Appendix 1.E. 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."

**Page citations in this review refer to A00270.pdf, unless otherwise specified.*

Overview

The purpose of this four-arm parallel group superiority study is to confirm the effectiveness, over placebo, of at least one dose of levocetirizine dihydrochloride (LCTZ; 2.5 mg, 5 mg, or 10 mg) oral tablets taken once daily in the evening in treating the symptoms and signs of chronic idiopathic urticaria (CIU) in adults 18 years and older. The primary efficacy analysis assesses change from baseline in adjusted mean subject-rated pruritus severity scores (reflective, prior 24 hours) over the first treatment week *and* over the total four week treatment period in the three LCTZ groups vs. placebo. Eligibility for randomization requires moderate to severe pruritus and urticaria be present on at least three days between Visit 1 (V1) and Visit 2 (V2).

Study Dates

March 2, 2001 – March 15, 2002
Investigators: Thirty-five investigators from 35 centers in France enroll subjects. The study follows good clinical practice (GCP) guidelines and regular monitoring visits to study centers are made (p 43).

Amendments

There are three protocol amendments:
Amendment 1: Cancels UK participation.
Amendment 2: Extends the study recruitment period and adds 10 additional investigators to permit enrollment of the appropriate number of subjects. Investigators may enroll more than 16 subjects; the original protocol maximum is eight (pp 46-47).
Amendment to the statistical analysis plan (SAP): Removes the term "centers" from the analysis of covariance due to the large number of centers with less than the original protocol minimum of eight subjects. The amendment groups centers with less than eight subjects for a sensitivity analysis of covariance for consistency of treatment effect which includes center, and interaction of center, by treatment (p 1025).

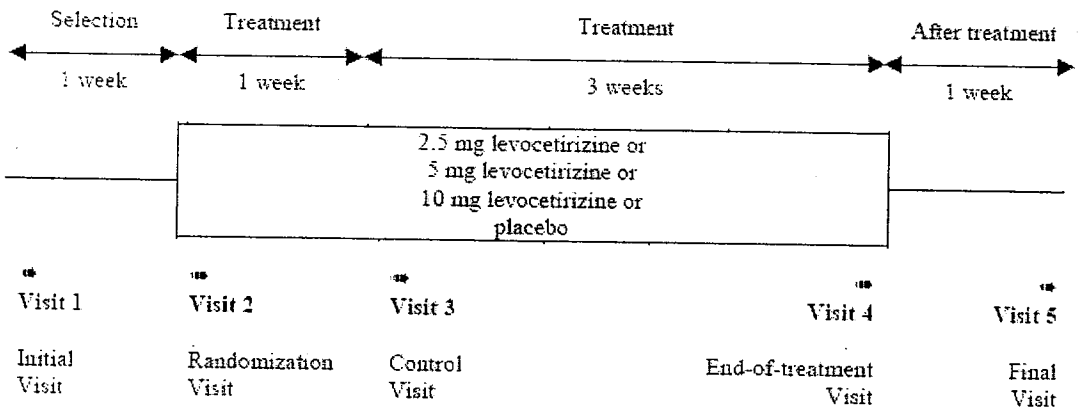
Protocol

The protocol describes a multi-center, randomized, double-blind, placebo-controlled, four-arm parallel group study in adults (18 years and older) to demonstrate the superiority at least one dose of LCTZ (2.5 mg, 5 mg, or 10 mg) once daily in the evening, over placebo, in treating the 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 study doses and evening administration are chosen to be consistent with previous (unspecified) studies in subjects with seasonal and perennial allergic rhinitis (p 34).

The study period (see Study Diagram, below) spans six weeks; during four consecutive weeks (weeks two through five) subjects receive LCTZ 2.5 mg, 5 mg, 10 mg, or placebo. The first study week (V1 to V2) screens subjects for eligibility and obtains baseline symptom scores. Subject must have symptoms on at least three of the days during the week between the screening (V1) and randomization (V2) visits for enrollment eligibility. Randomization to a study arm and onset of treatment begins at V2. Visit 3, one week after Visit 2, is a multi-purpose visit: Investigator performs physical and specific examinations (as per V1), reviews the subject's Daily Record Card (DRC), records AEs and concomitant medications, and dispenses the second container of study medication for subjects continuing in the study. Visit 4, the end of treatment visit, is similar in scope to V3, but also includes blood sampling for safety laboratory tests, per protocol pregnancy testing, and recording of the subject's global evaluation of treatment. The final visit (V5) occurs one week after completion of the four week treatment period. Investigator reviews laboratory tests obtained on the final day of treatment (V4) and repeats general physical and specific examinations (as in V1).

Schematic study diagram



Patient Population: The study population includes men and women 18 years and older with a history of CIU (see next section). In addition to the general inclusion criteria for clinical trials, the protocol requires female subjects to have a negative pregnancy test and to be following a medically acceptable method of contraception if of child-bearing potential. Screening laboratory results are available and in the clinically acceptable reference range prior to randomization (p 31).

Chronic Idiopathic Urticaria: Subject is eligible for the study if a history 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)

is present. The following CIU criteria are met at the randomization visit (V2): at least three days with moderate or severe pruritus and wheals present during the one-week baseline (V1 to V2) period (i.e., a 24 hour reflective pruritus score ≥ 2 [scale = 0-3, with 3 being severe], and, a number of wheal score ≥ 1 [from 1-6 wheals present]). Prohibited medication throughout the treatment period (V1 through V4), and before the start of the study (washout period in parentheses), are: astemizole (12 weeks), systemic and topical corticosteroids (four weeks), ketotifen (two weeks), doxepin (10 days), and other systemic antihistamines, both H_1 and H_2, (0 days). The protocol permits all other medications. Subject records concomitant medications in the DRC, and Investigator in the Case Report Form (CRF). The protocol provides no relief or rescue medicines (pp 31-32, p 35).

