scores over four or six weeks, and by treatment week (A00266, A00303, A00304). The choice of endpoints, general conduct of the studies, and statistical analyses were appropriate. All four studies showed statistically significant efficacy for levocetirizine over placebo for the primary endpoints. For most secondary endpoints, the analysis also favored levocetirizine.

Two dose ranging studies for adult allergic rhinitis (A00217 and A00265) showed statistically significant efficacy for all three doses of levocetirizine (2.5, 5, and 10 mg) over placebo for the primary endpoints. Although only study A00217 showed evidence of a linear dose-response, the preponderance of data from all dose-ranging studies suggests that, while 2.5 mg once daily may be the lowest effective LCTZ dose for some patients 12 years and older, 5 mg once daily is safe, effective, and the appropriate dose for most patients in this age group. Adult dose-response studies, two well-conducted clinical trials in children (A00303 and A00304), and literature-derived pharmacokinetic data indicate that the safest and most effective dose of levocetirizine in children 6-11 years is 2.5 mg once daily in the evening.

Two adult studies for the CIU indication (A00269 and A00270) show statistically significant efficacy for levocetirizine over placebo for the primary (improvement in pruritus severity) and key secondary (change in wheal number and size) endpoints. Study A00270 includes dose-ranging (for levocetirizine 2.5, 5, and 10 mg) which, while showing efficacy for all three doses, supports 5 mg as the safest (less sedation-related effects) and most effective dose.

Two adult allergic rhinitis comparative efficacy trials of levocetirizine with cetirizine (A00379 and A00412) were completed. Both trials show similar statistically significant efficacy over placebo for all levocetirizine and cetirizine doses studied (levocetirizine 2.5 and 5 mg; cetirizine 5 and 10 mg). However, study A00412, comparing two doses of each, fails to demonstrate an effect difference between the two drugs, or evidence of dose-ranging. The failure to adequately characterize the relationship between the two drugs implies that reference to cetirizine for levocetirizine dose and clinical response may be inappropriate.

Results from 6 active-controlled trials comparing levocetrizine with loratadine are difficult to interpret as these trials did not include a placebo arm and non-inferiority designs are not appropriate for allergic rhinitis studies in view of the variable nature of the disease and the difficulty in establishing a non-inferiority margin.

Approval of levocetirizine tablets for treatment of allergic rhinitis and chronic idiopathic urticaria symptoms in patients 12 years and older would add another safe and effective long-

acting, once daily, oral antihistamine to the four others available in the U.S. for both indications: cetirizine, fexofenadine, loratadine, and desloratadine.

1.3.3 Safety

The safety review findings show adverse events previously reported with other oral antihistamines; the safety profile is similar to the racemate, cetirizine. The safety database included the applicant's Integrated Summary of Safety (data from 54 clinical trials, 44 of which are pooled for analysis), the 120-Day Safety Update, the applicant's global post-marketing reports, and a literature review. Number of levocetirizine-exposed subjects and exposure duration is discussed in section 1.3.1.

Safety data for the 10 adult confirmatory and supporting studies in the clinical review are satisfactory and include appropriate physical examination and laboratory assessments. Safety assessments for the two pediatric confirmatory trials do not include laboratory parameters. Studies of levocetirizine effect on the QTc interval are negative for prolongation.

There are no on-treatment deaths in the clinical development program. The most common, clinically-relevant treatment-emergent adverse events, occurring more than placebo in levocetirizine-exposed subjects, are sedation-related effects. Sedation-related effects are the most common adverse events causing study discontinuation in levocetirizine-exposed subjects (33 of 71 dropouts). Adverse events reporting for adult clinical trials of LCTZ 5 mg given once daily in the evening for one to four weeks duration shows sedation-related effects 6% greater in levocetirizine than in placebo groups.

Levocetirizine 2.5 and 5 mg oral tablets are safe for use in patients 12 years and older. The safety profile is similar to cetirizine. Although clinical trials show that levocetirizine 5 mg is effective for children age 6-11 years, literature-derived pharmacokinetic data suggest that 2.5 mg once daily in the evening, [redacted] is the safer and more appropriate dose for this age group.

1.3.4 Dosing Regimen and Administration

The levocetirizine clinical development program exposed most pediatric and adult subjects to 5 mg given orally once daily in the evening. The principal exceptions were the dose-ranging studies, where subjects received one of three levocetirizine doses (2.5 mg, 5 mg, or 10 mg) per day. Most subjects (3,134; 77%) received levocetirizine for two to six weeks; 154 subjects received levocetirizine 5 mg/day for more than 26 weeks. All of the subjects in the adult and pediatric confirmatory efficacy trials received levocetirizine in the evening.

Given the preponderance of the evidence from the adult clinical program generally, and the allergic rhinitis dose-ranging trials specifically, it appears, in most cases, that the 2.5 mg dose in adults is likely to be as effective as the 5 mg dose, and with less sedation, which is clinically relevant if the drug is inadvertently taken during the daytime. The proposed label recommending once daily dosing of LCTZ 2.5 or 5 mg for adults is reasonable from an efficacy standpoint.

However, since all of the pertinent clinical trials in the NDA dose levocetirizine in the evening, and sedation-related effects of daytime use are not characterized in the application, the label recommendation should be for evening dosing only.

While the pediatric development program (age 6-11 years) has demonstrated efficacy and relative safety for LCTZ 5 mg once daily, literature-derived PK data show (by AUC) that pediatric exposure is twice that of adult exposure at the 5 mg dose. The preponderance of the evidence from the adult and pediatric clinical trials as well as the PK data suggests that 2.5 mg once daily in the evening is the safest and most effective dose for children 6-11 years old.

1.3.5 Drug-Drug Interactions

The clinical development program conducted no formal drug-drug interaction studies. The applicant references the racemate cetirizine, based on the similar metabolic profiles of the two drugs. Experience with cetirizine suggests that there are no clinically significant drug-drug interactions, with the exception of probenecid, which may reduce urinary clearance, and for which dose adjustment may be necessary. The levocetirizine post-marketing database does not suggest that clinically relevant drug interactions occur. Referencing cetirizine for levocetirizine drug-drug interactions appears reasonable; there is no evidence to suggest further specific studies of levocetirizine are warranted at this time.

1.3.6 Special Populations

Notwithstanding issues in the pediatric population discussed section 1.1, there do not appear to be special safety or efficacy considerations based on age, gender, or race. The placebo-controlled confirmatory efficacy and supporting trials, however, did not include subgroup analyses.

Levocetirizine excretion is primarily renal, and its clearance correlates with that of creatinine clearance. Use in older subjects is discussed below; since there are no known clinically relevant gender or racial differences in creatinine clearance, no significant dose adjustment for these differences seems indicated. The clinical development program in adults 65 years and older did not expose enough subjects (N = 42) to levocetirizine to permit generalization of findings to the elder population. A pharmacokinetic study of nine subjects older than 65 years shows that the elimination half-life of levocetirizine is prolonged by 30-50%, suggesting reduction in clearance due to age-related changes in renal function. The results are similar to findings in cetirizine-exposed elderly subjects, which show that clearance is dependent upon subject renal function rather than age. Dose adjustments in older populations should, therefore, be based on renal function.

Pharmacokinetic studies in males and females 12 years and older exposed to the same levocetirizine dose show the drug half-life to be slightly shorter in females than males; adjustment for body weight, however, shows comparable clearance rates for both sexes, and the recommended daily dose is therefore the same. Adverse events data from 11 short-term (2 weeks) and long-term (≥ 4 weeks) placebo-controlled studies in subjects 12 years and older

shows females reported more adverse events than males, but the findings were similar for both placebo and levocetirizine exposure: 41.3% of males and 53.1% of females on placebo reported adverse events, while 39.9% of males and 50.8% of females on levocetirizine reported adverse events. The findings suggest that no dose adjustment is necessary for males and females 12 years and older.

Approximately 90% of subjects in the clinical development program were Caucasian. Although 166 Asian subjects were studied in four short-term active-control trials, other racial and ethnic minorities are under-represented in the program and no subgroup analyses of them were performed. The limited data available suggests no difference in laboratory parameters, but no definitive conclusions can be made regarding safety and efficacy in these sub-populations.

Levocetirizine exposure in pregnant and lactating women has not been studied and its use in this population [redacted]

Studies of levocetirizine in patients with renal insufficiency show that total body and renal clearance are reduced. Patients with moderate or severe renal impairment (creatinine clearance $\leq$ 50 mL/min) require reduced daily doses and/or longer dosing intervals than patients with normal renal function; levocetirizine is contraindicated when creatinine clearance is $<$ 10 mL/min.

Issues regarding pediatric exposure to levocetirizine are discussed in Section 1.1. The applicant requests a deferral from PREA requirements for levocetirizine tablets in children less than six years old. This request is reasonable given that the tablet formulation is not appropriate for patients under 6 years of age (safety risk). [redacted]

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Xyzal® (USAN: levocetirizine dihydrochloride), the R-enantiomer of the racemate cetirizine, is an oral tablet H_1-receptor antagonist proposed for use in the symptomatic treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU) in adults and children six years of age and older. The applicant recommends a dose of [redacted]

2.2 Currently Available Treatment for Indications

Four long-acting oral antihistamines are available for some or all of the proposed product indications; a summary is in Table 1.

Table 1. Available Long-acting Oral Antihistamines

Name	Indications	Dose	Age Range
Cetirizine hydrochloride (Zyrtec®)	SAR, PAR, CIU	2.5 mg to 10 mg once daily	6 months and older
Fexofenadine hydrochloride (Allegra®)	SAR, CIU	30 mg to 60 mg twice daily, or 180 mg once daily	6 years and older
Desloratadine (Clarinex®)	SAR, PAR, CIU	1 mg to 5 mg once daily	6 months and older

In addition, one antihistamine nasal spray (azelastine) and several nasal steroids are approved for the treatment of allergic rhinitis symptoms.

2.3 Availability of Proposed Active Ingredient in the United States

Levocetirizine dihydrochloride (LCTZ) is not marketed in the U.S., nor is it an active ingredient in any product marketed in the U.S. The drug is, however, marketed in 80 countries worldwide (refer to Section 2.6).

2.4 Important Issues with Pharmacologically Related Products

Somnolence and fatigue are more common in subjects taking products pharmacologically related to LCTZ, and labels recommend caution with driving and operating dangerous machinery. Several other related products (Zyrtec®, Allegra®, Clarinex®) recommend dose adjustment for renal impairment.

2.5 Presubmission Regulatory Activity

Levocetirizine dihydrochloride is not marketed in the U.S. All clinical studies in support of the NDA are conducted overseas.

A Type B meeting (pre-IND 72,233; June 14, 2005) addresses the following salient issues:

1) NDA submission under 505(b)(2) provisions: FDA agrees that such a submission may be appropriate for LCTZ.
2) 505 (b)(2) clinical data presentation: FDA states "clinical program is expected to demonstrate and support equal exposure and pharmacodynamic efficacy from levocetirizine 2.5 mg and 5 mg compared to cetirizine 5 mg and 10 mg, respectively.
3) Pediatric indication: FDA states "you appear to have adequate data and reasoning to support an application down to the age of 6 years." [redacted]

(Sources: Fax response to pre-IND 72,233 questions, June 13, 2005; MO review of pre-IND 72,233 meeting package, February 15, 2006 [T. Purohit-Sheth]).

2.6 Other Relevant Background Information

Clinical development of LCTZ began in 1992. First marketing approval of levocetirizine 5 mg oral tablets was in Germany (2001). Levocetirizine is currently available in over 80 countries under various names, including Xyzal, for use in children and adults 6 years and older. Most of the approvals occurred since 2003.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review is by Dr. Arthur Shaw, who finds adequate drug manufacture and control, the application approvable, and makes no recommendations for Phase 4 commitments, agreements, or risk management steps (if the NDA is approved).

Levocetirizine dihydrochloride is the R-enantiomer of cetirizine hydrochloride (the active ingredient in the approved product Zyrtec®). The applicant reports that the R-enantiomer is responsible for the H_1-histamine receptor antagonist activity of cetirizine. Initial preparation of the R-enantiomer involves [redacted] The clinical studies used drug substance prepared in this manner. Preparation of the commercial product varies [redacted] Levocetirizine has no polymorphs. It is freely soluble in water. The S-enantiomer is controlled at [redacted] individual

identified impurities at NMT [redacted], unidentified impurities at NMT [redacted], and total impurities at NMT [redacted] A Division pharmacology/toxicology consultation performed by Dr. Lawrence Sancilio indicated [redacted] is permissible up to [redacted] The drug substance is stable at [redacted]

The drug product is a scored, film-coated 5 mg tablet prepared by [redacted] The specifications, including dissolution of [redacted] at 30 minutes, are supported by batch analysis by validated test methods. Impurities are adequately controlled and stability data support a 36 month expiration date for product packaged in 15mL bottles, [redacted]

3.2 Animal Pharmacology/Toxicology

Dr. Lawrence Sancilio conducted a detailed pharmacology/toxicology review. The applicant references cetirizine and also submits pre-clinical pharmacology/toxicology studies of LCTZ. The animal pharmacology/toxicology profiles for LCTZ and CTZ are similar. Levocetirizine is not mutagenic by the Ames test, and is not found to be clastogenic by mouse lymphoma assay, *in vivo* rat micronucleus test, or human lymphocyte assay. A male rat toxicologic study shows LCTZ does not impair spermatogenesis at an oral dose 60 times the recommended daily oral dose in adults on a mg/m^2 basis. Referencing CTZ, the applicant states that fertility and general reproductive performance in mice is unaffected at an oral dose 25 times the recommended daily oral dose in adults on a mg/m^2 basis. In rats and rabbits LCTZ is not found to be teratogenic at doses 100-200 times the maximum recommended adult daily oral dose on a mg/m^2 basis. There are no studies of LCTZ exposure in pregnant women. No carcinogenicity studies have been performed with LCTZ; for CTZ, no carcinogenic effect was observed at therapeutic dose levels.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Data in this review are from the applicant's overseas clinical development program. The NDA includes fifty-four clinical studies, all completed in foreign countries. The efficacy review is based on reviews of five confirmatory efficacy trials and seven supporting trials (refer to Table 2 for a summary of these 12 studies), while the safety data are derived from the safety information from all the clinical studies submitted in the NDA as well as the from the 120-safety update submitted November 20, 2006.

The efficacy studies A00268 and A00266 are confirmatory adult SAR and PAR trials, respectively, with a similar statistical analysis plan (SAP): the primary endpoint is change from baseline in the 24 hour reflective total symptom score, T4SS (which is sneezing, rhinorrhea, nasal pruritus, and ocular pruritus), over the first treatment week, and over two weeks (A00268)

and over four weeks (A00266). Studies A00303 (clinical confirmatory for SAR) and A00304 (PAR) are conducted in the pediatric (ages 6-12 years) allergic rhinitis population, and the SAP for each primary endpoint is analogous to the adult program. Studies A00269 and A00270 are confirmatory adult CIU trials. The primary endpoint for each is change from baseline in mean pruritus severity over the first treatment week, and over the total four week treatment period. Key secondary endpoints for these two studies are change in the number and size of wheals. Additionally, A00270 is a dose-ranging study (LCTZ 2.5, 5, and 10 mg).

In addition to A00304, the principal supporting studies are: A00412, an adult SAR EEU comparative efficacy trial seeking to bridge two doses of levocetirizine (2.5 and 5 mg) with two doses of cetirizine (5 and 10 mg); A00379, similar in design to A00412, but comparing only one dose of levocetirizine (5 mg) with one dose of cetirizine (10 mg); A00217 (adult SAR) and A00265 (adult PAR), which are two LCTZ dose-ranging studies (2.5, 5, and 10 mg) with primary endpoints similar to A00268 and A00266; A00264, an adult PAR study seeking to demonstrate persistence-of-effect over six months; and A00373, a pharmacodynamic adult inhibition of wheal and flare study.