Exclusions: Exclusion criteria (in addition to the general exclusion criteria of clinical trials) include: senile pruritus, urticaria not consistent with CIU (e.g., acute; cholinergic, solar, heat, cold water, or drug-induced; delayed pressure; or contact urticaria), urticarial vasculitis, hereditary angio-neurotic edema, urticaria refractory to anti-histamines, dermatologic disease that interferes with evaluation of therapeutic response, autoimmune disorders, lymphoma, leukemia, generalized cancer, or presence of another clinically significant disease disturbing absorption, distribution, metabolism, or excretion of the investigational drug. Exclusions at the randomization visit (Visit 2) include: baseline period (V1—V2) shorter than three or longer than nine days, no record (for at least three distinct days) of pruritus score ≥ 2 and/or the number of wheal scores ≥ 1 (see below for explanation of scoring system), or for use of prohibited medications during baseline (p 32).

Study Procedure

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

(pp 992-993)

Definition of baseline period and scores: The baseline period spans V1 (the initial screening visit) and V2 (the randomization visit), and can not be shorter than three days or longer than nine days. The protocol requires eligible subjects to record (in the DRC) at least three days of

moderate to severe pruritus (24 hour reflective; severity score ≥ 2) and an instantaneous number of wheal score of ≥ 1 (see Efficacy Parameter Scales, above).

Visit 1: Initial selection visit. The Investigator screens subject for eligibility: verifies inclusion and exclusion criteria, confirms presence of pruritus and wheals, assesses other baseline parameters (e.g., presence of dermatographism, pressure association), performs safety laboratory tests, and records concomitant medications and AEs. Subject completes exploratory variables questionnaires, receives daily record card (DRC), evaluates and records average severity and duration of pruritus score (24 hour reflective), lists concomitant medication use and AEs, and receives an appointment for V2 [one week later] (pp 28-29).

Visit 2: Randomization visit. Subject returns with DRC; randomization occurs if symptoms and signs of CIU are present in the preceding week per inclusion criteria, laboratory results are available and in the clinically acceptable range, and, for females, the pregnancy test is negative. Investigator randomizes eligible subjects to either LCTZ 2.5, 5, or 10 mg oral tablets (once daily in the evening), or matching placebo, assigns a treatment number, and gives a container of study medication corresponding to the first week of treatment (p 29).

Visit 3: Control visit. Occurs one week after treatment begins. Investigator completes per protocol physical and specific examinations (as in V1), records AEs and concomitant medications, verifies the DRC, collects and tabulates the first container of study medication, records exploratory endpoint parameters, and gives continuing subjects another DRC and second study medication container (pp 29-30).

Visit 4: End-of-treatment visit. Occurs three weeks after V3. Investigator completes per protocol examinations, collects DRC, verifies (against DRC) and records AEs and concomitant medications in the CRFs, collects and tabulates the second container of study medication, assesses exploratory endpoint parameters, and distributes DRC for final week (a non-treatment week) AEs and concomitant medications. Subject complete global evaluation of treatment questionaire, comparing current disease state with baseline condition at V2 [using a seven-point scale, see below for details] (p 30).

Visit 5: Final visit. Investigator verifies laboratory tests from V4, completes per protocol examinations, records (in the CRF) AEs and concomitant medications from the subject DRC (p 30).

Statistical and Analytical Plan

Efficacy Parameters: The primary efficacy variables are the mean of the daily patient-recorded (in DRC) 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 three LCTZ arms versus the placebo arm (pp 44-45).

Reviewer comment:

The designation of pruritus severity over the first treatment week, and over the total treatment period, as the two primary endpoints is not appropriate, since pruritus represents but one indicator of CIU. A more appropriate set of primary endpoints for the CIU indication is pruritus severity and number of wheals, thus including both a subjective and objective measure for efficacy assessment.

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 (p 45).

Other secondary endpoints, evaluated at each visit, are Investigator variables including pruritus score, number and size of wheals, presence of dermatographism, Quincke's edema, and pressure association (p 45).

Safety Assessments: Safety parameters include assessment of adverse events throughout the study and the following laboratory assessments from V1 and V4: biochemistry (AST/SGOT, ALT/SGPT, total and direct bilirubin, urea, and creatinine), hematology (hemoglobin, hematocrit, RBCs, WBCs, differential, platelets), and per protocol pregnancy tests. Electrocardiograms were not performed (p 42).

Medication Compliance: Subject returns medication container and unused medication to the Investigator at V3 and V4. Investigator counts and records remaining tablets in subject's presence [for ease of reconciling discrepancies] (p 35).

Primary Efficacy Analysis: Primary efficacy variables analysis is on the ITT and PP populations. The ITT population consists of all randomized subjects taking at least one dose of study medication; the PP population is a subset of the ITT population consisting of those subjects with no major protocol violations affecting the primary efficacy variable (pp 43-44). 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 (see Amendment to SAP, p 1, above). 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 (p 44). 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 (p 45).
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 (P 84).

Secondary Efficacy Analysis: 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 (p 45).
A frequency table summarizes Investigator-observed secondary endpoints (p 45).

Sample Size Determination: 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% (p 46).

Results

Patient Disposition: 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 (see Table 1, below).