4.2 Tables of Clinical Studies

Table 2. Clinical Studies

Study #	Location	Indication	Objective	Treatment Arms	Primary Endpoint	N Randomized	N Completed
A00268 (Confirmatory efficacy)	South Africa	Adult SAR	Efficacy of LCTZ 5 mg over placebo	LCTZ 5 mg; placebo	Change from baseline in 24 hour reflective T4SS over first week and two weeks	237	232
A00266 (Confirmatory efficacy)	South Africa	Adult PAR	Efficacy of LCTZ 5 mg over placebo	LCTZ 5 mg; placebo	Change from baseline in 24 hour reflective T4SS over first week and four weeks	294	276
A00303 (Confirmatory efficacy)	France & Germany	Pediatric SAR	Efficacy of LCTZ 5 mg over placebo	LCTZ 5 mg; placebo	Change from baseline in 24 hour reflective T4SS over two weeks	177	145
A00304 (Supportive)	South Africa	Pediatric PAR	Efficacy of LCTZ 5 mg over placebo	LCTZ 5 mg; placebo	Change from baseline in	306	297

					24 hour reflective T4SS over first two weeks		
A00269 (Confirmatory efficacy)	Germany & Switzerland	Adult CIU	Efficacy of LCTZ 5 mg over placebo	LCTZ 5 mg; placebo	Change from baseline in 24 hour reflective pruritus severity over one week and four weeks	164	124
A00270 (Confirmatory efficacy)	France	Adult CIU	Efficacy of LCTZ 2.5, 5, and 10 mg over placebo; dose-ranging	LCTZ 2.5, 5, and 10 mg; placebo	Change from baseline in 24 hour reflective pruritus severity over one week and four weeks	257	202
A00412 (Supportive)	Canada	Adult SAR	2-day EEU Comparative Efficacy: two doses LCTZ (2.5, 5 mg) with two doses cetirizine (5, 10 mg)	LCTZ 2.5 mg, 5 mg; cetirizine 5 mg, 10 mg; placebo	Change from baseline in Major Symptom Complex Score (nasal and non-nasal sx's)	551	546
A00379 (Supportive)	Canada	Adult SAR	2-day EEU Comparative Efficacy: one dose LCTZ (5 mg) with one dose cetirizine (10 mg)	LCTZ 5 mg; cetirizine 10 mg; placebo	Change from baseline in Major Symptom Complex Score (nasal and non-nasal sx's)	570	563
A217 (Supportive)	France & Germany	Adult SAR	Dose-Ranging (LCTZ 2.5, 5, 10 mg)	LCTZ 2.5, 5, 10 mg; placebo	Change from baseline in 24 hour reflective T4SS over first two weeks	470	406
A00265	France &	Adult PAR	Dose-Ranging	LCTZ 2.5, 5,	Change	521	482

(Supportive)	Germany		(LCTZ 2.5, 5, 10 mg)	10 mg; placebo	from baseline in 24 hour reflective T4SS over first week and first four weeks		
A00264 (Supportive)	Europe	Adult PAR	Persistence-of-effect	LCTZ 5 mg; placebo	Effect on QOL after 4 weeks	551	421
A00373 (Supportive)	France		Suppression of wheal and flare	LCTZ 5 mg; desloratadine 5 mg; placebo	Change in wheal and flare over 24 hours	18	18

4.3 Review Strategy

The applicant submitted data in a hybrid electronic Common Technical Document format. The NDA has data from 53 clinical studies (48 of which are completed); the review was conducted from these materials. Additionally, the pre-IND 72,233 clinical review of June 14, 2005, by Dr. Warner Carr, was reviewed.

The clinical review strategy accounts for replicate confirmatory efficacy trials for each of the three indications the applicant seeks: (adult and pediatric [6-12 years] SAR, PAR [A00268, A00266, A00303, A00304], and adult CIU [A00269, A00270]). Key supporting studies in the review include comparative efficacy of LCTZ to cetirizine (A00412, A00379), recommended dose (dose-ranging studies A00217, A00265, and A00270), pharmacodynamic effects (A00412, A00379, and A00373), and labeling.

Twelve studies were reviewed separately and discussed with the Medical Team Leader. Five confirmatory efficacy studies (A00268, A00266, A00303, A00269, A00270), reflecting support for each indication, underwent a detailed written review, and are included as an Appendix to this document. The Appendix primarily summarizes efficacy results; the safety section of this review fully assesses safety results.

4.4 Data Quality and Integrity

An audit by the Division of Scientific Investigations (DSI) was conducted at the following site in South Africa:
UCT Lung Institute
Corner George & Falmouth Roads
7925 Observatory Western Cape
South Africa
Although the 45-day review did not identify specific data integrity issues, the audit was requested because all the data for this application are from international sites. The site selected

for audit was chosen because the principal investigator, Dr. Peter Potter, conducted three of the twelve studies in this review, each involving 20 or more study centers. These three studies comprise 26% of all subjects for the adult and pediatric SAR and PAR indications.
(The DSI review is incomplete at the time the clinical review is filed).

4.5 Compliance with Good Clinical Practices

The studies are conducted in accordance with ICH Notes for Guidance on Good Clinical Practice (ICH/CPMP/135/95) and all applicable regulations, including the Declaration of Helsinki. All study protocols and amendments undergo review and approval by an IRB or an independent national, regional, or investigational center ethics committee. Informed consent is obtained from all subjects (or parent or legal representative). Subjects may withdraw from study at any time.

4.6 Financial Disclosures

UCB certifies on FDA Form 3454 that it does not enter into any financial arrangement with the clinical investigators that could affect study outcome as defined in 21 CFR 54.2(a), that clinical investigators required to disclose a proprietary interest in the product deny such interests, and that no investigator is the recipient of significant payment of other sorts. The applicant states that financial disclosure information is routinely collected from participating investigators in studies begun after enactment of the Financial Disclosure Final Rule on February 2, 1999. (This covers all studies reviewed in this document, except A00217).

5 CLINICAL PHARMACOLOGY

Dr. Partha Roy conducted a detailed clinical pharmacology review.

5.1 Pharmacokinetics

Levocetirizine has a linear pharmacokinetic profile, is essentially completely absorbed after oral administration, and is not extensively metabolized in humans; it is excreted, largely unchanged, in urine by glomerular filtration and active tubular secretion. Food delays LCTZ absorption by 1.25 hours and reduces C_{max} by 35%, but does not affect AUC. These findings indicate LCTZ can be taken with or without food.

Levocetirizine is primarily bound to albumin in humans. Tissue distribution data for humans is generally not available; however, skin concentrations are found (Study A00373). In animals, LCTZ crosses the placenta and is found in fetal blood. Like CTZ, it is expected that LCTZ is excreted in breast milk, and LCTZ exposure to nursing mothers is not recommended.

Exposure to LCTZ increases proportionally with dose over a range of doses (2.5 to 30 mg). Total body clearance, half-life, and relative urinary excretion are dose-independent. There is no evidence of time-dependent PK changes for LCTZ. *In vitro* studies demonstrate that LCTZ does not inhibit major CYP (P450) isoforms and it is not expected to affect clearance of drugs metabolized by cytochrome P450, although no formal drug interaction studies with LCTZ have

been conducted (CTZ is referenced). Regarding urinary excretion of LCTZ, it is expected, like CTZ, that probenecid-like drugs will delay clearance: the mean half-life of CTZ roughly doubles in the presence of probenicid.

Two studies of LCTZ inpatients with renal insufficiency (A230 and A2340) show that total body and renal clearance are reduced. Patients with moderate or severe renal impairment (creatinine clearance $\leq$ 50 mL/min) require reduced daily doses and/or longer dosing intervals than patients with normal renal function. The clinical pharmacology review team (Dr. Tayo Fadiran and Dr. Partha Roy) recommend the following dose and dosing interval adjustments for renal impairment: 2.5 mg once daily for mild dysfunction, 2.5 mg once every two days for moderate dysfunction, and 2.5 mg every three days for severe dysfunction. LCTZ is contraindicated when creatinine clearance is < 10 mL/min.

No hepatic impairment studies of LCTZ have been conducted. Referencing CTZ suggests that no dose adjustment in patients with isolated hepatic dysfunction is warranted, although patients with hepato-renal disease should receive dose adjustments.

For elderly patients, CTZ data suggests that disposition is dependent on renal function rather than age. Satisfactory data for elderly patients taking LCTZ does not exist, but the applicant recommends dose adjustment reflecting renal function rather than age. The applicant asserts, based on the principal PK study in children 6-11 years (PSM 1216) that "The major pharmacokinetic parameters (mean values) in this population are similar to those in adults" (Module 2, Section 2.5, p 23). The literature reference was reviewed by clinical pharmacologist Dr. Partha Roy and shows, however, a roughly 2-fold systemic exposure for 6-11 year olds, by AUC and C_{max}, compared to adults, for the 5 mg oral dose. This strongly suggests that a 2.5 mg (or lower) dose, rather than 5 mg, once daily, is more appropriate for this age group. (Additionally, efficacy results in multiple adult allergic rhinitis and CIU dose-ranging studies suggest that efficacy, versus placebo, for LCTZ 2.5 mg is similar to 5 mg).

When adjusted for differences in body weight, there are no differences in LCTZ PK parameters between men and women. There is no LCTZ PK data for racial subgroups. Since LCTZ is primarily renally excreted, the applicant cites CTZ, and the absence of significant racial differences in creatinine clearance, in suggesting that major differences due to race are unlikely.

5.2 Pharmacodynamics

The applicant states that clinical studies assessing the PD profile of LCTZ show that, at the level of the skin and nose, it (LCTZ, the R-enantiomer) is solely responsible for the *in vivo* pharmacologic activity of the racemate, CTZ; the S-enantiomer is without activity. Based on this finding, 5 mg of LCTZ (half the adult label dose of CTZ) is chosen for comparative clinical trials.

Study A184, a randomized, DB, crossover trial of CTZ (the racemate), LCTZ (the R-enantiomer), and the S-enantiomer shows LCTZ and CTZ to be statistically equivalent for

maximum wheal and flare inhibition when given in equimolar doses, while the S-enantiomer has no effect. Study A190, a randomized, DB, PC, four-way crossover histamine nasal provocation study of CTZ 10 mg, LCTZ 5 mg, and 5 mg of the S-enantiomer shows that LCTZ and CTZ are equally effective at sneezing attenuation; both are statistically superior to placebo and the S-enantiomer, and the S-enantiomer is the same as placebo. Studies A00379 and A00412 (refer to clinical efficacy review in section 6.5) are randomized, DB, PC, EEU allergen exposure trials in ragweed sensitive subjects comparing LCTZ to CTZ (A00379 compares LCTZ 5 mg to CTZ 10 mg, and A00412 compares LCTZ 2.5 and 5 mg to CTZ 5 and 10 mg, respectively). Both LCTZ and CTZ doses are statistically superior to placebo in improving allergic rhinitis symptom scores and suggest, by descriptive data, that both drugs have a rapid onset of action (within two hours) and duration of effect of at least 24 hours.

Multiple clinical studies show no evidence that LCTZ significantly affects the QTc interval. Refer to section 7.1.9 of the review for a detailed review of the studies.

5.3 Exposure-Response Relationships

Although three studies (A184, A00373, and A254) include both PK and PD data, the NDA contains no formal PK/PD study. The three studies show that no linear PK/PD relationship exists for LCTZ. While peak plasma concentrations of LCTZ occur within two hours of administration, maximum PD effects are noted three to six hours later, and may last as long as 24 hours.

Study A184 shows an 80% inhibition of both wheal and flare at four and eight hours after a 2.5 mg oral LCTZ dose in healthy volunteers, with a similar effect at the 5 mg dose. Study A00373 shows 75% or greater inhibition of both wheal and flare at four and seven hours after a 5 mg oral LCTZ dose in adult allergic volunteers; the inhibition effect at 24 hours is 25% and 69% for wheal and flare, respectively. Study A254 assessed mediator release and cell recruitment in the skin of allergic volunteers after antigenic stimulation and found evidence of LCTZ effect on activation of vascular endothelium, cutaneous vaso-permeability, and eosinophil recruitment.

6 INTEGRATED REVIEW OF EFFICACY

The NDA is for three indications, SAR, PAR, and CIU, in two populations, children ages 6 to 11 years (the "pediatric population" in this review), and adolescents and adults (the "adult population" in this review) age 12 and older. This section assesses the development programs for adult allergic rhinitis, pediatric allergic rhinitis, and CIU separately. Distinctions between SAR and PAR studies are made in appropriate sections of the document; the review links SAR and PAR studies based on FDA guidance that to receive both label indications one adequate and well-controlled confirmatory efficacy trial of each is satisfactory, provided adequate dose-ranging studies have been conducted. Discussion of two key supporting dose-ranging studies for the adult allergic rhinitis program (A217 and A00265, section 6.2) follows the adult confirmatory efficacy section (6.1). The NDA has no pediatric dose-ranging studies; one of the two confirmatory CIU studies is a dose-ranging study, and is discussed in section 6.4.

Of note in the product development program is the absence of pediatric pharmacokinetic studies and the absence of pediatric efficacy studies for the CIU indication.

This section of the review also includes assessments of four pertinent supporting studies: two bridging studies relevant to the NDA's 505(b) (2) status referencing cetirizine (A00412 and A00379), an inhibition of wheal and flare study (A00373), and a persistence-of-effect study (A00264).

Refer to Table 2, section 4.2, for a tabular summary of confirmatory efficacy and supporting studies reviewed in this section.

6.1 Indication

Adult SAR and PAR

6.1.1 Methods

There are two adult allergic rhinitis confirmatory efficacy trials, A00268 (SAR) and A00266 (PAR), and two allergic rhinitis dose-ranging trials, A217 (SAR) and A00265 (PAR). All four are randomized, DB, PC, multi-center trials of LCTZ oral tablets administered once daily in the evening, versus placebo, to reduce allergic rhinitis symptoms. The confirmatory efficacy trials administer LCTZ 5 mg, and the dose-ranging trials 2.5, 5, or 10 mg. The primary efficacy analysis for all four trials is the change from baseline in the in subject-recorded (24-hour reflective) adjusted mean symptom scores over various treatment intervals: the first week of treatment and for the total two week treatment period (A00268); the first week of treatment and the four week treatment period (A00266 and A00265); and for the two week treatment period (A217). The study populations, demographics, general study designs (except for the multiple LCTZ doses), and SAP's are similar across the four trials. The two confirmatory efficacy trials (A00268 and A00266) are discussed in detail in Sections 6.1.2, 6.1.3, and 6.1.4. Given the similarity in study design, endpoints, and SAP across all four studies, the summary results of the dose-ranging trials (A217 and A00265) are presented at the end of Section 6.1.4.

6.1.2 General Discussion of Endpoints

The primary and key secondary endpoints for both studies are change from baseline in total symptom score for various treatment intervals. The analysis used a "total symptom score" with four components: sneezing, rhinorrhea, nasal pruritus, and ocular pruritus (the "T4SS"). (The Division determined that it was necessary to separate nasal from non-nasal symptoms in determining efficacy, so the applicant also analyzed the endpoints using a re-configured symptom score, the T3SS: sneezing, rhinorrhea, and nasal pruritus, removing ocular pruritus from the total symptom score). Additional salient secondary endpoints include change from baseline in individual symptom scores (sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal obstruction). Section 6.1.3, Study Design, discusses the specifics of symptom scoring.

For allergic rhinitis trials, FDA guidance recommends inclusion of both instantaneous and reflective symptom scores. Instantaneous scores give duration-of-effect and appropriateness-of-dosing interval information that reflective scores do not. Of note in the allergic rhinitis development program (for both adult and pediatric indications) is that study A00268 is the only one of the four confirmatory efficacy trials (A00266, and A00303, A0304 [discussed in section 6.2]) to analyze instantaneous scores (as a key secondary endpoint: change from baseline in the T4SS over each treatment week and the two-week treatment period).

Notwithstanding the above discussion, the primary and key secondary endpoints are otherwise in accordance with FDA guidance for allergic rhinitis drug development and generally appropriate for the indications sought; additional specific endpoint details are discussed in the Study Design section.

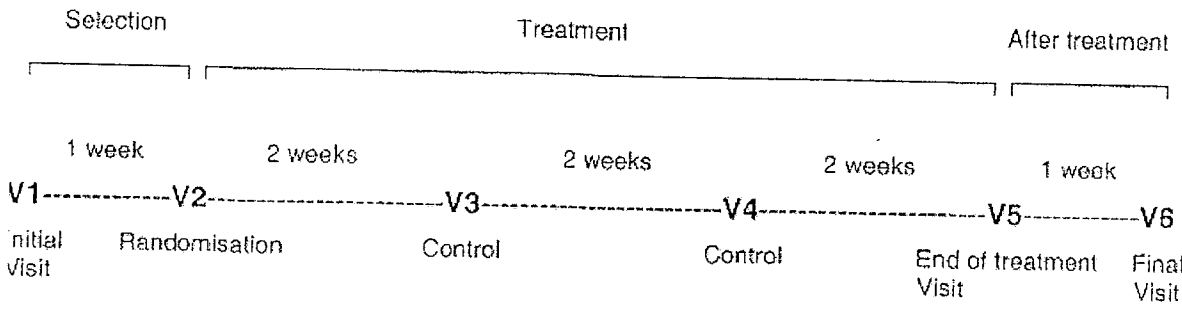
6.1.3 Study Design

Study A00268: "A randomized, double-blind, placebo-controlled, multi-center, Phase 3 study of the efficacy and safety of 5 mg levocetirizine dihydrochloride tablets, administered once daily in the evening, for two weeks, to subjects suffering from grass pollen allergic rhinitis."

Study A00266: "A randomized, double-blind, placebo-controlled, multi-center, Phase 3 study of the efficacy and safety of 5 mg levocetirizine dihydrochloride tablets, administered once daily at bedtime, for six weeks, to subjects suffering from perennial allergic rhinitis associated with house dust mites."

The study designs for A00268 and A00266 are analogous; specific relevant differences in the protocols are cited.
Figure 1 is a schematic diagram of the study plan for A00266 and, with the exception of the difference in the number of visits for the two studies, is analogous to the plan for A00268 (and for the pediatric studies A00303 and A00304, discussed below).

Figure 1. Diagram of study plan for A00266



Both studies compare oral LCTZ 5 mg, given in the evening, with placebo. The subjects have allergic rhinitis symptoms for at least two years. The applicant chooses the 5 mg LCTZ dose

because previous clinical trials show efficacy at this dose, the LCTZ 10 mg dose causes more somnolence, and the 10 mg dose of the reference drug, the racemate CTZ is effective.

Study A00268 randomizes 237 subjects (118 placebo, and 119 LCTZ) and A00266 randomizes 294 (144 placebo, and 150 LCTZ).

Inclusion and Exclusion criteria are similar for the studies.
Inclusion: Males and females 12 years of age and older with allergic rhinitis symptoms for at least two years and appropriate allergy confirmed by investigator with positive skin test or RAST. Females of child-bearing potential must have negative pregnancy test and consent to use acceptable contraception; all subjects must have laboratory data within protocol range at randomization visit. At the randomization visit all subjects must have eligible mean daily 24-hour reflective symptom scores (minimum of three days during the prior week; these are the baseline scores) based on the following grading: 0 = absent, 1 = mild (present but not disturbing), 2 = moderate (disturbing but not hampering day-time activities, or sleep), and 3 = severe (hampering activities and sleep). Each of five symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, and ocular pruritus) are graded, and subjects must have a score ≥ 5 (A00266) or ≥ 6 (A00268) for inclusion.
Exclusion: SAR that may change subject's symptom score (if in the PAR study), and PAR if in the SAR study. Other relevant exclusions are for pregnancy, lactation, recent URI, asthma requiring daily treatment other than beta-agonist, antihistamine or steroid requiring dermatitis or urticaria, vasomotor rhinitis, nasal obstruction from polyposis or septal deformity, clinically significant organ system diseases, and known allergy to piperazine-derived medications or excipients. Additional exclusions at randomization include abnormal laboratory data, positive pregnancy test, use of prohibited medication during run-in period (3-9 days), and below criteria mean total symptom scores.
Prohibited medications: Without appropriate washouts the following drugs were prohibited: astemizole, loratadine, intranasal and systemic corticosteroids, ketotifen, nedocromil, cromoglicate, anti-leukotrienes, short-acting antihistamines, decongestants, non-inhaled beta-agonist asthma medications, and ascending phase desensitization.

Study Procedure

The run-in period (Visit 1 to Visit 2, 3-9 days long) is used to obtain baseline symptom scores and verify inclusion criteria. Randomization of eligible subjects occurs at Visit 2 and subjects take the study medication in the evening and grade symptoms on the four-point scale (described above) in the daily record card. The scores are 24-hour reflective in both studies; instantaneous scores are also recorded in study A00268.
Additional parametric scales (for some secondary endpoints) are a four-point "Global Evaluation of Efficacy Scale" and, for study A00268, the Rhinitis Quality of Life Questionnaire (RQLQ).

Statistical and Analytical Plan

Primary Efficacy Endpoints

The primary efficacy variables are the adjusted mean T4SS (24-hour, reflective), compared with baseline, for the first treatment week *and* for the total two-week treatment period (A00268) or four-week treatment period (A00266). The primary efficacy analysis is on the ITT population (randomized subjects taking at least one dose of study medication). Analysis of the primary variables uses an ANCOVA model including the mean baseline score as covariate, and treatment and center as factors. All statistical analyses are two-tailed at the 5% level of significance. The analysis presents 95% confidence intervals of the difference in the adjusted means between placebo and LCTZ 5 mg. An ANCOVA model analyzes relative improvement from baseline (the ratio of the difference between the adjusted means for the change from baseline for LCTZ 5 mg and placebo over the adjusted mean for the change from baseline for placebo. The Shapiro-Wilk test, a stem and leaf plot, and a normal probability plot verify underlying ANCOVA assumptions. Likelihood Ratio test checks homogeneity of variance; an interaction assessment (for treatment and center) is at the 10% significance level.

Secondary Efficacy Endpoints: A00268

The secondary endpoints, by protocol order, are 1) mean T4SS (R) over the second treatment week, 2) mean T4SS (I) over each treatment week and over the total treatment period, 3) mean individual symptom scores (R and I) over each treatment week and over the total treatment period, 4) baseline versus end-of-treatment RQLQ scores, and 5) end-of-treatment global evaluation scores. The RQLQ is a disease-specific, seven-domain (ADL's, sleep, non-nasal and eye symptoms, practical problems, emotions, nasal symptoms, and eye symptoms), six-point scale (0 = untroubled, 6 = extremely troubled) recorded at Visits 1, 2, and 3. The Global Evaluation of Efficacy Scale is a four-point scale that compares subject symptoms at treatment completion with symptoms present at Visit 2 (0 = worse, 1 = unchanged, 2 = slight – moderate improvement, 3 = good – excellent improvement). Analysis of secondary variables (except for global evaluation of efficacy) uses an ANCOVA model with baseline as covariate and treatment and center as factors. The RQLQ analysis uses an ANCOVA model to assess differences between baseline and end-of-treatment scores. Global Evaluation of Efficacy analysis uses the Cochran-Mantel-Haenszel test.

Power and Sample Size: A00268

A sample size of 116 subjects per study arm has 95% power to detect a difference of 1.0 in the mean T4SS (R) between placebo and LCTZ 5 mg (alpha = .05, SD 2.1). Overall power for difference detection for week one and for the total treatment period is at least 90% (.95 X .95). A difference of 1.0 for the mean T4SS (R) corresponds to a 50% change from baseline over placebo [assumptions: baseline score = 7.8; placebo improvement from baseline = 25%].

Patient Disposition and Compliance: A00268

The ITT population is 236 subjects (there is one exclusion from the placebo group for failure to take any medication) and 232 (98.3%) complete the study. Of the four drop-outs, there is one each for withdrawal of consent, headache, somnolence, and unspecified reasons. Protocol deviations are relatively infrequent; the most common major deviation is use of prohibited

medication, and is greater in the placebo (6.0%) than LCTZ group (2.5%). Mean compliance for the total treatment period is 99.92%.

Secondary Efficacy Endpoints: A00266

Secondary endpoints, by protocol order, are 1) mean T4SS (R) [for this study's secondary endpoints, the applicant was not requested by the Division to re-configure the total symptom score to exclude ocular pruritus] over the total six week treatment period, 2) mean T4SS (R) over the second, third, fourth, fifth, and sixth week of treatment, 3) mean individual symptom scores (R) over the first treatment week and over the total six week treatment period, and 4) subject end-of-treatment global assessment scores. Each secondary variable undergoes descriptive analysis. The analysis presents 95% confidence intervals and p-values for difference in adjusted means between placebo and LCTZ (based on an ANCOVA model with baseline as covariate, and treatment and center as factors). Global evaluation of efficacy analysis uses the Cochran-Mantel-Haenszel test.

Power and Sample Size: A00266:

A sample size of 125 subjects per study arm has 95% power to detect a difference of 1.0 in the mean T4SS (R) between placebo and LCTZ 5 mg for the first treatment week, and 85% power to detect a difference of 0.8 for the first four treatment weeks (alpha = .05, SD 2.1). A difference of 1.0 for the mean T4SS (R) corresponds to a 50% change from baseline over placebo [assumptions: baseline score = 6.8; placebo improvement from baseline = 28%].

Patient Disposition and Compliance: A00266

The ITT population is 294 subjects and 276 (93.9%) complete the study. Eighteen subjects drop out, and the most common reason is lack of efficacy, eight from the placebo group, and two from the LCTZ group. No subject in the LCTZ group drops out for an AE. Of the other eight who drop out, three withdraw consent (all placebo), two have AE's (both placebo), one is lost to follow-up (LCTZ), and two for unspecified reasons (LCTZ). Protocol violations are relatively infrequent; the most common major violation is use of prohibited medications, and is twice as likely in the placebo as LCTZ group (20% versus 10%, respectively). Mean compliance for the total treatment period is 98.5%.

6.1.4 Efficacy Findings

Primary Efficacy Results: A00268 (SAR)

Change from baseline in adjusted mean T4SS (R) and T3SS (R) over Week 1 and over the total (two week) treatment period: LCTZ 5 mg produces a greater reduction in both T4SS (R) and T3SS (R) scores than placebo, compared to baseline scores, over Week 1, and for the total

treatment period. Results are statistically significant for both intervals: adjusted mean difference in T4SS (R) for Week 1 is 0.96 (95% CI 0.39; 1.53), p = 0.001; adjusted mean difference for the total treatment period is 0.89 (95% CI 0.30; 1.47), p = 0.003. These results compare favorably to T3SS (R) analysis (that is, with ocular pruritus removed from the total symptom score): adjusted mean for Week 1 is 0.77 (95% CI 0.32; 1.21), p < 0.001; for the total treatment period the adjusted mean is 0.69 (95% CI 0.23; 1.15), p = 0.003. Comparative analyses of the original T4SS and T3SS data by Dr. James Gebert, Biostatistician, strongly suggest that ocular pruritus does not drive overall efficacy. For the T4SS analysis, the relative improvement for LCTZ over placebo is 48% for the first week, and 38% for the two week total treatment period. Summary of T4SS and T3SS results are in Tables 3A and 3B, respectively.

Table 3A. Summary of Mean T4SS (R) Results, Primary Efficacy Period

Period	Treatment	N (ITT)	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo [(a)] Adj. Mean (95% CI)	p-value
Week 1	Placebo LCTZ 5 mg	117 118	6.59 (2.42) 5.56 (2.54)	6.45 5.49	0.96 (0.39; 1.53)	0.001
Total Treatment	Placebo LCTZ 5 mg	117 118	6.22 (2.43) 5.28 (2.53)	6.09 5.20	0.89 (0.30; 1.47)	0.003

(a) The differences are "Placebo minus LCTZ 5 mg"

Table 3B. Summary of Mean T3SS (R) Results, Primary Efficacy Period

Period	Treatment	N (ITT)	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo [(a)] Adj. Mean (95% CI)	p-value
Week 1	Placebo LCTZ 5 mg	117 118	6.47 (1.29) 6.53 (1.37)	5.04 4.27	0.77 (0.32; 1.21)	< 0.001
Total Treatment	Placebo LCTZ 5 mg	117 118	6.47 (1.29) 6.53 (1.37)	4.79 4.09	0.69 (0.23; 1.15)	0.003

(a) The differences are "Placebo minus LCTZ 5 mg"

Primary Efficacy Results: A00266 (PAR)

Change from baseline in adjusted mean T4SS (R) and T3SS (R) over Week 1 and over the first four week treatment period: LCTZ 5 mg produces a greater reduction in both T4SS (R) and T3SS (R) scores than placebo, compared to baseline scores, over Week 1, and for the first four weeks of treatment. The results are statistically significant for both periods: adjusted mean difference for Week 1 is 1.22 (95% CI 0.73; 1.71), p < 0.001; adjusted mean for the first four week treatment period is 1.22 (95% CI 0.76; 1.69), p < 0.001. These results compare favorably to the T3SS (R) analysis (that is, without ocular pruritus): adjusted mean difference for Week 1 is 1.00 (95% CI 0.63; 1.38), p < 0.001; for the first four week period the adjusted mean difference is 0.99 (95% CI 0.64; 1.34), p < 0.001. Comparative analyses by Dr. Gebert are consistent with A00268 and also strongly suggest that ocular pruritus does not drive the efficacy results favoring LCTZ. The relative improvement of LCTZ over placebo for the first treatment week is 86%, and

56% for the first four-week treatment period. Summary of T4SS and T3SS results are in Tables 4A and 4B, respectively.

Table 4A. Summary of Mean T4SS (R) Results, Primary Efficacy Period

Period	Treatment	N (ITT)	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo [(a)] Adj. Mean (95% CI)	p-value
Week 1	Placebo LCTZ 5 mg	142 150	6.10 (2.28) 5.00 (2.38)	6.16 4.94	1.22 (0.73; 1.71)	< 0.001
First 4 Treatment weeks	Placebo LCTZ 5 mg	142 150	5.34 (1.41) 4.21 (1.38)	5.39 4.17	1.22 (0.76; 1.69)	< 0.001

(a) The differences are "Placebo minus LCTZ 5 mg"

Table 4B. Summary of Mean T3SS (R) Results, Primary Efficacy Period

Period	Treatment	N (ITT)	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo [(a)] Adj. Mean (95% CI)	p-value
Week 1	Placebo LCTZ 5 mg	142 150	5.79 (1.41) 5.98 (1.38)	4.87 3.86	1.00 (0.63; 1.38)	< 0.001
First 4 Treatment weeks	Placebo LCTZ 5 mg	142 150	5.79 (1.41) 5.98 (1.38)	4.28 3.29	0.99 (0.64; 1.34)	< 0.001

(a) The differences are "Placebo minus LCTZ 5 mg"

Secondary Efficacy Results: A00268 (SAR)

Of the three secondary endpoints in this trial, the analysis of instantaneous T3SS results is the most clinically relevant: this is the only endpoint assessing instantaneous scores in the adult allergic rhinitis program, and has implications for dosing interval and duration-of-effect claims. It is, therefore, presented in more detail than the other two endpoints.

Change from baseline in adjusted mean T3SS (I) over Week 1 and over the total two week treatment period: LCTZ 5 mg produces a greater reduction in T3SS (I) scores than placebo, compared to baseline scores, over Week 1, and over the total treatment period. The results are statistically significant and support a once daily dosing regimen for LCTZ 5 mg in adolescents and adults with allergic rhinitis. Table 5 summarizes the findings.

Table 5. MeanT3SS (I) Comparisons for Week 1 and the Two Week Total Treatment Period

Period	Treatment	N (ITT)	Baseline Mean (SD)	On-treatment Adj. Mean	Diff vs Placebo Adj. Mean (95% CI)	p-value
Week 1	Placebo LCTZ 5mg	117 118	5.60 (1.73) 5.54 (1.79)	4.33 3.70	0.63 (0.21; 1.04)	0.003

Total Treatment	Placebo LCTZ 5 mg	117 118	5.60 (1.73) 5.54 (1.79)	4.14 3.56	0.58 (0.15; 1.01)	0.008

The two other secondary endpoints are change from baseline in adjusted mean T3SS(R) for the second treatment week and change from baseline in adjusted mean individual symptom scores (R) for the first week and the total treatment period. LCTZ 5 mg produces a greater reduction in T3SS(R) scores than placebo, compared to baseline scores, for the second treatment week. The adjusted mean difference is 0.77 (95% CI 0.07; 1.47). For the five individual symptom scores (sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal obstruction) the analysis favors LCTZ over placebo for reduction in sneezing (both treatment periods), reduction in rhinorrhea (both periods), and ocular pruritus (both periods). There is no difference between treatment groups for nasal pruritus or nasal obstruction scores. These results suggest that LCTZ efficacy is mostly a function of reduction in sneezing and rhinorrhea. The finding of results favoring improvement in ocular pruritus suggests LCTZ is effective for some non-nasal allergic symptoms.