Table 1. Number (%) of subjects discontining study by reason and treatment

Reason	Placebo (N = 63)	LCTZ 2.5 mg (N = 70)	LCTZ 5 mg (N = 65)	LCTZ 10 mg (N = 59)	Total (N = 257)
Lack of efficacy	20 (31.7%)	10 (14.3%)	4 (6.2%)	3 (5.1%)	37 (14.4%)
AE	2 (3.2%)	2 (2.9%)	1 (1.5%)	5 (8.5%)	10 (3.9%)
Other	2 (3.2%)	0	2 (3.1%)	1 (1.7%)	5 (1.9%)
Withdrawal of consent	1 (1.6%)	0	0	1 (1.7%)	2 (0.8%)
Lost to F/U	1 (1.6%)	0	0	0	1 (0.4%)

(p 49)

Protocol Deviations: Investigators identify major and minor protocol violations prior to un-blinding of the database. The most common pre-randomization violation is baseline score out of range. After randomization 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. Other frequent major

protocol violations are over-compliance (> 120%) or unknown compliance, use of proscribed medication during the baseline period, insufficient washout time, or missing DRC (pp 49-50).

Treatment Compliance: Compliance is the ratio of the number of tablets actually taken by the subjects over the number of tablets specified in the protocol. 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 (p 59).

Demographics: The average age of the 257 ITT subjects is 41.4 years (range 18.2 – 85.1). More females than males are in the study, 72.4% versus 27.6%, respectively). Habit parameters (tobacco use, alcohol and caffeine consumption) are equally distributed among the four groups. Demographic characteristics are summarized in Table 2.

Table 2. Summary of demographic characteristics – ITT population

Demographic Characteristic	Placebo (N = 63)	LCTZ 2.5 mg (N = 70)	LCTZ 5 mg (N =65)	LCTZ 10 mg (N = 59)	Total (N = 257)
Age: mean	42.1	40.1	42.5	40.9	41.4
range	18.8-76.4	18.2-74.7	18.7-80.6	18.6-85.1	18.2-85.1
Gender:					
Female	42	54	44	46	186
Male	21	16	21	13	71
Ethnicity:					
Asian	2	4	3	3	12
Black	4	1	2	3	10
White	56	61	59	51	227
Other	1	4	1	2	8
Weight (kg)					
Mean	69.4	66.4	66.5	65.8	67
Range	48-120	50-106	48-100	42-114	42-120
Height (cm)					
Mean	166.7	164.3	166.4	163.8	165.3
Range	148-192	151-187	150-189	148-178	148-192

(p 52)

Concomitant Medications: The most commonly used medications during the study treatment period are sex hormones and related therapies (39.7%), analgesics (31.5%), other gynecologicals (19.5%), and systemic anti-histamines (15.6%). More subjects in the placebo group (28.6%) take anti-histamines compared to the LCTZ groups (2.5 mg, 14.3%; 5 mg, 9.2%; 10 mg, 11.9%). See Table 3 for detailed summary.

Table 3. Concomitant drug use (therapeutic class) by > 5% of any study arm

Therapeutic Class	Placebo (N = 63) %	LCTZ 2.5 mg (N = 70) %	LCTZ 5 mg (N = 65) %	LCTZ 10 mg (N = 59) %
Analgesics	27	31.4	36.9	30.5

Antacids	3.2	7.1	13.8	10.2
Antiasthmatics	4.8	4.3	6.2	8.5
Antibacterials	6.3	8.6	7.7	11.9
Antihistamines (Systemic)	28.6	14.3	9.2	11.9
Antiinflammatories	11.1	14.3	7.7	10.2
Anticholinergics	7.9	4.3	4.6	5.1
Antithrombotics	7.9	2.9	4.6	0
Beta blockers	6.3	5.7	3.1	3.4
Calcium channel blockers	6.3	1.4	3.1	0
Corticosteroids (Topical)	0	2.9	1.5	5.1
Endocrine Therapy	9.5	57	3.1	8.5
Nasal preparations	6.3	2.9	7.7	5.1
Ophthalmologicals	4.8	8.6	7.7	8.5
Other gyn	15.9	24.3	18.5	18.6
Psycholeptics	12.7	2.9	3.1	6.8
Serum lipid reducers	7.9	5.7	10.8	5.1
Sex hormones	31.7	38.6	38.5	50.8
Thyroid therapy	4.8	2.9	6.2	5.1
Vasoprotectives	3.2	7.1	13.8	3.4

(pp 153-156)

Primary Efficacy Results

Change from baseline in mean pruritus severity over the previous 24 hours during the first week of treatment [per subject DRC] (ITT population):

Pruritus severity over the first week of treatment decreases significantly more in all three LCTZ arms than in the placebo arm. 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 ($p > 0.10$). Results are summarized in Table 4, below.

Table 4. Mean pruritus severity (24 hour reflective) during first treatment week

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

Change from baseline in mean pruritus severity score over the previous 24 hours during the total treatment period [per subject DRC] (ITT population):
For the total treatment 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. The result of the PP analysis is consistent with the results of the analysis of the ITT population. See Table 5, below, for details.

Table 5. Mean pruritus severity (24 hour reflective) during total treatment period

Period	Treatment	N	Mean (SD)	Adjusted mean[a]	Diff. vs. Placebo[b] [98% CI]	p-value[c]
Baseline	Placebo	60	2.25 (0.50)			
	LCTZ 2.5 mg	69	2.08 (0.53)			
	LCTZ 5 mg	62	2.07 (0.50)			
	LCTZ 10 mg	55	2.04 (0.57)			
Total Treatment Period	Placebo	60	1.89 (0.74)	1.84		
	LCTZ 2.5 mg	69	1.00 (0.78)	1.02	0.82 [0.53;1.11]	< 0.001
	LCTZ 5 mg	62	0.91 (0.71)	0.92	0.91 [0.62;1.21]	< 0.001
	LCTZ 10 mg	55	0.70 (0.57)	0.73	1.11 [0.81;1.41]	< 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 63)

Reviewer comment:
There is no statistical evidence to suggest that outliers drive the primary efficacy assessment. The use of an efficacy parameter scale with a narrow range (0-3 for pruritus severity) mitigates against an outlier effect. Furthermore, more subjects discontinue the study due to 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.