Secondary Efficacy Results: A00266 (PAR)

Change from baseline in adjusted mean T4SS(R) for the first six treatment weeks: LCTZ 5 mg produces a greater reduction in T4SS(R) scores than placebo, compared to baseline scores, for the total six week treatment period. The adjusted mean difference is 1.17 (95% CI 0.70; 1.64) and the results compare favorably to the T3SS analysis (without ocular pruritus scores).
Change from baseline in adjusted mean T4SS (R) for each treatment week (two thru six): LCTZ 5 mg produces a greater reduction in T4SS (R) scores than placebo, compared to baseline scores, for each treatment week (two thru six). The adjusted mean differences range from 0.89 to 1.42, and the results are similar to a T3SS analysis, which also favors LCTZ over placebo for each treatment week.
Change from baseline in adjusted mean individual symptom scores (R) sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal obstruction for the first week, the first four treatment weeks, and the total six week treatment period: LCTZ 5 mg produces a greater reduction than placebo in each of the five individual symptom scores for the first week, the first four treatment weeks, and for the entire six week treatment period. The finding favoring improvement in ocular pruritus replicates the findings in A00268 and suggests that LCTZ is effective in treating some non-nasal allergic symptoms.
Subject Global Evaluation of treatment: Seventy-seven percent of subjects in the LCTZ 5 mg indicate a slight to moderate or good to excellent improvement in symptoms compared to 64% of placebo subjects.

For both studies the baseline demographic characteristics and inclusion/exclusion criteria are appropriate. Neither study, however, performs subgroup analyses, so extrapolation of efficacy findings of LCTZ to ethnic subgroups and elderly patients from these studies alone should be done cautiously.

Dose-Ranging Studies A217 and A00265: Summaries and Efficacy Findings

Both studies are randomized, DB, PC, multi-center four-arm, parallel group trials comparing LCTZ 2.5, 5, and 10 mg (given once daily in the evening) with placebo. Study A217 (SAR) is two treatment weeks, and A00265 (PAR) is four treatment weeks. For A217 the primary endpoint is change from baseline in the adjusted mean T4SS(R) for the two week treatment period, compared to placebo. Key secondary endpoints are change in T4SS(R) by week and change in individual symptom scores (sneezing, rhinorrhea, nasal pruritus, nasal obstruction, and ocular pruritus) over two weeks. For A00265 the primary endpoint is change from baseline in the adjusted mean T4SS(R) for the first week and for the four week treatment period. Key secondary endpoints are change in T4SS(R) by week and in individual symptom scores (same as A217) for first week and four weeks. Table 6 compares pertinent study features.

Table 6. Comparison of Study A217 and A00265

Study	Treatment Length	Placebo N	LCTZ 2.5 N	LCTZ 5 N	LCTZ 10 N	Primary Endpoint
A217	2 weeks	118	116	115	118	Change in T4SS (R) over 2 weeks
A00265	4 weeks	128	133	127	129	Change in T4SS (R) over 1st week and four weeks

Efficacy Results

For the primary endpoints, both studies show that all three LCTZ doses are statistically more significant than placebo in reducing the T4SS(R). The most relevant difference in the two studies is that a dose-ranging effect is found in A217, but not A00265. In A217 a linear dose-effect relative to placebo ($p = 0.0001$) shows that LCTZ 2.5, 5, and 10 mg are 34%, 41%, and 61% more effective than placebo, respectively. No such effect is seen in A00265. The Table 7 summarizes the primary efficacy findings of the studies.

Table 7. Summary of Primary Efficacy for A217 and A00265

A217					
Period	**Treatment**	**N**	**Mean (SD)**	**Adjusted Mean**	**Difference vs Placebo (95% CI)**
Baseline	Placebo	118	7.94 (2.06)		
	LCTZ 2.5 mg	116	7.83 (2.14)		
	LCTZ 5 mg	115	7.45 (2.07)		
	LCTZ 10 mg	118	7.15 (2.08)		
Two Treatment Weeks	Placebo	118	5.33 (2.46)	5.17	
	LCTZ 2.5 mg	116	4.37 (2.38)	4.27	0.91 (0.27;1.55)*
	LCTZ 5 mg	115	4.00 (2.14)	4.06	1.11 (0.47;1.75)**
	LCTZ 10 mg	118	3.37 (2.16)	3.57	1.61 (0.96;2.25)**
A00265					

Baseline	Placebo	128	7.22 (1.75)		
	LCTZ 2.5 mg	133	7.14 (1.64)		
	LCTZ 5 mg	127	7.18 (1.68)		
	LCTZ 10 mg	129	7.58 (1.79)		
First Week	Placebo	128	5.64 (2.31)	5.77	
	LCTZ 2.5 mg	133	4.32 (2.02)	4.52	1.25 (0.08;1.71)***
	LCTZ 5 mg	127	4.54 (2.23)	4.68	1.09 (0.62;1.57)***
	LCTZ 10 mg	129	4.71 (2.19)	4.66	1.11 (0.64;1.58)***
Four Treatment Weeks	Placebo	128	5.17 (2.24)	5.29	
	LCTZ 2.5 mg	133	3.93 (2.02)	4.12	1.17 (0.71;1.63)***
	LCTZ 5 mg	127	3.93 (2.01)	4.07	1.22 (0.76;1.69)***
	LCTZ 10 mg	129	4.23 (2.18)	4.19	1.10 (0.64;1.57)***

* $p = 0.001$; ** $p = 0.0001$; *** $p < 0.001$

For secondary efficacy endpoints, A217 shows all three doses of LCTZ favored over placebo for the first week of treatment, while only the 10 mg LCTZ group beats placebo for both weeks. For individual symptom scores, all three LCTZ doses beat placebo for sneezing, rhinorrhea, and nasal pruritus, while the 5 and 10 mg LCTZ doses are favored over placebo for ocular pruritus. Nasal congestion fails for all three LCTZ doses.

For secondary endpoints in A00265, results favor all three LCTZ doses over placebo for each treatment week. For individual symptom scores, the results favor all three doses for all individual symptoms except nasal congestion, which fails all three LCTZ doses.

Additional pertinent findings include evidence from both studies that sedation-related effects are greatest at the LCTZ 10 mg dose; in A00265, five of eight dropouts on LCTZ do so for somnolence, which is higher in the 5 and 10 mg doses.

6.1.5 Efficacy Conclusions

Studies A00268 and A00266

Levocetirizine 5 mg oral tablet, taken daily, once in the evening, is statistically superior to placebo for reducing grass pollen (SAR) and dust mite (PAR) allergic rhinitis nasal symptoms, assessed as change from baseline in the reflective T4SS (sneezing, rhinorrhea, nasal pruritus, and ocular pruritus). The two studies supporting these findings are adequate and well-controlled, and the replicate results are clinically relevant and statistically consistent. The duration of LCTZ exposure in each study is appropriate for the specific allergic rhinitis claim (i.e., two weeks for SAR and at least four weeks for PAR).

For key secondary endpoints in both trials, analysis favors LCTZ over placebo for the following: 1) T4SS (I) for the first week and a two week treatment period, 2) T4SS (R) for individual treatment weeks up to six weeks of therapy, and a six week treatment period, 3) for reflective sneezing, rhinorrhea, and ocular pruritus individual symptom scores for the first week and up to

six weeks of therapy (improvement in nasal pruritus and obstruction were seen in only one of the two studies [A00266]), and 4) subject global evaluation of treatment.

Re-analysis of T4SS (omitting ocular pruritus) as T3SS does not affect the robust efficacy LCTZ demonstrates when ocular pruritus is included, suggesting that LCTZ's effect on ocular pruritus does not drive efficacy. The analysis also suggests: 1) improvements in sneezing and rhinorrhea are the primary determinants of LCTZ efficacy, 2) ocular pruritus improves on LCTZ, and 3) nasal pruritus, a core T3SS symptom, does not consistently improve with LCTZ.

Analysis of T4SS (I) scores support a 24 hour duration of effect and suggest that the 24 hour dose interval for LCTZ 5 mg in allergic rhinitis is appropriate for adults and adolescents.

Indirect indicators of efficacy for both studies are more subjects using prohibited medications in the placebo than the LCTZ group, and no study dropouts in the LCTZ groups for lack of efficacy.

The results of these studies support the use of LCTZ 5 mg tablets, taken once in the evening, for the treatment of nasal symptoms and ocular pruritus associated with SAR and PAR in adolescents and adults.

Dose-ranging studies A217 and A00265

Of the two dose-ranging studies, A217 shows evidence of a linear dose-response, although all three doses of LCTZ in both studies show statistically significant efficacy over placebo for the primary endpoints. The finding of increased sedation, particularly at the 10 mg dose, coupled with the linearity findings of A217 and overall efficacy of LCTZ over placebo in both studies, supports either LCTZ 2.5 mg or 5 mg as reasonable once daily doses for adults and children 12 years and older. Therefore, the proposed product label for LCTZ 2.5 or 5 mg per day for adults and children 12 years of age and older is reasonable.

These two studies, as do A00268 and A00266, support efficacy of LCTZ 5 mg for ocular pruritus.

6.2 Indication

Pediatric (ages 6 to 11 years) SAR and PAR

6.2.1 Methods

There are two pediatric allergic rhinitis confirmatory efficacy trials: A00303 (SAR) and A00304 (PAR). Both are randomized, DB, PC, multi-center trials of LCTZ 5 mg oral tablets administered once daily in the evening, versus placebo, to reduce allergic rhinitis symptoms. The primary efficacy analysis for both trials is the change from baseline in the in subject-recorded (24-hour reflective) adjusted mean symptom scores over the first two weeks of treatment. Of note is the applicant's choice of LCTZ ——— once daily in the evening, ——— the dose for the adult

allergic rhinitis program. Further discussion of this is in section 6.2.5, Efficacy Conclusions. Lastly, the total exposed ITT population (to LCTZ 5 mg) of these two studies, 243 subjects, comprises the entire pediatric (ages 6-11 years) cohort in the pooled safety database for the NDA.

6.2.2 General discussion of endpoints

The primary and key secondary endpoints for both studies are change from baseline in total symptom score (T4SS, comprised of sneezing, rhinorrhea, nasal pruritus, and ocular pruritus assessed over 24 hours), and are similar to the adult study endpoints for SAR and PAR. (As in the adult SAR and PAR studies, the Division requested a re-configured, re-analyzed symptom score, removing ocular pruritus. Study A00303 reflects this change to T3SS, while A00304 does not. The Division did not request re-analysis of efficacy data for A00304 since re-configured scores for A00303, and the adult allergic rhinitis studies A00268 and A00266, showed satisfactory evidence of efficacy with ocular pruritus removed from the total symptom score). Section 6.1.1, Study Design, discusses the specifics of symptom scoring for the adult studies, which is the same for the pediatric studies.

For allergic rhinitis products FDA recommends at least two weeks of drug exposure for SAR, and four weeks exposure for PAR, indications. In principle, this exposure should be reflected in choice of primary endpoint. The primary endpoint in both pediatric trials is change from baseline in total symptom score for the first *two* weeks of treatment (rather than for the four weeks expected of the PAR trial, A00304). For both studies assessment over the first four weeks of treatment is a key secondary endpoint. As discussed in section 6.2.4 (Efficacy Findings), studies A00303 and A00304 satisfactorily replicate efficacy for these endpoints, and there is no compelling reason to find them unacceptable to support both SAR and PAR indications.

For allergic rhinitis trials, FDA guidance recommends inclusion of both instantaneous and reflective symptom scores. Instantaneous scores give duration-of-effect and appropriateness-of-dosing interval information that reflective scores do not. Of note in the pediatric allergic rhinitis development program is the absence of instantaneous symptom scores.

Notwithstanding the above discussion, the primary and key secondary endpoints are otherwise in accordance with FDA guidance for allergic rhinitis drug development and generally appropriate for the indications sought; additional specific endpoint details are discussed in the Study Design section.

6.2.3 Study Design

Study A00303: "A double-blind, placebo-controlled, randomized, multi-center, Phase 4 trial: Evaluation of the efficacy and safety, for children from 6 to 12 years old, suffering from seasonal allergic rhinitis, of LCTZ 5 mg tablets, administered orally once daily in the evening, for 6 weeks."

Study A00304: "A double-blind, placebo-controlled, randomized, multi-center, Phase 3 trial: Evaluation of the efficacy and safety, for children from 6 to 12 years old, suffering from perennial allergic rhinitis due to house dust mites, of LCTZ 5 mg tablets, administered orally once daily in the evening, for 4 weeks."

The study designs for A00303 and A00304 are nearly identical, and are analogous to the adult SAR and PAR studies A00266 and A00268 (reviewed above in section 6.1.3); therefore, only specific, relevant differences in the protocols are cited.

Both studies compare oral LCTZ 5 mg, given in the evening, with placebo. The subjects have allergic rhinitis symptoms for at least one year. The applicant chooses the 5 mg LCTZ dose because previous clinical trials show efficacy at this dose and the 10 mg dose of the reference drug, the racemate CTZ, is used in adults and children aged 6 years and older.

Study A00303 randomizes 177 subjects (88 placebo, and 89 LCTZ) and A00304 randomizes 306 (152 placebo, and 154 LCTZ).

Inclusion and Exclusion criteria, and prohibited medications, are similar for both studies and analogous to the adult studies; specific differences relevant to the pediatric age group are:
Inclusion: male or female, aged 6-12 years (inclusive); consent from subject and parent(s) or legal representative; during the one week run-in period (Visit 1 [screening visit] and Visit 2 [randomization visit]) and on the day before Visit 2 a mean total symptom score ≥ 6 for SAR (A00303) and ≥ 5 for PAR (A00304).
Exclusion: temperature $\geq 38.5°$ C is the only significant exclusionary criterion that differs from the adult studies. Prohibited medications are analogous.

Study Procedure

The run-in period (Visit 1 to Visit 2, 3-9 days long) is used to obtain baseline symptom scores and verify inclusion criteria. Randomization of eligible subjects occurs at Visit 2 and subjects take the study medication in the evening and grade symptoms (grading is based on the child's assessment although adults may assist in recording responses) on the four-point scale (described in section 6.1.3, above) in the daily record card. (Refer to Figure 1 in section 6.1.3 for a diagram of the study plan for A00266 which, with only minor differences, is analogous to the pediatric study plans). Study A0303 includes six treatment weeks, and A00304 four treatment weeks. The scores are 24-hour reflective in both studies. An additional parameter (for one A00304 secondary endpoint) is a seven-point investigator-recorded global evaluation of disease evolution scale (marked worsening to marked improvement) completed at the end of treatment.

Statistical and Analytical Plan

Primary Efficacy Endpoints

The primary efficacy variables are the adjusted mean T4SS (24-hour, reflective), compared with baseline, for the first two-week treatment period. The primary efficacy analysis is on the ITT

population (randomized subjects taking at least one dose of study medication). Analysis of the primary variables uses an ANCOVA model including the mean baseline score as covariate, and treatment and center as factors. All statistical analyses are two-tailed at the 5% level of significance. The analysis presents 95% confidence intervals of the difference in the adjusted means between placebo and LCTZ 5 mg. An ANCOVA model analyzes relative improvement from baseline (the ratio of the difference between the adjusted means for the change from baseline for LCTZ 5 mg and placebo over the adjusted mean for the change from baseline for placebo.

Secondary Efficacy Endpoints: A00303

The clinically relevant secondary endpoints, by protocol order, are 1) mean T4SS (R) over the four and six weeks of treatment, and by study week, and 2) mean individual symptom scores over two, four, and six weeks of treatment and over each treatment week.

Power and Sample Size: A00303

A sample size of 146 subjects per study arm has 90% power to detect a difference of 0.8 in the mean T4SS (R) between placebo and LCTZ 5 mg (alpha = .05, SD 2.1).

Patient Disposition and Compliance: A00303

The ITT population is 177 subjects with an age range between 6.0 and 13.0 years; 145 (81.9%) complete the study. More than twice as many subjects are between 9 and 12 years (69.5%) than between 6 and 8 years (29.9%). Boys outnumber girls 66.1% to 33.9%. Fourteen of the 32 dropouts do so for lack of efficacy (nine placebo and five LCTZ). There are 11 dropouts for other reasons (holidays and non-compliance) essentially equal between groups, one for consent withdrawal, and one for an AE (a placebo subject with asthma). The most common major protocol deviations are use of prohibited medications during treatment (13.0%), insufficient washout (11.3%), baseline score out-of-range (6.8%), and low compliance with study medications (6.8%). Insufficient washout is more common in the placebo group (14.8%) than LCTZ group (7.9%). Mean compliance for the total treatment period is 96.5%.

Secondary Efficacy Endpoints: A00304

The clinically relevant secondary endpoints, by protocol order, are 1) mean T4SS (R) over four treatment weeks, and by treatment week, 2) mean T5SS (R) [T5SS = T4SS + nasal congestion] over the first two weeks and over four treatment weeks, and 3) mean individual symptom scores over the first two weeks of treatment, over four weeks of treatment, and by each treatment week.

Power and Sample Size: A00304:

These are analogous to study A00303.

Patient Disposition and Compliance: A00304

The ITT population is 306 subjects and 297 (97.1%) complete the study. Nearly twice as many subjects are between 9 and 12 years (66.0%) than between 6 and 8 years (34%). Boys outnumber girls 60.8% to 39.2%. Of the nine subjects dropping out, four have AE's (two in each group; in the LCTZ group, one has asthma and the other a URI), three have lack of efficacy (two placebo and one LCTZ), one uses prohibited medication, and one withdraws consent. Protocol violations are relatively infrequent; the most common major violation is use of prohibited medications (2.6% for each group) and compliance with study medicine intake. Mean compliance for the total treatment period is 98.7%.

6.2.4 Efficacy Findings

Primary Efficacy Results: A00303 (SAR)

Change from baseline in adjusted mean T4SS (R) over the first two weeks of treatment: LCTZ 5 mg produces a greater reduction in T4SS (R) scores than placebo, compared to baseline scores, over the first two weeks of treatment. Results are statistically significant: adjusted mean difference is 1.29 (95% CI 0.66; 1.92), $p < 0.001$. These results compare favorably to the analysis excluding ocular pruritus (T3SS): adjusted mean is 1.11 (95% CI 0.64; 1.59), $p < 0.001$. Comparative analyses of the original T4SS and T3SS data by Dr. James Gebert, Biostatistician, strongly suggest that ocular pruritus does not drive overall efficacy. For the T4SS analysis, the relative improvement for LCTZ over placebo is 94.1%. Summary of T4SS and T3SS comparisons are found in Tables 8A and 8B.

Table 8A. Summary of Mean T4SS (R) Comparisons, Primary Efficacy Period ITT

Period	Treatment	N	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo [(a)] Adj. Mean (95% CI)	p-value
First two Treatment weeks	Placebo LCTZ 5 mg	87 87	7.67 (1.73) 7.61 (1.36)	6.27 4.98	1.29 (0.66; 1.92)	< 0.001

(a) The differences are "Placebo minus LCTZ 5 mg"

Table 8B. Summary of Mean T3SS (R) Comparisons, Primary Efficacy Period ITT

Period	Treatment	N	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo [(a)] Adj. Mean (95% CI)	p-value
First two Treatment weeks	Placebo LCTZ 5 mg	87 87	5.80 (1.46) 5.70 (1.19)	4.83 3.72	1.11 (0.64; 1.59)	< 0.001

(a) The differences are "Placebo minus LCTZ 5 mg"

Primary Efficacy Results: A00304 (PAR)

Change from baseline in adjusted mean T4SS (R) over the first two week treatment period: LCTZ 5 mg produces a greater reduction in T4SS (R) scores than placebo, compared to baseline scores, over the first two weeks of treatment. The results are statistically significant: adjusted mean difference for the two week treatment period is 0.69 (95% CI 0.27; 1.12), p = 0.001. The relative improvement of LCTZ over placebo is 90.9%. Summary of T4SS comparisons is in Table 9.

Table 9. Summary of Mean T4SS (R) Comparisons, Primary Efficacy Period ITT

Period	Treatment	N	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo [a] Adj. Mean (95% CI)	p-value
First two Treatment weeks	Placebo LCTZ 5 mg	152 154	7.51 (1.85) 7.53 (1.85)	6.76 6.06	0.69 (0.27; 1.12)	0.001

(a) The differences are "Placebo minus LCTZ 5 mg"

Secondary Efficacy Results: A00303 (SAR)

1) Change from baseline in adjusted mean T4SS(R) for the first four and six treatment weeks, and over each week: LCTZ 5 mg produces a greater reduction in T4SS(R) scores than placebo, compared to baseline scores, for the first four and six week treatment periods. The adjusted mean difference is 1.32 (95% CI 0.66; 1.98) for the first four weeks and 1.22 (95% CI 0.54; 1.90) for the first six weeks. These results compare favorably to the re-configured score (T3SS) with ocular pruritus removed. Analysis by treatment week favors LCTZ for all except the sixth week.
2) Change from baseline in adjusted mean individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal obstruction over the first two, four,and six week treatment periods, and by treatment week: Results favor LCTZ 5 mg over placebo for reduction of sneezing, rhinorrhea, and nasal pruritus for the two, four, and six week periods, but not for ocular pruritus or nasal congestion for any of the intervals. The results for individual treatment weeks are similar, although efficacy at weeks five and six is lacking for nasal pruritus, and at week six for sneezing and rhinorrhea. Ocular pruritus (except for one week) and nasal obstruction (except for two weeks) do not improve.

Secondary Efficacy Results: A00304 (PAR)

Change from baseline in adjusted mean T4SS(R) for each week and for the four treatment weeks: LCTZ 5 mg produces a greater reduction in T4SS(R) scores than placebo, compared to baseline scores, for the first and second treatment weeks (p = 00.1 and 0.012, respectively), and for the four week period (p = 0.008). For weeks three and four LCTZ does not beat placebo (p = 0.054 and 0.193, respectively).
Change from baseline in adjusted mean T5SS (R) for the first two and first four week treatment periods: LCTZ 5 mg produces a greater reduction in T5SS (R) scores than placebo, compared to baseline scores, for the two week (p = 0.017), but not the four week treatment period (p = 0.054).

Change from baseline in adjusted mean individual symptom scores (R) sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal obstruction for the first two week and four week treatment periods: The efficacy analysis favors LCTZ over placebo only for sneezing (both intervals) and nasal pruritus (two, but not four weeks).

6.2.5 Efficacy Conclusions

Pediatric studies A00303 and A00304 demonstrate that LCTZ 5 mg taken daily, once in the evening, is statistically superior to placebo for reducing SAR and PAR nasal symptoms in children 6 to 12 years old for two and four week treatment periods. Although some secondary endpoints fail versus placebo, replicate efficacy for the primary and most clinically relevant secondary endpoint (efficacy for a four week treatment period, by change in adjusted mean T3SS or T4SS from baseline) supports use of LCTZ for both SAR and PAR indications.

Indirect indicators of efficacy are more subjects using prohibited medications and dropping out for lack of efficacy in the placebo than the LCTZ groups.

Sneezing is the only individual symptom score for which replicate efficacy for up to four weeks of treatment with LCTZ is demonstrated.

Although for both studies the baseline demographic characteristics and inclusion/exclusion criteria are generally appropriate, the pediatric program exposes a total of only 79 subjects in the six to eight year old demographic. Additionally, neither study performs subgroup analyses; extrapolation of efficacy findings of LCTZ to ethnic subgroups should be done cautiously.

While the results of these studies, *prima facie,* support the use of LCTZ 5 mg tablets for the treatment of the nasal symptoms of SAR and PAR in children 6 to 12 years old, they must be viewed in the context of the entire adult and pediatric development program. The adult allergic rhinitis dose-ranging studies (A217 and A00265) are inconsistent: A217 shows evidence supporting a linear dose-effect, but all three LCTZ doses (2.5, 5, and 10 mg) show statistically significant efficacy compared to placebo. Study A00265 shows no D-R effect, and all LCTZ doses beat placebo. Study A00412, an adult EEU comparative efficacy trial of multiple CTZ and LCTZ doses (refer to section 6.4 for summary), shows similar efficacy for all active treatments over placebo, and no evidence of D-R. Most importantly, a pediatric (6-11 years) PK study (PSM 1216) of LCTZ 5 mg shows that children receive roughly twice the drug exposure of subjects 12 years and older, and suggests that LCTZ 2.5 mg is the appropriate dose for this age group.

The preponderance of the evidence from both the adult and pediatric clinical development programs, therefore, suggests that the most effective and safest dose of LCTZ in the 6-11 year age group is 2.5 mg, rather than 5 mg, given once daily in the evening.

6.3 Indication

Adult chronic idiopathic urticaria (CIU)

6.3.1 Methods

There are two studies to support the adult (18 years and older) CIU indication, A00269 and A00270. The study endpoints and overall designs are analogous, the only relevant difference being that A00270 is a dose-ranging study. The two studies will, therefore be discussed together except efficacy findings or as noted.

The studies are randomized, double-blind, placebo-controlled, multi-center Phase 2 (A00270 [dose-ranging]) and Phase 3 (A00269) studies of LCTZ (four treatment weeks) in subjects with at least a three month history of symptoms and signs of CIU (defined as regularly occurring [at least three times per week for at least six weeks during the previous three months] episodic hives of characteristic wheal and flare appearance, without identifiable cause. The primary endpoints are change from baseline in mean pruritus severity over the first treatment week and the four-week treatment period. Principle secondary endpoints are change in wheal number and size.

6.3.2 General Discussion of Endpoints

The primary endpoints are change in the adjusted mean pruritus severity score (24-hour reflective), compared to baseline, over the first treatment week and over the total four week treatment period. Principal secondary endpoints are change in pruritus severity for individual treatment weeks two, three, and four, and change from baseline in number and size of wheals (instantaneous, prior to the once daily evening dose) for each treatment week and the total treatment period.

Ideally, a well-designed CIU confirmatory efficacy study has a subjective *and* objective variable as co-primary endpoints, for example, pruritus severity and number of wheals. Although these two studies use only a subjective measure of change as the primary endpoint, the efficacy analyses (discussed below in section 6.4.4), demonstrating statistically significant replicate results, favoring LCTZ over placebo, mitigate endpoint design concerns.

6.3.3 Study Design

Study A00269: "A randomized, double-blind, placebo-controlled, multi-center, Phase 3 study of the efficacy and safety of 5 mg levocetirizine dihydrochloride tablets, administered orally, once daily in the evening, for four weeks, to adults suffering from chronic idiopathic urticaria."

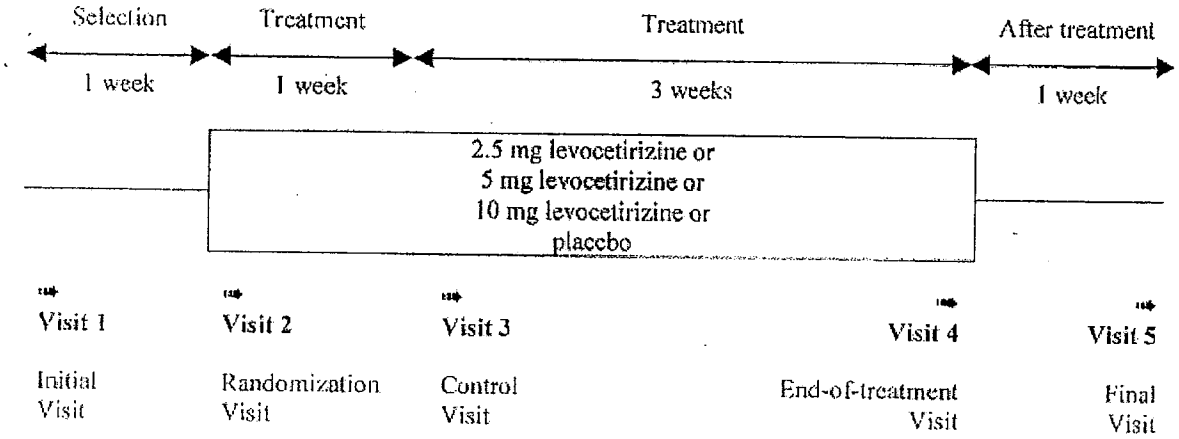
Study A00270: "A randomized, double-blind, placebo-controlled, multi-center, Phase 2 study of the efficacy and safety of 2.5 mg, 5 mg, and 10 mg levocetirizine dihydrochloride tablets administered orally, once daily in the evening, for four weeks, to adults suffering from chronic idiopathic urticaria."

The study designs for A00269 and A00270 are analogous except for the dose-ranging of A00270.

Both studies compare oral LCTZ tablets, given in the evening, with placebo. The subjects have CIU signs and symptoms for at least three months. The applicant chooses the 5 mg LCTZ dose as the target dose due to prior demonstration of efficacy in the allergic rhinitis program, and based upon the use of the reference drug, the racemate CTZ, at a dose of 10 mg.

The studies are six week trials, with four treatment weeks. The first visit, for screening, is followed one week later by the enrollment eligibility and randomization visit. The third visit is a control assessment after the first treatment week. For those continuing the study, the fourth visit, an end-of-treatment visit, occurs three weeks later, and the fifth and final visit occurs one week later, at the end of the sixth study week. Figure 2 diagrams the study plan of A00270, which is identical to A00269.

Figure 2. A00270 Study Plan Diagram



Study A00269 randomizes 166 subjects (85 placebo, and 81 LCTZ 5 mg) and A00270 randomizes 257 (63 placebo, 70 LCTZ 2.5, 65 LCTZ 5, and 59 LCTZ 10 mg).

Inclusion and Exclusion criteria are identical for both studies. Listed below are specific criteria unique to these protocols; general criteria typical for clinical trials are not listed.

Inclusion: Males or females 18 years and older with CIU (defined in section 6.4.1). Necessary criteria at the randomization visit (Visit 2, which concludes the three to nine day baseline period) include at least three days of moderate or severe pruritus (severity score [defined below] ≥ 2) and wheals present (wheal score ≥ 1), laboratory tests within accepted protocol limits, and, for females, a negative pregnancy test.

Exclusion: Pregnant or lactating females; various non-CIU conditions resulting in pruritus, urticaria, or angioedema (senile pruritus, acute urticaria, cholinergic or environmentally-induced urticaria, drug-related and contact urticaria, vasculitis, and hereditary angioneurotic edema); subjects known to be antihistamine non-responders; generalized dermatological diseases; and a history of auto-immune or other clinically significant diseases.

Prohibited medications: Without appropriate washouts the following drugs were prohibited: astemizole, topical and systemic corticosteroids, ketotifen, doxepin, tranquilizers, anti-depressants, sedatives, hypnotics, antiepileptics and other CNS active agents, H_{1+2} antihistamines, and non-steroidal anti-inflammatory drugs.

Study Procedure

The baseline period (Visit 1 to Visit 2, 3-9 days long) obtains baseline symptom scores and verifies inclusion criteria. Randomization of eligible subjects occurs at Visit 2; subjects take the study medication in the evening and grade symptoms in the daily record card. The pruritus severity scores are 24-hour reflective; wheal number and size scores are instantaneous.

Statistical and Analytical Plan

Efficacy Parameter Scales

Pruritus Severity:
0 = absent
1 = mild (present, but not disturbing)
2 = moderate (disturbing, but not hampering ADLs/sleep)
3 = severe (hampering ADLs/sleep)

Number of Wheals:
0 = no wheal
1 = from 1 to 6
2 = from 7 to 12
3 = more than 12

Size of Wheals:
0 = no wheal
1 = less than or equal to 1.5 cm
2 = more than 1.5 and less than or equal to 3 cm
3 = more than 3 cm

Primary Efficacy Endpoints

The primary efficacy variables are the mean of the daily patient-recorded pruritus severity score (reflective over 24 hours, recorded in the evening, just prior to taking the study medication) over the first treatment week, and over the total treatment period (four weeks), compared to the baseline pruritus severity score, in the LCTZ arms versus the placebo arm. Primary efficacy variables analysis is on the ITT population. (The ITT population consists of all randomized subjects taking at least one dose of study medication). Analysis of each primary efficacy variable uses an ANCOVA model that includes the mean DRC baseline pruritus severity score (24 hour reflective) as covariate, and treatment and center as factors. The model compares each dose of LCTZ to placebo using a t-test at an alpha of 2% and presents a 98% confidence interval of the difference in the adjusted means between placebo and each LCTZ dose. A linear combination of adjusted means tests the linear and quadratic nature of the relationship between the dose and

treatment effect. Underlying assumptions of the ANCOVA model are assessed by verifying the normality of residuals using the Shapiro-Wilk test, a stem and leaf plot, and a normal probability plot. Levene's test checks for homogeneity of variance. Evaluation of the interaction between the treatment and baseline score is at the 10% significance level. Dose-effect association is assessed for the primary efficacy endpoints. Tests for linear and quadratic trends are performed (alpha error 10%) based on a linear combination of the adjusted means with one-way ANCOVA.