The applicant analyzes three populations: the ITT population (defined as that population consisting of all randomized subjects who took at least one dose of study medication) not accounting for missing data, the ITT population using LOCF methodology to account for missing data, and the PP population. All three analyses show statistically significant efficacy favoring LCTZ. This approach seems reasonable since most of the missing data relate to subjects in the placebo group dropping out for lack of efficacy.

Secondary Efficacy Results

Change from baseline in mean pruritus severity over the previous 24 hours during weeks 2, 3, and 4:
Analysis of the differences for LCTZ versus placebo in the ITT population favors LCTZ for all three doses, and for all three weeks of comparison. More dropouts for lack of efficacy occur in

the placebo group than in any LCTZ group; a LOCF analysis of all dropouts for lack of efficacy suggests that the treatment effect of LCTZ may be underestimated (p 65).

Change from baseline in mean number of wheals by treatment week and for the total treatment period:

Comparisons of difference from baseline in the mean number of wheals by LCTZ group compared to placebo in the ITT population support all three doses of LCTZ being 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 (pp 67-68). Results are summarized in Table 6, below.

Table 6. Mean number of wheals by treatment week and total treatment period

Period	Treatment	N	Baseline Mean (SD)	Mean (SD)	Adjusted Mean[a]	Diff vs. Placebo[b] [98% CI]	p-value[c]
Week 1	Placebo	61	1.97 (0.93)	1.83 (0.93)	1.83		
	LCTZ 2.5 mg	69	1.98 (0.72)	1.16 (0.97)	1.15	0.68 [0.36; 1.10]	< 0.001
	LCTZ 5 mg	64	1.91 (0.66)	0.89 (0.79)	0.92	0.91 [0.58; 1.23]	< 0.001
	LCTZ 10 mg	55	1.97 (0.75)	0.91 (0.87)	0.90	0.93 [0.59; 1.26]	< 0.001
Week 2	Placebo	43	2.02 (0.79)	1.45 (0.94)	1.42		
	LCTZ 2.5 mg	61	1.93 (0.72)	0.91 (0.90)	0.92	0.50 [0.12; 0.88]	0.002
	LCTZ 5 mg	62	1.92 (0.66)	0.99 (0.87)	1.01	0.41 [0.03; 0.79]	0.012
	LCTZ 10 mg	50	1.96 (0.77)	0.78 (0.84)	0.78	0.64 [0.25; 1.04]	< 0.001
Week 3	Placebo	36	2.06 (0.80)	1.32 (0.88)	1.27		
	LCTZ 2.5 mg	59	1.89 (0.70)	0.86 (0.90)	0.89	0.38 [-0.10; 0.81]	0.036
	LCTZ 5 mg	62	1.92 (0.66)	0.99 (0.96)	1.00	0.27 [-0.15; 0.70]	0.131
	LCTZ 10 mg	48	1.97 (0.76)	0.63 (0.85)	0.62	0.65 [0.21; 1.10]	< 0.001
Week 4	Placebo	35	2.06 (0.82)	1.24 (1.06)	1.19		
	LCTZ 2.5 mg	55	1.91 (0.72)	0.83 (0.90)	0.86	0.34 [-0.10; 0.77]	0.071
	LCTZ 5 mg	58	1.93 (0.68)	0.97 (0.90)	0.98	0.21 [-0.22; 0.64]	0.256
	LCTZ 10 mg	48	1.97 (0.76)	0.63 (0.83)	0.62	0.57 [0.12; 1.02]	0.003
Total Treatment Period	Placebo	61	1.97 (0.78)	1.68 (0.89)	1.68		
	LCTZ 2.5 mg	69	1.98 (0.72)	1.08 (0.91)	1.07	0.61 [0.30; 0.93]	< 0.001
	LCTZ 5 mg	64	1.91 (0.61)	0.96 (0.79)	0.99	0.69 [0.37; 1.01]	< 0.001
	LCTZ 10 mg	56	1.98 (0.75)	0.81 (0.82)	0.80	0.88 [0.55; 1.21]	< 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 68)

Change from baseline in mean size of wheals by treatment week and during the total treatment period:

Comparisons of difference from baseline in the mean size of wheals by LCTZ group compared to placebo in the ITT population show results similar to those obtained with the number of wheals. Results 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 (p 69). Results are summarized in Table 7, below.