Secondary Efficacy Endpoints

Principal secondary endpoints (from DRC parameters), are mean of the 24 hour reflective daily pruritus severity score over Weeks 2, 3, and 4, and the mean scores of each of the other DRC variables: number and size of wheals (instantaneous, prior to evening dose), and pruritus duration (24 hour reflective), computed by week (Week 1 to Week 4), and over the total treatment period, compared to baseline scores. Analysis of secondary efficacy variables also uses an ANCOVA model: baseline score is covariate, and treatment and center (after pooling) are factors. The analysis presents a 98% confidence interval of the difference in the adjusted means between placebo and each LCTZ group.

Power and Sample Size:

For A00269, the study needs 77 subjects per group (minimum total of 154 in the ITT population) to obtain a power of 95% to detect a 0.5 difference between placebo and LCTZ in the mean pruritus severity score (24 hour reflective) at an alpha of 5% (and a standard deviation of 0.85). The overall power to detect this difference over the first treatment week and over the total treatment period (the two co-primary endpoints) is at least 90% [i.e., .95 x .95 = .9]. For A00270, the study needs 64 subjects per group to obtain a power of 90% to detect a difference between placebo and one of the doses of LCTZ of 0.5 in the mean pruritus severity score (24 hour reflective) at an alpha level of 2% (to have an overall alpha error of 5% per Dunnett adjustment for multiple comparisons) and a common standard deviation of 0.77. The overall power to detect this difference over the first treatment week and over the total treatment period (the two co-primary endpoints) is at least 80%.

Patient Disposition and Compliance: A00269

The study screens 186 subjects and randomizes 166: 85 subjects to the placebo group and 81 subjects to the LCTZ 5 mg group. One hundred and twenty-four randomized subjects complete the study (74.7%). Forty-two subjects discontinue the study prematurely (33 in the placebo group and nine in the LCTZ group). Lack of efficacy is the most common reason for early termination (30/42 subjects). The most common major protocol violations are low compliance (below 80%) and the use of prohibited medication. More subjects in the placebo group than the LCTZ group have low compliance (14.1% vs 2.5%) and/or use prohibited medication (12.9% vs 2.5%). The mean compliance for the total treatment period is 97.4%.

Patient Disposition and Compliance: A00270

The study screens 303 subjects and randomizes 257 to one of four treatment arms:
1) Placebo: N = 63
2) LCTZ 2.5 mg: N = 70
3) LCTZ 5 mg: N = 65
4) LCTZ 10 mg: N = 59
The 257 randomized subjects are the ITT population.
A total of 202 subjects complete the study (78.6%). Fifty-five subjects drop out: 26 in the placebo group, 12 in the LCTZ 2.5 mg group, 7 in the LCTZ 5 mg group, and 10 in the LCTZ 10 mg group. The most common reason for early termination is lack of efficacy. The most common major protocol violations are the use of prohibited medication (13.2%) and low compliance (11.7%). Forbidden medication use is greater in the placebo group (27%) than in any of the LCTZ groups: 2.5 mg (10%), 5 mg (7.7%), and 10 mg (8.5%). Low compliance (less than 80%) occurs more in the placebo (15.9%) and LCTZ 10 mg (15.3%) than the LCTZ 2.5 mg (8.6%) and LCTZ 5 mg (7.7%) groups. Mean compliance is assessed for three intervals: over the first treatment week, over the last three treatment weeks, and over the total treatment period. For the first week of treatment, the overall mean compliance is 97.3%, with lower compliance noted in the placebo group (92.7%), than in the LCTZ groups (2.5 mg, 96.8%; 5 mg, 100.6%; 10 mg, 99.3%). For the last three weeks of treatment, compliance is lowest for the LCTZ 10 mg group, 91.4% (placebo = 98.2%, LCTZ 2.5 mg = 98.7%, LCTZ 5 mg = 96.3%). The mean compliance for the total treatment period is 94.7%, and similar across all groups.

6.3.4 Efficacy Findings

Primary Efficacy: Study A00269

Change from baseline in mean pruritus severity over the previous 24 hours during the first week of treatment and during the total four week treatment period:
Pruritus severity decreases more in the LCTZ 5 mg group, compared to the placebo group, during both treatment periods. The adjusted mean difference for the first week is 1.02 for the LCTZ group and 1.80 for the placebo group. The 0.78 difference (95% CI [0.53; 1.04]) in adjusted means between the two groups is statistically significant ($p < 0.001$). For the four week treatment period the adjusted mean difference is 0.93 for the LCTZ group and 1.54 for the placebo group. The 0.62 difference (95% CI [0.38; 0.86]) in adjusted means is statistically significant ($p < 0.001$). More subjects discontinue the study due to lack of efficacy in the placebo group (26 subjects) compared to the LCTZ group (4 subjects). Sensitivity analysis using the Last Observation Carried Forward (LOCF) confirms treatment effect. Table 10 summarizes primary efficacy findings.

Table 10. Mean pruritus severity (24 hour reflective) during first treatment week And for the total treatment period (ITT)

Period	Treatment	N	Mean (SD)	Adjusted Mean[a]	Diff. vs Placebo[b] [95% CI]	p-value[c]
Baseline	Placebo LCTZ 5 mg	82 79	2.06 (0.57) 2.07 (0.61)			
First Week	Placebo	82	1.80 (0.84)	1.80		

	LCTZ 5mg	79	1.02 (0.85)	1.02	0.78 [0.53;1.04]	< 0.001
Total Treatment Period	Placebo LCTZ 5mg	82 80	1.54 (0.87) 0.93 (0.75)	1.56 0.94	0.62 [0.38; 0.86]	< 0.001

(a) Mean adjusted for baseline score and type of center

(p 58)

(b) Placebo minus LCTZ 5 mg

(c) p-value was obtained from an ANCOVA with baseline score as covariate and center and treatment as factors

Primary Efficacy: Study A00270

Change from baseline in mean pruritus severity over the previous 24 hours during the first week and for the four week total treatment period:

Pruritus severity over the first week and for the entire treatment period decreases significantly more in all three LCTZ arms than in the placebo arm. For the first week, all three LCTZ groups are statistically superior to placebo ($p < 0.001$). The differences in adjusted means between the placebo and LCTZ groups are 0.93 [98% CI (0.63; 1.23)] for LCTZ 2.5 mg, 1.10 [98% CI (0.80; 1.40)] for LCTZ 5 mg, and 1.14 [98% CI (0.83; 1.46)] for LCTZ 10 mg, respectively. There is a tendency favoring a linear dose-effect relationship which is not statistically significant ($p > 0.10$). For the four week period, all three LCTZ groups are statistically superior to placebo ($p < 0.001$). The differences in the adjusted means between the placebo and LCTZ groups are 0.82 [98% CI (0.53; 1.11)] for 2.5 mg, 0.91 [98% CI (0.62; 1.21)] for 5 mg, and 1.11 [98% CI (0.81; 1.41)] for 10 mg, respectively. There is a statistically significant linear dose-effect relationship between the three doses of LCTZ ($p = 0.02$), with efficacy increasing with dose. Table 11 summarizes primary efficacy results.

Table 11. Mean pruritus severity (24 hour reflective) during first treatment week And total four week treatment period

Period	Treatment	N	Mean (SD)	Adjusted Mean[(a)] (SE)	Diff. vs. placebo[(b)] [98% CI]	p-value[(c)]
Baseline	Placebo LCTZ 2.5 mg LCTZ 5 mg LCTZ 10 mg	60 69 62 55	2.25 (0.50) 2.08 (0.53) 2.07 (0.50) 2.04 (0.57)			
First Week	Placebo LCTZ 2.5 mg LCTZ 5 mg LCTZ 10 mg	60 69 62 55	2.07 (0.69) 1.08 (0.83) 0.91 (0.71) 0.86 (0.65)	2.02 (0.09) 1.10 (0.09) 0.93 (0.09) 0.88 (0.10)	 0.93 [0.63; 1.23] 1.10 [0.80; 1.40] 1.14 [0.83; 1.46]	 < 0.001 < 0.001 < 0.001
Total Treatment Period	Placebo LCTZ 2.5 mg LCTZ 5 mg LCTZ 10 mg	60 69 62 55	1.89 (0.74) 1.00 (0.78) 0.91 (0.71) 0.70 (0.57)	1.84 1.02 0.92 0.73	 0.82 [0.53;1.11] 0.91 [0.62;1.21] 1.11 [0.81;1.41]	 < 0.001 < 0.001 < 0.001

(a) Mean adjusted for baseline score

(b) Placebo minus LCTZ 2.5 mg/Placebo minus LCTZ 5 mg/Placebo minus LCTZ 10 mg

(c) p-value was obtained from ANCOVA with baseline score as covariate and treatment as factor

(p 62)

Secondary Efficacy Results

The most clinically relevant secondary efficacy results are for wheal number and size; the results of both studies are discussed together. A more detailed analysis can be found in Appendix 1.A and B.

Change from baseline in mean number of wheals by treatment week and during the total treatment period:
For study A00269, comparisons of difference from baseline in mean number of wheals between LCTZ 5 mg and placebo by treatment week, and for the total treatment period, show statistically significant differences favoring LCTZ for the first week, and for the total treatment period. There are smaller differences favoring LCTZ (but not statistically significant) for Weeks 2, 3, and 4. The lessening of treatment effect may be due to dropouts (for lack of efficacy) in the placebo group. For the dose-ranging study, A00270, the analysis supports all three doses of LCTZ being statistically significantly more efficacious in reducing the number of wheals in Weeks 1, 2, and for the total treatment period. The most consistent difference favoring LCTZ is for the 10 mg dose (for each week, and for the total treatment period). The differences between placebo and the lower LCTZ doses (i.e., 2.5 and 5 mg) are less over Weeks 2, 3, and 4 than for Week 1, and are not statistically significant for Weeks 3 and 4. Treatment effect may be underestimated due to a greater number of dropouts for lack of efficacy in the placebo group vs. the LCTZ groups.

Change from baseline in mean size of wheals by treatment week and during the total treatment period:
For study A00269, comparisons of difference from baseline in mean size of wheals between LCTZ 5 mg and placebo by treatment week, and for the total treatment period, favor LCTZ for the first week, and for the total treatment period; the results are statistically significant. Smaller differences (not statistically significant) favor LCTZ for Weeks 2, 3, and 4. The lessening of treatment effect may be due to dropouts (for lack of efficacy) in the placebo group. For study A00270, the analysis shows results similar to those obtained with the number of wheals. Results that are statistically significant favor all three doses of LCTZ over placebo for Week 1 and for the total treatment period. For each week the largest difference in adjusted means between LCTZ and placebo is in the 10 mg group. For Weeks 3 and 4, lower doses of LCTZ (i.e., 2.5 and 5 mg) are not significantly more efficacious than placebo; this may be due to the greater drop out rate for lack of efficacy in the placebo group.

6.3.5 Efficacy Conclusions

For study A00269, LCTZ 5 mg tablet, taken once daily in the evening, is statistically superior to placebo in reducing pruritus severity during the first week of treatment ($p < 0.001$) and for the total four week treatment period ($p < 0.001$) in subjects with CIU. The difference in adjusted means between LCTZ and placebo is 0.78 [95% CI (0.53; 1.04)] for the first week of treatment and 0.62 [95% CI (0.38; 0.86)] for the total treatment period. Analysis also favors LCTZ over placebo in reducing the number and size of wheals (secondary endpoints) during the first treatment week and for the total four week treatment period.

Indirect indicators supporting efficacy for LCTZ include observations that more subjects discontinue the study due to lack of efficacy in the placebo group (26 subjects, 30.6%) than in

the LCTZ group (4 subjects, 4.9%) and, conversely, more subjects in the placebo group than in the LCTZ group take proscribed antihistamines during the four week treatment period, 12.9% vs. 2.5%, respectively.

For the dose-ranging study, A00270, all three LCTZ doses (2.5, 5, or 10 mg) taken orally, once daily in the evening, are more efficacious than placebo. The differences in adjusted mean values from baseline for all three doses of LCTZ vs. placebo are statistically significant ($p < 0.001$) for the primary efficacy endpoints (the first treatment week and the total four week treatment period). There is also a statistically significant linear dose-response relationship for the total treatment period of the pruritus severity score ($p = 0.02$).

Analysis of secondary endpoints suggests that all three doses of LCTZ are more efficacious than placebo: mean pruritus severity is reduced for each treatment week, and for the total treatment period; number and size of wheals is reduced in Weeks 1 and 2, and for the total treatment period; and mean pruritus duration is reduced for each treatment week, and for the total treatment period.

Indirect indicators supporting efficacy for LCTZ include the observations that more subjects discontinue the study for lack of efficacy in the placebo group (20 subjects, 31.7%) than in the LCTZ groups: 10 subjects (14.3%) in the 2.5 mg group, 4 subjects (6.2%) in the 5 mg group, and 3 subjects (5.1%) in the 10 mg group. Furthermore, more subjects in the placebo group take proscribed antihistamines during the study than in the LCTZ groups.

Study A00270 also suggests the optimal LCTZ dose to be 5 mg based on the following: 1) although the analysis shows statistically significant efficacy over placebo for all three LCTZ doses, more subjects in the LCTZ 2.5 mg drop out due to lack of efficacy or take proscribed medications during the treatment period than subjects in the other two LCTZ groups, 2) the relative risk of somnolence is significantly higher in the LCTZ 10 mg group, compared to the other LCTZ groups; all three study subjects who discontinue study medication due to somnolence are in the LCTZ 10 mg group, and 3) there is a statistically significant linear dose-response relationship for pruritus severity over the total treatment period.

The results of these studies can be used to support the use of LCTZ 5 mg taken once daily for treatment of the symptoms and signs of CIU in adults.

For both studies the designation of two measures of pruritus severity at different treatment intervals as co-primary endpoints is not ideal. For the indication sought, a more appropriate study design designates one pertinent subjective endpoint (e.g., pruritus severity) and one pertinent objective endpoint (e.g., number of wheals) as co-primary endpoints. Notwithstanding this design flaw, both studies demonstrate efficacy for both the primary (subjective) endpoints, pruritus severity, and the secondary (objective) endpoints, wheal number and size, which are satisfactorily robust to support the indication sought.

Neither study SAP includes a subgroup analysis, so extrapolation of results should be done with caution.

6.4 Review of Comparative Efficacy Studies

The NDA references the racemate cetirizine to support filing under 505(b)(2) status and contains two comparative efficacy studies, A00373 and A00412, that seek to bridge LCTZ to CTZ. The original bridging study (A00379) compares one dose of LCTZ to CTZ (and placebo), a design deemed unsatisfactory by FDA for bridging purposes because two doses of each drug were not compared. Study A00412, comparing two doses of LCTZ with two doses of CTZ (and placebo), was, therefore, conducted. Since study design, except for the two-dose comparison of A00412, is analogous, the review combines the studies, citing specific differences as appropriate.

6.4.1 Methods

Both studies are randomized, PC, DB, double dummy, parallel group, environmental exposure unit (EEU) trials in subjects with SAR, coordinated by the same clinical investigator, and at the same facility, in Canada. Study A00379 compares the efficacy of a single 5 mg dose of LCTZ to a single 10 mg dose of CTZ, while A00412 compares the efficacy of a single dose of LCTZ 2.5 mg oral drops to a single dose of CTZ 5 mg oral drops, and one dose of LCTZ 5 mg tablets to one dose of CTZ 10 mg tablets. An EEU location is an appropriate setting for this type of study.

Although it is important for the study to demonstrate efficacy for LCTZ and CTZ against placebo, the main rationale for these studies, particularly A00412, is to show a dose-dependent difference in effect size that links putatively equivalent doses of LCTZ to CTZ. Ideally, the 2.5 mg dose of LCTZ, the R-enantiomer of CTZ, should have efficacy similar to CTZ 5 mg, and the higher dose of each should behave analogously, while demonstrating a dose-response. The study findings are presented in section 6.5.4, Efficacy Findings, and discussed in section 6.5.5, Efficacy Conclusions.