Table 7. Mean size of wheals by treatment week and total treatment period

Period	Treatment	N	Baseline Mean (SD)	Mean (SD)	Adjusted Mean[a]	Diff vs. Placebo[b] [98% CI]	p-value[c]
Week 1	Placebo	60	2.10 (0.65)	1.84 (0.83)	1.76		
	LCTZ 2.5 mg	69	1.90 (0.70)	1.09 (0.96)	1.10	0.66 [0.33; 0.99]	< 0.001
	LCTZ 5 mg	60	1.83 (0.72)	0.90 (0.84)	0.94	0.82 [0/48; 1.17]	< 0.001
	LCTZ 10 mg	57	1.83 (0.75)	0.81 (0.72)	0.85	0.92 [0.57; 1.26]	< 0.001
Week 2	Placebo	42	2.12 (0.70)	1.52 (0.91)	1.44		
	LCTZ 2.5 mg	60	1.89 (0.72)	0.94 (0.95)	0.95	0.49 [0.10; 0.88]	0.004
	LCTZ 5 mg	60	1.85 (0.71)	1.01 (0.91)	1.04	0.40 [0.04; 0.79]	0.019
	LCTZ 10 mg	51	1.81 (0.78)	0.69 (0.70)	0.72	0.71 [0.31; 1.12]	< 0.001
Week 3	Placebo	35	2.19 (0.71)	1.43 (0.87)	1.32		
	LCTZ 2.5 mg	58	1.87 (0.72)	0.89 (0.93)	0.91	0.41 [-0.01; 0.88]	0.022
	LCTZ 5 mg	58	1.85 (0.72)	0.97 (0.95)	1.00	0.32 [-0.10; 0.73]	0.077
	LCTZ 10 mg	49	1.85 (0.77)	0.54 (0.71)	0.57	0.75 [0.32; 1.18]	< 0.001
Week 4	Placebo	34	2.19 (0.72)	1.30 (1.07)	1.19		
	LCTZ 2.5 mg	55	1.90 (0.72)	0.88 (0.98)	0.90	0.30 [-0.15; 0.74]	0.122
	LCTZ 5 mg	54	1.87 (0.73)	0.96 (0.94)	0.99	0.21 [-0.24; 0.65]	0.285
	LCTZ 10 mg	49	1.85 (0.77)	0.52 (0.68)	0.56	0.64 [0.18; 1.09]	0.001
Total Treatment Period	Placebo	60	2.10 (0.65)	1.69 (0.81)	1.61		
	LCTZ 2.5 mg	69	1.90 (0.70)	1.05 (0.94)	1.06	0.55 [0.23; 0.87	< 0.001
	LCTZ 5 mg	61	1.83 (0.71)	0.69 (0.830	1.00	0.66 [0.28; 0.95]	< 0.001
	LCTZ 10 mg	57	1.83 (0.75)	0.72 (0.70)	0.76	0.85 [0.51; 1.19]	< 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 69)

Change from baseline in mean pruritus duration (24 hour reflective) by treatment week and during total treatment period:
Mean pruritus duration decreases from baseline in all three LCTZ groups compared to placebo for all treatment weeks, and for the total treatment period (pp 70-71).

Multi-center Analysis

Evaluation for the presence of a treatment by center interaction by including center and treatment by center interaction effects in the ANCOVA model for the primary efficacy variables (centers with fewer than eight subjects were grouped) shows no evidence of an effect: $p = 0.222$ over the first week of treatment, and $p = 0.330$ over the total treatment period (p 83).

Subgroup Analysis

No subgroup analyses are performed in this study (p 83).

Safety Assessments

No deaths occur during the study. Overall, 50.6% of subjects experience at least one treatment-emergent AE. The most commonly reported treatment-emergent AEs are somnolence and

headache. The highest incidence of headache occurs in the placebo group; the incidence of somnolence is higher in all three LCTZ doses vs. placebo, and there is a positive correlation between increasing LCTZ dose and somnolence: the relative risk for somnolence (with 95% CI) is 1.50 (0.37; 6.02) for 2.5 mg, 2.59 (0.72; 9.30) for 5 mg, and 3.56 (1.03; 12.30) for 10 mg (p 88).

Two subjects in the LCTZ groups report serious adverse events: a right ankle fracture (in the 5 mg group) and peritonitis (in the 10 mg group) treated with oral antibiotics. The Investigator rates each event as unlikely related to the study medication (pp 414-415).

Seven subjects (two in the LCTZ 2.5 mg and five in the 10 mg group) discontinue study medication due to AEs: three develope insomnia, one agitation, two have an unintended pregnancy detected (in one of which a male child with hypospadias [attributed to family history] is born), and one a photosensitivity reaction (pp 415-416).

No clinically relevant changes between baseline and post-treatment laboratory values are observed (p 90). See Table 8, below, for a summary of treatment-emergent AEs.

Table 8. Treatment-emergent AEs with an incidence ≥ 5% (ITT population)

Preferred Term	Placebo (N = 63) N %	LCTZ 2.5 mg (N = 70) N %	LCTZ 5 mg (N = 65) N %	LCTZ 10 mg (N = 59) N %
Asthenia	0	0	0	5 (8.5%)
Fatigue	1 (1.6%)	0	4 (6.2%)	1 (1.7%)
Fever	0	0	0	3 (5.1%)
Influenza-like	0	6 (8.6%)	4 (6.2%)	2 (3.4%)
Headache	8 (12.7%)	5 (7.1%)	8 (12.3%)	7 (11.9%)
Back pain	2 (3.2%)	1 (1.4%)	5 (7.7%)	2 (3.4%)
Somnolence	3 (4.8%)	5 (7.1%)	8 (12.3%)	10 (16.9%)
Pharyngitis	3 (4.8%)	4 (5.7%)	4 (6.2%)	3 (5.1%)

(p 88)

Study Conclusions

Efficacy:

Levocetirizine 2.5 mg, 5 mg, or 10 mg, taken orally, once daily in the evening, is more efficacious than placebo in treating the symptoms and signs of CIU in adults. The differences in adjusted mean values (for change in score from baseline) for all three doses of LCTZ vs. placebo are statistically significant ($p < 0.001$) for the first treatment week, and for the total four week treatment period, for the primary efficacy endpoints.

There is a statistically significant linear dose-response relationship for the total treatment period of the pruritus severity score (a primary efficacy endpoint; $p = 0.02$).