6.4.2 General Discussion of Endpoints

The studies use the same two symptom complex parameters for subject eligibility and to assess change from baseline after active treatment exposure. The parameters are aggregate subject-recorded scores of individual nasal and non-nasal symptoms that are commonly seen in allergic rhinitis. Assessment of the primary endpoint for the single dose study (A00379) is Day 2, and for the multiple dose study (A00412), Day 1. The secondary endpoints are various permutations assessing post-treatment change from baseline over the 29 hour observation period. (Refer to section 6.5.3, Study Design, for an explanation of the efficacy parameters and the overall study design). The scoring systems for eligibility and post-exposure assessment are satisfactory and incorporate key allergic symptoms included in FDA guidance for the design of trials of drugs for allergic rhinitis.

6.4.3 Study Design

The study designs including allergen exposure (ragweed), study population, schema, inclusion/exclusion criteria, and efficacy parameters are analogous. Figure 3 presents a

schematic study diagram, and Figure 4 shows detail of the Phase III, the baseline and post-exposure portion of the study (A00412).

Figure 3. Schematic Study Diagram (A00412)

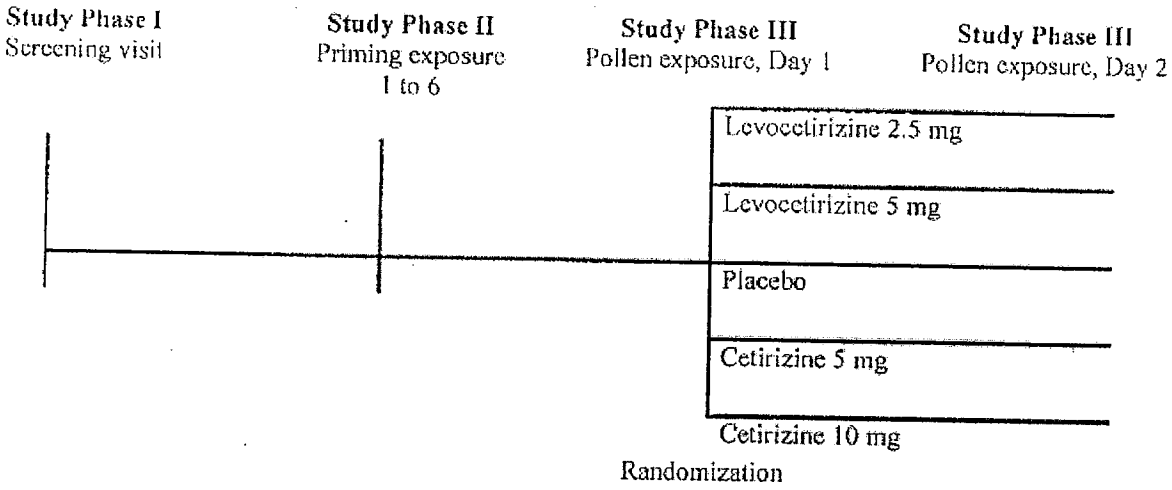
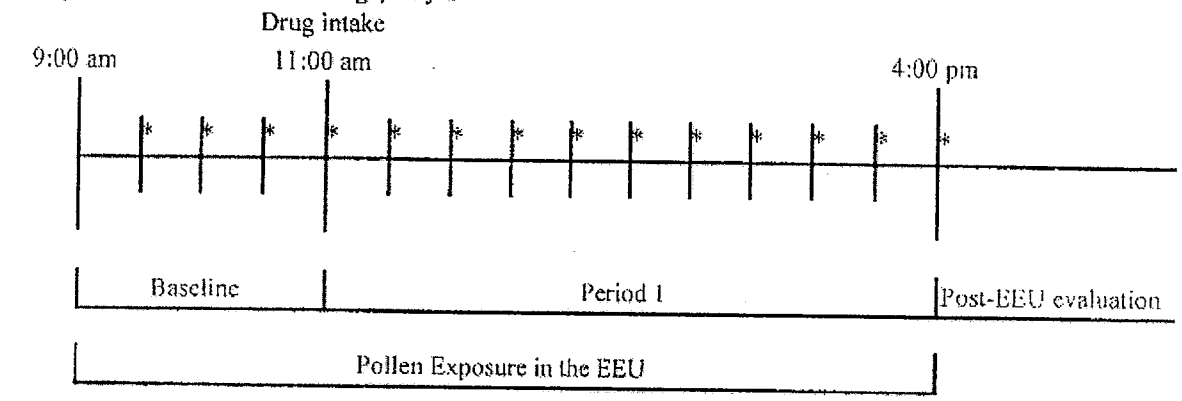
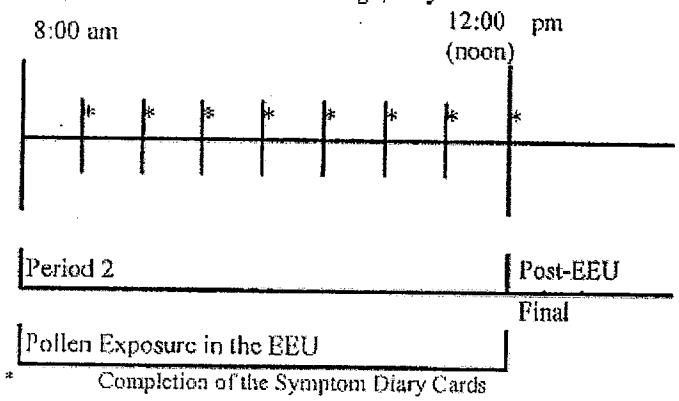


Figure 4. Diagram of Phase III (A00412)

Study Phase III: Pollen challenge, Day 1



Study Phase III: Pollen challenge, Day 2



There are two symptom scores: the Major Symptom Complex (MSC) Score and the Total Symptoms Complex (TSC) Score. The MSC is the efficacy assessment parameter and consists of the following six individual symptoms: runny nose (right and left), itchy nose (right and left), sniffles, nose blows, sneezes, and watery eyes. (Rhinorrhea, nasal pruritus, and sneezing are symptoms recommended for inclusion in allergic rhinitis scoring systems by FDA guidance). The TSC is the study eligibility parameter and includes the MSC and the following individual symptoms: itchy eyes and ears, itchy throat, cough, and postnasal drip. Nasal congestion severity is scored individually. Table 12 summarizes the symptoms severity rating system for the individual symptoms that comprise the MSC and TSC.

Table 12. Symptoms Severity Rating

Score	Intensity	Definition
0	None	No symptoms whatsoever
1	A little	Very mild symptoms which are barely noticeable and do not interfere with any activity
2	Moderate	Mild symptoms which are noticeable and do not interfere with any activity
3	Quite a bit	Symptoms which are bothersome and interfere slightly with activity

4	Severe	Symptoms which are very bothersome and interfere modestly with activity
5	Very severe	Symptoms which are very bothersome and disabling

The inclusion and exclusion criteria, and prohibited medications, are analogous to those of the other allergic rhinitis studies in this review. Pertinent to these two studies are subject age (16 years and older) and a minimum score of 18 on the TSC during the priming exposure and at the three 30-minute intervals just prior to treatment exposure in Phase III.

The study proceeds as follows:
Phase I is the screening visit to verify inclusion and exclusion criteria.
Phase II is the priming exposure phase. Subjects make one to six EEU visits to verify sensitivity to ragweed pollen challenge.
Phase III is the double-blind treatment and pollen challenge phase. This phase is two visits with pollen challenge after single drug exposure in the EEU and is divided into two study periods: Period 1 (Day 1), from drug intake to 5 hours after drug intake (11:00 AM – 4:00 PM), and Period 2 (Day 2), from 21 hours to 25 hours after drug intake (8:00 AM – 12 PM).

Treatments administered for study A0379 are LCTZ 5 mg tablets and placebo, and for study A00412, LCTZ 2.5 mg oral drops, LCTZ 5 mg tablets, CTZ 5 mg oral drops, CTZ 10 mg tablets, and placebo.

The study timeline is four periods:

- Baseline The four half-hourly pre-treatment values on Day 1 (9:30 AM to 11:00 AM)
- Period 1 The first 10 half-hourly post-dose measurements on Day 1 (11:30 AM to 4:00 PM)
- Period 2 The eight half-hourly post-dose measurements on Day 2 (8:30 AM to 12:00 PM)
- Period 1 + 2 The 18 half-hourly post-dose measurements on Day 1 (11:30 AM to 4:00 PM) and Day 2 (8:30 AM to 12:00 PM)

The primary efficacy variable for study A00412 is the mean change from baseline of the MSC over evaluation Period 1; for study A00379 it is the mean change from baseline of the MSC over Period 2. The secondary variables for the studies are numerous, with some overlap. Similar secondary endpoints for both studies are: 1) mean change from baseline in MSC over Period 2 and over Period 1 + 2, 2) change from baseline in TSC over Period 1, Period 2, and Period 1 + 2, and 3) change in baseline in individual scores over all three periods. Salient secondary endpoints specific to the multiple dose study (A00412) are comparative efficacy of the lower to higher dose of each active drug (for Period 1), pair-wise comparisons of the two lower active doses and the two higher active doses, and the dose-effect relationship for each of the active treatments.

Study A00379 randomizes 570 subjects as follows: placebo, 95; LCTZ 5 mg, 240; and CTZ 10 mg, 235. Study A00412 randomizes 551 subjects as follows: placebo, 78; LCTZ 2.5 mg, 116;

LCTZ 5 mg, 119; CTZ 5 mg, 119; and CTZ 10 mg, 119. The sample size determination for A00379 was chosen to provide 81% power to detect a 1.35 reduction from baseline in MSC for the primary endpoint at a 5% significance level. For study A00412, the sample size was chosen to provide 85% power to detect a 2 point reduction in MSC from baseline for the primary endpoint at a 5% significance level.

6.4.4 Efficacy Findings

Study A00379

For the primary endpoint both LCTZ and CTZ show statistically significant efficacy versus placebo ($p < 0.001$). However, the difference *between* LCTZ and CTZ is not statistically significant.

Study A00412

For the primary endpoint both doses of LCTZ and both doses of CTZ are statistically significantly better than placebo ($p < 0.001$), but there is no significant difference in effect size between LCTZ and CTZ at either dose comparison (LCTZ 2.5 mg and CTZ 5 mg; LCTZ 5 mg and CTZ 10 mg), and no evidence of dose-response: all four doses show similar efficacy versus placebo.

6.4.5 Efficacy Conclusions

Studies A00379 and A00412 show efficacy for all four treatment doses (LCTZ 2.5, 5 mg and CTZ 5, 10 mg) that is similar and statistically significant versus placebo. Study A00412, however, fails to demonstrate a difference in effect size when the lower doses of each drug are compared to the higher doses of each. Similarly, there is no evidence of dose-response for LCTZ or CTZ.

The inability to demonstrate an effect difference between LCTZ and CTZ indicates that these two studies cannot be used to support the Applicant's conclusion that LCTZ provides equivalent efficacy to CTZ at half the dose of CTZ and the efficacy and safety of LCTZ must be supported with independent studies.

Of note is that the applicant cites study A00379 for support of label onset-of-action and duration-of-effect claims. However, the applicant did not submit specific data for each time point in study 412, so there is no assurance of replication of the findings of study A00379. Results from EEU studies can be used to support an onset of action claim if replicated.

6.5 Additional Supporting Studies

This section will briefly review additional supporting studies of wheal and flare inhibition (A00373) and persistence-of-effect (A00264).

Study A00373

This is a Phase 1 PD study of wheal and flare inhibition in 18 allergic adult volunteers. The study design is a randomized, DB, PC three-way crossover approach comparing LCTZ 5 mg with desloratadine 5 mg and placebo. There are three single dose treatment periods separated by 14-21 day washout periods.

Primary efficacy is AUC (time-response curve) after allergen skin-prick from pre-dose to 24 hours post-dose between LCTZ, desloratadine, and placebo for wheal and flare areas. Efficacy analysis shows the largest mean wheal and flare areas 1.5 to 24 hours post-dose for placebo, and smallest for LCTZ. The difference in inhibition between LCTZ and desloratadine favors LCTZ and is statistically significant.

Study A00264

The applicant cites this study in support of an up to 6 month persistence-of-effect label claim for LCTZ 5 mg. This is a Phase 2 randomized, DB, PC, multi-center, parallel group quality of life exploratory trial comparing LCTZ 5 mg once daily and placebo in 509 subjects (placebo = 252; LCTZ 5 mg = 257) with PAR. The primary objectives compare the effects on health-related quality of life measured by change from baseline for the overall RQLQ score and the mean 24-hour reflective T5SS (sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal congestion) over four weeks of treatment. Secondary endpoints include RQLQ and T5SS assessments after various on-treatment intervals, including 3, 4.5, and 6 months.

The efficacy analysis shows statistically significant results favoring LCTZ over placebo for the primary endpoints. The analysis of secondary endpoints also favors LCTZ over placebo, but, while FDA requires evidence of efficacy over two weeks for SAR and four weeks for PAR, establishing persistence of effect over prolonged treatment durations (e.g. 6 months) is of dubious clinical relevance. There is high degree of variability in the allergic rhinitis population making a long duration of treatment less desirable for establishing efficacy. Furthermore, the study as designed with more than one primary efficacy endpoint does not establish appropriate statistical adjustments for multiplicity. This study, therefore, while supporting efficacy findings favoring LCTZ over placebo that are consistent with other adult allergic rhinitis trials in the development program, cannot be used to support a prolonged persistence-of-effect claim.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety findings from the safety review reveal adverse events previously reported with other oral antihistamines. The type of adverse events seen with LCTZ, based on this review, is of a similar type to those seen with the racemate, cetirizine.

Data sources for the safety review are the applicant's Integrated Summary of Safety (ISS), which includes data from 54 clinical studies (44 of which have been pooled for analysis), the clinical study safety assessments from the 12 confirmatory and supporting trials identified in this review, applicant-reported post-marketing reports, and a literature review.

All marketing experience with LCTZ is from foreign countries. The applicant states that none of the more than 80 countries that market LCTZ have withdrawn it for safety or efficacy reasons.

The ISS database contains 6,632 subjects receiving LCTZ or placebo. The pooled safety database consists of 4,067 subjects from 44 studies exposed to LCTZ from 1 day to 6 months; 1,871 (46 %) were male and 2,196 (54%) female. The mean subject age in the pooled database is 30 years; 243 (6%) are between 6 and 12 years of age, and only 64 (1.6%) subjects are 65 years or older. Approximately 90% are Caucasian. The applicant conducted no subgroup analyses for the safety variables.

Of the 4,067 pooled subjects, 3,134 received LCTZ 5mg, 484 received LCTZ 2.5 mg, and 438 received LCTZ 10 mg. An additional 688 subjects received LCTZ in four non-pooled studies, and six studies are ongoing at the time of the ISS cut-off date (March 31, 2006). Of the studies in the pooled data base, 25 are clinical pharmacology studies in healthy or allergic volunteers, 11 are short-term (one to six week) placebo-controlled, double-blind trials in subjects with SAR, PAR, and CIU, and two are long-term (4 to 6 month) trials in SAR or PAR subjects. About 75% of subjects in placebo-controlled trials received treatment for six weeks or less; no trials in the clinical development program exceeded six months.

Table 13 summarizes the safety assessments performed for the 12 clinical studies in the NDA review. Of note is that the total of 2,298 subjects exposed to LCTZ in the 12 studies represents 48.3% of the 4,755 subjects in the applicant's pooled and non-pooled databases of completed studies.

Table 13. Summary of Safety Assessments Performed in Reviewed Clinical Studies

Study Number	N exposed To LCTZ	AE	VS	PE	Pregnancy test	CBC	Alkaline phosphatase	SGOT/ SGPT	Total bilirubin	Direct bilirubin	Urea	Creatinine
A00268	119	√	√	√	√	√		√	√	√	√	√
A00266	150	√	√	√	√	√		√	√	√	√	√
A00303	89	√	√	√								
A00304	154	√	√	√								
A00269	81	√	√	√	√	√	√	√	√	√	√	√
A00270	194	√	√	√	√	√	√	√	√	√	√	√
A00412	235	√	√	√	√							
A00373	18	√	√	√	√							
A217	349	√	√	√	√	√	√	√	√		√	√
A00379	240	√	√	√	√							
A00265	391	√	√	√	√	√		√	√	√	√	√
A00264	278	√	√	√	√	√		√	√	√	√	√

TOTAL	2,298											

Eight randomized, placebo-controlled, double-blind, adult short-term (2 – 6 weeks) trials, representing all three indications, are analyzed separately, as they provide a reasonable approximation of proposed "real world use" of LCTZ (A217, A219, A222, A00265, A00266, A00268, A00269, A00270). These eight studies include 2,838 subjects, of whom 1,918 were exposed to one of three LCTZ doses: 2.5 mg (N = 425), 5 mg (N = 1,079), and 10 mg (N = 414).

Generally, the incidence of TEAE's is similar between placebo and LCTZ-treated groups. Headache and sedation-related side effects (somnolence/asthenia/fatigue) are the most common AE's across the eight studies; the incidence of headache is similar between placebo and LCTZ groups. In all eight studies sedation-related effects are more common in LCTZ than placebo-treated groups with an incidence range of 6.0% (A219, A222, A00266) to 17.2% (A00270) for LCTZ compared to a range of 1.2% (A00269) to 9.9% (A00265) for placebo. The incidence of sedation is greatest in subjects receiving LCTZ 10 mg, 15.0%, compared with 10.5% in the LCTZ 5 mg group and 7.3% in the LCTZ 2.5 mg group (overall incidence for placebo-receiving subjects was 3.7%) . There were 13 sedation-related dropouts in the LCTZ groups, 8 received 10 mg, 3 received 5 mg, and 2 received 2.5 mg. Pharyngitis and dry mouth also occurred more frequently in the LCTZ than placebo groups. Table 14 summarizes adverse events for the eight studies.

Table 14. Adverse events reported in ≥ 2%*of subjects, and more frequently in LCTZ – receiving subjects, from 8 placebo-controlled studies (1 – 4 weeks duration) in patients aged 12 years and older

Adverse event n (%)	**XYZAL 2.5 mg (n=425)**	**XYZAL 5 mg (n =1081)**	**Placebo (n = 920)**
Headache	41 (9.6%)	154(14%)	80 (9%)
Pharyngitis	30 (7%)	41 (4%)	33 (4%)
Somnolence	22 (5%)	65 (6%)	16 (2%)
Fatigue	4 (<1%)	37 (3%)	13 (1%)
Dry mouth	10 (2%)	15 (1%)	12 (1%)
Astenia	12(2%)	10 (<1%)	7 (<1%)

**Rounded to the closet unit percentage.*
Data from studies A00268, A00219, A217, A00265, A00266, A00269, A00270, A222

The occurrence of SAE's in the eight studies was low (N = 5) and included cholecystitis, appendicitis, peritonitis, self-inflicted injury, and elevated hepatic transaminase levels (which were also elevated at baseline). Thirty subjects discontinued a study due to a TEAE; 13 were sedation-related, and the 17 others included pregnancy (3), asthma (2), restlessness/agitation (2), cholecystitis (1), appendicitis (1), headache (1), heartburn (1), sciatica (1), uterine fibroma (1), pharyngitis (1), photosensitivity (1), insomnia (1), and one placebo subject with somnolence.

In the pooled safety database, most of the 4,067 subjects exposed to LCTZ, regardless of study indication, design, or duration, completed study participation (92.5%; N = 3,763). Adverse

events account for discontinuation of 71 subjects (1.7%). The incidence of adverse events is 42.0% (477 of 1137) and 43.0% (910 of 2114) in placebo and LCTZ groups, respectively, in the short-term (six weeks or less) placebo-controlled, double-blind trials. Table 15 summarizes reasons for discontinuation in the ISS population (from final study deposition form). The review notes the following: a higher percentage of subjects in the placebo group (13.5%) discontinued studies compared to the LCTZ groups (7.4%), and discontinuation for lack of efficacy is greater in the placebo compared to the LCTZ groups.

Table 15. Subject numbers and reasons for discontinuation ISS population

	Placebo (N = 2,565) n (%)	**LCTZ (2.5, 5, 10 mg daily) (N = 4,067) n (%)**
Completed studies	2,218 (86.5%)	3,763 (92.5%)
Discontinued from studies	345 (13.5%)	301 (7.4%)
Adverse event	49 (1.9%)	71 (1.7%)
Lack of efficacy	208 (8.1%)	129 (3.2%)
Protocol violation	2 (0.1%)	11 (0.3%)
Lost to follow-up	9 (0.4%)	18 (0.4%)
Withdrawal of consent for personal reasons unrelated to AE or efficacy	39 (1.5%)	34 (0.8%)
Other reason	38 (1.5%)	38 (0.9%)
Unknown	2 (0.1%)	3 (0.1%)

Headache is the most common treatment-emergent AE, and the incidence was similar between placebo (13.6%) and LCTZ (12.6%) groups. The most common adverse events in subjects 12 years and older from the pooled database with 2.5 mg or 5 mg per day LCTZ exposure (and more common than placebo exposure) are somnolence/fatigue/asthenia (10.4%), and dry mouth (1.2%). In three dose-ranging studies (A217, A00265, and A00270), subjects receiving LCTZ 10 mg per day had a higher incidence of somnolence/fatigue/asthenia than subjects in the LCTZ 2.5 mg and 5 mg per day groups. Somnolence was also more common in pediatric subjects (6-12 years) receiving LCTZ than placebo (2.9%). Given that all the LCTZ doses in the two pediatric allergic rhinitis confirmatory studies are 5 mg per day (the same dose as most adult subjects), somnolence is likely under-reported, given the constraints of subject reporting in pediatric clinical trials. In one of two pediatric confirmatory studies (A00303), epistaxis occurred more frequently in the LCTZ group (5.6%, n = 5) than placebo group (1.1%, n = 1); it was not reported in any subjects in the companion study, A00304), and it is unclear that this finding in one pediatric study is clinically relevant. (In the adult confirmatory studies of the LCTZ 5 mg dose for SAR, PAR, and CIU, given from two to six weeks, the incidence of epistaxis was 1.5% for placebo and 1.2% for LCTZ). Sixty-four subjects (out of 4,067; 1.6%) in the pooled database permanently discontinue LCTZ for an AE recorded on AE forms. The most common reasons for discontinuation are somnolence/fatigue/asthenia (n = 29) and headache (n = 7).

Sixty-four subjects (out of 4,067; 1.6%) in the pooled database permanently discontinue LCTZ for an AE recorded on AE forms. The most common reasons for discontinuation are

somnolence/fatigue/asthenia (N = 29) and headache (N = 7). Table 16 summarizes those from the ISS with treatment-emergent adverse events (TEAE's) permanently discontinuing a study.

Table 16. Number (%) of subjects with TEAE's and permanent study discontinuation recorded on adverse event forms

System Organ Class Preferred Term	Placebo N = 2565 N (%)	LCTZ N = 4,067 N (%)
# Subjects Permanently Discontinue due to TEAE	**51 (2.0%)**	**64 (1.6%)**
Eye Disorders		
Conjunctivitis	2 (0.1%)	0
Gastrointestinal Disorders		
Abdominal pain	0	2 (< 0.1%)
Dry mouth	0	2 (< 0.1%)
Nausea	3 (0.1%)	1 (< 0.1%)
Vomiting	0	2 (< 0.1%)
General Disorders		
Asthenia	1 (< 0.1%)	4 (0.1%)
Fatigue	2 (0.1%)	4 (0.1%)
Infections		
Bronchitis	3 (0.1%)	0
Nasopharyngitis	4 (0.2%)	3 (0.1%)
Sinusitis	1 (< 0.1%)	1 (< 0.1%)
Nervous System Disorders		
Headache	3 (0.1%)	7 (0.2%)
Somnolence	2 (0.1%)	21 (0.5%)
Pregnancy	1 (< 0.1%)	8 (0.2%)
Respiratory		
Asthma	9 (0.4%)	1 (< 0.1%)
Pharyngolaryngeal pain	0	2 (< 0.1%)
Rhinitis	3 (0.1%)	0
Skin and Subcutaneous Disorders		
Pruritus	3 (0.1%)	1 (< 0.1%)
Urticaria	2 (0.1%)	0

The pooled study database shows 15 LCTZ-exposed subjects with treatment emergent serious adverse events (placebo groups report 12 serious adverse events). Study investigators do not attribute LCTZ or placebo to any of the events, and, with the exception of an elevated hepatic transaminase (ISS# 2112, Table 17), this seems plausible. Table 17 summarizes subjects with LCTZ-exposed serious adverse events from all studies. Of the two subjects with "head injury," one (ISS # 3916, study A00264) was in a parked car struck by an out-of-control vehicle. A complete report on subject number 5602 (study A00333) is unavailable. A review of CRF's for the subjects listed in Table 17 suggests that somnolence/fatigue/asthenia, the most common adverse events in the LCTZ groups, and the ones most likely to cause study discontinuation, did not have a significant role in the serious adverse events reported from all studies.

Table 17. Summary of LCTZ subjects with serious adverse events (all studies)

ISS #	Study	Age/Sex	MeDRA Preferred Term	Dose (mg/day)	Onset (Days)	Action Taken
1131	A00270	43.4/F	Ankle fracture	5	2	DC
2011	A00270	36.0/F	Peritonitis	10	18	None
2112	A217	30.5/M	Alanine aminotransferase increased	10	15	None
3186	A219	25.1/F	Cholecystitis	5	4	DC
5602	A00333	20.5/M	Head injury	5	20	None
6120	A00265	12.7/M	Acute appendicitis	5	22	None
464	A00306	55.6/M	Inguinal hernia	5	68	None
1758	A00264	38.0/F	Appendicitis	5	132	N/A
3369	A00264	28.8/F	Abortion induced	5	90	N/A
3916	A00264	26.3/F	Tympanic membrane disorder Retinal detachment Head injury	5	218	N/A N/A None
3985	A00264	25.9/M	Abnormal coordination Hemianopia Migraine	5	79	None None None
5386	A00264	19.9/F	Abdominal pain	5	20	None
5440	A00264	19.6/M	Acute appendicitis	5	15	None
5691	A00306	20.8/M	Testicular torsion	5	33	N/A
6697	A00315	2.0/F	Pneumonia	2.5	40	N/A

See section 7.1.7 (Laboratory Findings) for a discussion of treatment-emergent laboratory abnormalities.

7.1.1 Deaths

No on-treatment deaths occurred in the clinical development program. A 12 year-old boy died from accidental electrocution [redacted] after the last study dose of placebo (study A00304).

The post-marketing database reports three fatalities: a patient undergoing chemotherapy for non-Hodgkin's lymphoma died from complications of thrombocytopenia, a 71-year old patient died from a cerebrovascular accident, and a 75-year old female on LCTZ (dose and length of treatment not reported) and 10 concomitant medications developed hepatitis leading to death from hepatic failure.

7.1.2 Other Serious Adverse Events

See section 7.1, text and Table 16, for serious adverse events that occur in clinical trials and are included in the ISS pooled database.

This section summarizes reports from the UCB Global Drug Safety database (which contains 747 post-marketing case reports, 650 submitted with the NDA, and 97 with the 120-Day Safety Update), that may meet the definition of serious adverse event in 21 CFR 312.32(a).

A) Somnolence/Fatigue/Asthenia: Of the 650 cases in the original UCB post-marketing database, 107 (16.5%) report somnolence, fatigue, asthenia, or malaise. (The 120-Day Safety Update states that an additional 97 cases of all types have been reported, but summarizes by MedDRA System, Organ, Class, not preferred term, and it is unclear how many additional sedation-related events have been reported). Two cases are singled out due to altered consciousness while on LCTZ therapy: an 81-year-old male (8000877) reported difficulty awakening in the morning after taking LCTZ at bedtime (dose and treatment duration unspecified), and a 40-year-old male experienced a 30-minute loss of consciousness after two months of LCTZ therapy (dose unspecified); LCTZ was discontinued and no further details are provided in the report. Also listed in the post-marketing database section on somnolence are six reports describing traffic accidents; three of these indicate patients experienced somnolence, "feeling drunk," or "in a trance" before the accident.

B) Anaphylaxis: Six reports involve anaphylaxis, and one is consistent with anaphylactic shock. The following discussion summarizes all pertinent clinical data provided in the ISS. The anaphylactic shock report is of a 30-year-old female (8003066) developing life-threatening bronchospasm, dyspnea, hypotension, and angioedema 30 minutes after taking a single LCTZ 5 mg tablet for allergic symptoms. She was successfully treated with full recovery over six hours; re-challenge three months later with LCTZ 2.5 mg is positive for generalized urticaria.

Of the five remaining cases, three involve hypersensitivity events with positive dechallenge (8006870, 8008226, 8011391, and 8003066). One (a 29 year-old pregnant female, 8006870) developed hypotension, dyspnea, nausea, and vomiting five minutes after taking LCTZ 5 mg and had resolution of symptoms on the same day without specific therapy; LCTZ was withheld and no additional symptoms occurred. In another case, an 18-year-old female (8008226) developed anaphylaxis requiring treatment with "adrenaline" after taking one 5 mg LCTZ tablet. A 27-year-old female (8011391) developed oropharyngeal edema and dyspnea after LCTZ treatment (dose and duration unspecified); she was treated with IV corticosteroids and other unspecified medications and recovered. Of the last two cases, one (a 19-year-old-male, 1003120) taking LCTZ (dose and duration unspecified) for acute urticaria developed dyspnea. The patient was hospitalized and treated with IV corticosteroids, and clemastine. The 6th case is that of a 32-year-old female, 1003125 who experienced an "anaphylactic reaction" after taking LCTZ (dose and treatment duration unspecified), acetylsalicylic acid, and budesonide inhaler; she recovered and continued treatment with LCTZ.

Laboratory and ECG abnormality discussions are below (sections 7.1.7 and 7.1.9, respectively).

C) Dermatologic Reactions: The post-marketing database contains 107 reports of skin and subcutaneous tissue disorders: 27 for pruritus, 25 for urticaria, 22 for unspecified rash, and 10 for angioneurotic edema. Of the 25 cases of urticaria, 18 were in females and 7 in males. Six were generalized, one localized, and 18 unspecified. Six cases required treatment with intravenous corticosteroids (one of whom is described above, 8008226), with five recovering, and one whose outcome is unknown (8006887): a 22 year-old female (8015362) developed urticaria one day after starting LCTZ therapy (dose unspecified); a 57 year-old female (8015417) with a history of urticaria experienced an exacerbation after a single LCTZ dose (unspecified); a 50 year-old male (8008547) with a history of urticaria to LCTZ (dose unspecified) underwent a positive in-hospital rechallenge, developing generalized urticaria after a single LCTZ dose (unspecified); a 33 year-old female (8010223) with a history of pruritus and urticaria after CTZ exposure developed generalized pruritus and urticaria one hour after in-hospital LCTZ 10 mg provocation; and a 36 year-old female (8006887) treated with LCTZ 5 mg (duration unspecified, but it appears to be a single dose) who developed urticaria and angioedema on the same day.

The 22 reports of rash are not individually detailed but include cases of erythematous, macular, papular, maculo-papular, and vesicular variants. No significant details regarding LCTZ dose or duration are included; 15 had positive dechallenge.

There are 10 reports of angioneurotic edema, three of which are insufficiently documented. The seven remaining include (8006887 is discussed above): a 56 year-old female (1006229) with a history of Quincke's edema who developed angioneurotic edema and was placed on LCTZ therapy (dose unspecified) without resolution; a 56 year-old female developed angioneurotic edema after first LCTZ exposure (dose unspecified) with resolution upon drug cessation; and a 14 year-old boy (8012192) on chronic LCTZ therapy for recurring urticaria (dose unspecified) who developed angioedema after ibuprofen exposure. The last three cases involve an 18 year-old male (8006727), a 27 year-old female (8011391), and a 49 year-old female (8002832), all of whom developed angioedema after a first LCTZ dose (all unspecified); all three recovered after dechallenge and intravenous corticosteroid therapy.

Laboratory and ECG abnormality discussions are below (sections 7.1.7 and 7.1.9, respectively).

7.1.3 Dropouts and Other Significant Adverse Events

Table 15 (section 7.1) summarizes the 64 LCTZ subjects from the pooled database dropping out of studies for treatment-emergent adverse events.

The applicant classified only four pregnancies diagnosed while on treatment as TEAE's. However, the applicant's ISS states that a total of eight subjects on LCTZ from the pooled and un-pooled databases became pregnant during studies. All eight subjects were discontinued from study participation, and it is unclear why only four were designated as TEAE's by the applicant.