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 the LCTZ arm include the observations that more subjects discontinue the study due to 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 (see Table 3).

The results of this study can be used to support the use of LCTZ, taken once daily in the evening, for the treatment of the symptoms and signs of CIU in adults. This study demonstrates the optimal dose to be 5 mg. 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. Additionally, 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.

Safety:
No unusual adverse events or safety signals are evident in this study.

Reviewer comments:
The designation of two measures of pruritus severity at different treatment intervals as co-primary endpoints is not appropriate. 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, Study A00270 demonstrates efficacy, versus placebo, for both the primary (subjective) endpoint, pruritus severity, and the secondary (objective) endpoints, wheal number and size, that is satisfactorily robust to support the indication sought.

The SAP does not include a subgroup analysis. Extrapolation of these results to subgroups such as racial minorities or elder populations should be done with caution.

Appendix 2A: Summary Tables of Primary Safety Database by Development Phase and Individual Study, and by Individual Study Safety Assessments

Table 28. Summary of primary safety database (pooled and non-pooled studies) and clinical development program by phase and individual study

Clinical Pharmacology Program				
Single-dose (SD) Studies in Healthy Volunteers				
Study	Date/Country	Total Subjects-ITT	(LCTZ [mg]) Number exposed	Design (Comparator)

		(Male/Female) [Age Range]		
A184	1992/UK	19 (19/0) [18-41]	(2.5) 18	SD croosover PK/PD [wheal & flare] (CTZ, dextro-CTZ)
A190	1993-94/Belgium	28 (9/19) [20-40]	(5) 28	DB, PC, SD crossover [histamine nasal provocation] (CTZ, dextro-CTZ, placebo)
A221	1997/Germany	24 (12/12) [20-55]	(10) 24	SD crossover, PK (CTZ)
A232	1997-98/France	24 (12/12) [20-55]	(5) 24	SD BE [clinical trial formulation], relative BA [oral solution]
A233	1997/Scotland	4 (4/0) [31-46]	(5) 4	SD mass balance study
A252	1999/UK	19 (19/0) [19-51]	(5) 19	SD crossover wheal & flare (ebastine, fexofenadine, loratadine, misolastine, placebo)
A00280	2001/France	18 (4/14) [21-47]	(5) 18	SD wheal & flare (desloratadine, placebo)
A00297	2001/Germany	24 (12/12) [18-55]	(5) 24 (tablet) 24 (drop)	SD crossover BE [tablets & oral drops]
A00305	2002/Gedrmany	18 (18/0) [22-43]	(5) 18	DB, PC, SD crossover [histamine-induced nasal skin temp. (desloratadine, placebo)
A00318	2002/Belgium	25 (13/12) [19-54]	(5) 25	SD crossover BE [tablets & oral solution]
A00351	2003/Germany	39 (30/0) [22-51]	(5) 30	DB, PC, SD crossover [histamine-induced nasal skin temp.]
A00380	2004/Germany	53 (53/0) [19-42]	(5) 44	DB, PC, double-dummy crossover [nasal histamine provocation]
Multiple-dose PK/PD Studies in Healthy Adult Volunteers				
A238	1998/France	21 (10/11) [20-37]	(5) 41	SD, food versus fasting with repeat 8-day dosing
A246	2000-2001/The Netherlands	51 (25/26)	(5) 49	BD, PC, 4-day crossover of driving

		[21-30]		and psychomotor performance
A00260	1999/France	19 (19/0) [20-39]	(5) 18	DB, PC, 5-day crossover cognitive/psychomotor function
A00263	2000/Belgium	36 (17/19) [21-74]	(30) 36	DB, PC, 6-day crossover ECG PK after single & repeat doses
Studies in Allergic Subjects				
A245	1999/Austria	39 (19/20) [19-40]	(5) 37	DB, PC crossover in PAR (loratadine, placebo)
A254	1999-2000/France	15 (6/9) [20-37]	(5) 15	DB, PC crossover of IgE-dependent hypersensitivity reaction after cutaneous challenge in allergic vlounteers
A256	2000-2001/Austria	73 (34/39) [19-34]	(5) 70	DB, PC crossover in SAR [grass pollen-sensitized subjects] (loratadine, placebo)
A00324	2002/Austria	94 (38/56) [18-44]	(5) 87	DB, PC, crossover in grass pollen-sensitized SAR (loratadine, placebo)
A00331	2002/Canada	373 (164/209) [16-74]	(5) 141	DB, PC in ragweed-sensitized SAR [EEU] (desloratadine, placebo)
A00373	2004-05/France	18 (9/9) [18-48]	(5) 18	DB, PC crossover for wheal and flare (desloratadine, placebo)
A00379	2004-05/Canada	570 (233/237) [16-69]	(5) 240	DB, double-dummy, PC EEU (CTZ, placebo)
Special Populations: Renal Impairment				
A230	1997-98/Belgium & Czech Repub.	18 (6/12) [46-72]	(5) 18	SD [6/18 = healthy volunteers]
A234	1998-99/Belgium	5 (3/2) [38-78]	(5) 5	SD pre & post hemodialysis study
Studies ≤ 6 weeks in SAR, PAR, CIU Subjects ≥ 12 years				
A217 (SAR)	1996/France & Germany	470 (235/235) [17-72]	(2.5) 117 (5) 116 (10) 118	DB, PC, 2-wk., parallel group dose comparison
A222 (SAR)	1997/France	797 (401/396) [12-66]	(5) 319	DB, PC, 7-day, parallel equivalence study

A00268 (SAR)	2000-2001/S.Africa	236 (89/147) [12-71]	(5) 119	DB, PC 2-wk parallel group study
A219 (PAR)	1996-97/ France	421 (205/216) [12-66]	(2.5) 105 (5) 103 (10) 109	DB, 4-wk., parallel-group, dose comparison study
A00265 (PAR)	2000-2001/France & Germany	519 (206/313} [12-74]	(2.5) 133 (5) 128 (10) 130	DB, 4-wk., parallel group, dose comparison
A00266 (PAR)	2000/S. Africa	294 (126/168) [12-71]	(5) 150	DB, 6-wk, parallel group study with ECG monitoring
A00333 (PAR)	2002-03/France	453 (167/286) [12-79]	(5) 226	DB, 4-wk., parallel group, Phase 4 study
A00269 (CIU)	2001/Germany, Switzerland	166 (68/98) [18-79]	(5) 81	DB, 4-wk., parallel group study
A00270 (CIU)	2001-02/France	257 (71/186) [18-85]	(2.5) 70 (5) 65 (10) 59	DB, 4-wk., parallel group study
Studies 16 weeks-6 months in SAR and PAR Subjects 12 Years and Older				
A00306	2004/France, Italy, Belgium	459 (203/256) [12-68]	(5) 150	DB, Parallel, PC, 16-wk. SAR & asthma prevention trial
A00264	2001-02/France, Belgium, Germany, Spain, Italy	551 (241/310) [18-70]	(5) 278	DB, PC, 6-momth study
Asian Short-term SAR, PAR, CIU Studies in Subjects ≥ 12 years				
A00348 (SAR)	2003/China	67 (40/27) [18-60]	(5) 34	Single-blind, active-control, 2-wk, parallel (loratadine)
A00299 (PAR)	2001-02/Taiwan	62 (11/51) [18-58]	(5) 30	DB, active-control, 2-wk., parallel (loratadine)
A00349 (PAR)	2003-04/China	71 (28/43) [17-60]	(5) 35	Single-blind, active-control, 2-wk., parallel (loratadine)
A00334 (CIU)	2003-04/China	134 (47/87) [81-59]	(5) 67	Single-blind, 2-wk study (loratadine)
Pediatric (≤ 12 years) Studies of SAR, PAR				
A00303 (SAR)	2002/France, Germany	177 (117/60) [6-13]	(5) 89	DB, PC, 6-wk., parallel group study
A00304 (PAR)	2002/S. Africa	306 (186/120) [6-13]	(5) 154	DB, PC, 4-wk parallel group study
A00315	2001-03/Australia, Czech Republic	15 (11/4) [1-2]	(0.25 mg/kg/day) 15	SD PK & open-label safety & efficacy study
A00385	2004/France	30	(1.25 mg b.i.d.)	Open-label, 4-wk.,

		(15/15) [2-6]	30	safety study
Non-pooled Completed Studies				
A00412 (PK/PD)	2006/Canada	551 (239/312) [16-72]	(2.5) 116 (5) 119 (10) 119	2-day DB, PC study in ragweed-sensitive/exposed subjects [EEU] (CTZ, Placebo)
A00340 (PK/PD)	2002/India	12 (12/0) [18-45]	(5) 12	BE of LCTZ produced in India, Europe [healthy subjects]
A00391 (SAR)	2005/Germany	200 [19-66]	(5) 100	DB, active-controlled, 2-wk parallel group study (desloratadine)
A00401 (SAR)	2005/France, Italy, Germany	765 (334/431) [18-77]	(5) 341	DB, P and active-control 2-wk parallel group study (desloratadine, placebo)

Table 29. Summary of development program safety assessments by study

Study No.	Visit Schedule	Adverse Events	Clinical Labs	BP/Pulse	ECG	PE
Safety Assessments in Single-dose PK/PD Studies (Healthy Volunteers)						
A184	Screening; 3 periods with 7day washouts	Each Period	Pre-dose and 24h after final dose	Screening	Screening	Screening only
A190	Screening; 4x4h periods with 7-14d washouts	Each Period	Screening only	Not done	Screening	Screening only
A221	Screening; 2x48-72h periods with 7d washout	Each Period	Pre-study; 48h after final dose	Pre-and 1,2,24h post-dose;48h post-final dose	Pre-study; 48 h after final dose	Pre-study; 48 h after final dose
A232	Screening; 3x48h periods with ≥7d washouts	Pre- and 1,2,4,12,24h post-dose	Screening; end of study	Pre-and 1,2,24h post-dose;6-10d post-final dose	Screening; pre-and 1,2,24h post-dose; 6-10d post-final dose	Screening; pre- and 24h post-dose; end of study
A233	Screening; single period of 168h	Monitored throughout	Screening; pre-and 168h post-dose	Screening; pre-and 3,24,168h post-dose	Screening; pre-and 24, 168h post-dose	Screening and 168h post-dose
A252	Screening; 6x48h periods with 7-14d washouts	Pre-and 3, 12,24h post-dose	Screening and 24h post-final dose	Screening; pre- and 24h post-dose	Screening; 24h post-final dose	Screening; 24h post final dose
A00280	Screening; 3x24h periods with ≥14d washouts	24h post-dose	Screening only	Screening; pre- and 24h post-dose	Screening only	Screening; 24h post-dose
A00297	Screening; 2x48h periods	Each period; at discharge	Screening and 2-9d	Screening; pre and 48h post-dose; 2-9d post final	Screening; 2-9d post-final dose	Screening; 2-9d post

	with 7d washouts		post-final dose	dose		final dose
A00305	Screening; histamine challenge, 3x1d periods with ≥10d washouts	Each Period	Not done	Screening; pre-dose; at discharge	Not done	Screening; D 1 of each period
A00318	Screening; 2x48 post-dose	Each period; at discharge	Screening and discharge	Screening; pre- and 1, 48h post-dose; at discharge	Screening; discharge	Screening; discharge
A00351	Screening; 3x2d periods with ≥9d washouts	Each Period	Not done	Screening; Days 1 and 2 of each period	Not done	Screening; D 1 of each period
A00380	Screening; 3x1d periods with ≥ 7d washouts	Each period; at discharge	Not done	Screening; each period; at discharge	Not done	Screening; each period
Safety Assessments in Multiple-dose PK/PD Studies (Healthy Adult Volunteers)						
A238	Screening; 2-single oral administrations with 7d washouts; repeat daily dosingX8d	Pre-and 1,2,4,12,24,48h post-dose and D 11-17:pre-and1.5h post-dose; D18:pre-and 1,2,4,12,24,48[h] post final dose	Screening and 6-10d post-final dose	Screening; pre-and 1,2,8,24h post-dose; 6-10d post-final dose	Screening; pre-dose (daily); 1.5h post-dose on intervening days; 1,2,24h post-final dose; 6-10d post-final dose	Screening; pre-dose; 24h post-final dose; 6-10d post-final dose
A246	3x4d cross-over periods with 3d washouts	Monitored throughout	Screening and discharge	At each visit and discharge	Screening and discharge	Each visit and discharge
A00260	Screening; 3x5d periods with ≥7d washouts	Monitored throughout	Screening; 24h post-dose	Screening; 24h post-dose; within 1wk post-final dose	Screening; pre-and 1h post-first and last doses; 24h post-final dose	Screening; 24h post-dose; within 1 wk post-final dose
A00263	Screening; 2x6d periods with ≥5d washouts	Monitored throughout	Screening; D 1 and 7 of each period	Screening; D 1 and 6 of each period; pre- and 1,2,6h post-dose; D 2-5 of each period; pre-dose; D 7 of each period: 24h post-dose	Screening; pre- and 0.5,1,1.5,2,4,6,12h post-dose on D 1 and 6 of each period; pre-dose on D 2-5 of each period; 24h post-dose on D 7 of each period	Screening and Discharge
Safety Assessments in Wheal & Flare (EEU or PD Challenge Chamber, Allergic Adult Subjects)						
A245	3-periods of 2d (consecutive) with ≥5d washouts	D 1 of each period: 2,6,8,10,12,14,16h post-dose D 2 of each period: Pre- and 2,6h post-dose	Screening	D 1 and 2 of each period: pre- and 6h post-dose	Not done	Screening
A254	2x2d (consecutive) periods with 3-5 wk washouts	Monitored throughout	Initial visit; on last day of 2[nd] period post-final dose	Initial visit; D 4 of each period; post-treatment visit	Initial visit; ≤1 wk of final dose	Initial visit; D 4 of each period; post-treatment visit
A256	3x2d (consecutive) periods with ≥5d washouts	D 1 of each period: 2,6,8,10,12,14,16h post-dose D 2 of each period: Pre- and 2,6h post-dose	Screening	D 1 & 2 of each period: pre and 6h post-dose	Not done	Screening
A00324	3x2d (consecutive) with ≥12d washouts	Monitored throughout	Not done	Before and after each allergen exposure	Not done	Screening
A00331	1-period of 2d (consecutive)	P-2, P-3, final evaluation and	Screening	Screening and final evaluation	Not done	Screening and final

		phone f/u				evaluation
A00373	3x2d periods with 14-21d washouts	Monitored throughout	Screening and discharge	Screening and discharge	Not done	Screening; at discharge
A00379	After priming, 1x2d (consecutive) in EEU with 5- and 21-29h post-dose observation	Monitored throughout	Screening	At discharge	Not done	Screening; at discharge
Safety Assessments in SD PK Studies Renally Impaired Subjects						
A230	Screening; 1x3-4d period	Monitored throughout	Screening and discharge	Screening; pre-and 1,2,4,8,10,24,48,72,96h post-dose; at discharge	Screening and discharge	Screening; at discharge
A234	Screening; 1x3d in-house period	Monitored throughout	Screening and discharge	Screening; pre- and 1,2,4,10,24,32,44,48,52h post-dose; at discharge	Screening and discharge	Screening; at discharge
Safety Assesments in Short-term (≤ 6 weeks) SAR, PAR, CIU Subjects ≥ 12 years						
A217	3 visits: 7d intervals	Monitored throughout	Pre-and post-treatment	Not done	Not done	Pre-treatment
A219	4 visits: Wks-1,0,2,4	Monitored throughout	At selection and final visits	Not done	Not done	At all visits
A222	2 visits: 7d interval	Monitored throughout	Pre-and post-treatment	Not done	Not done	Pre-and post treatment
A00265	5 visits: 1 wk, 2x2 wks, 1 wk	Monitored throughout	At selection and final visits	Not done	Not done	At all visits
A00266	6 visits: 1 wk, 3x2 wks, 1 wk	Monitored throughout	At selection and final visits	Not done	Visit 1, if possible, and Visit 3	At all visits
A00268	4 visits: 1 wk, 2 wks, 1 wk	Monitored throughout	Pre-and post-treatment	Not done	Not done	At all visits
A00269	5 visits: 2x1 wk, 3 wks, 1 wk	Monitored throughout	At selection and final visits	Not done	Not done	At all visits
A00270	5 visits: 2x1 wk, 3 wks, 1 wk	Monitored throughout	At selection and final visits	Not done	Not done	At all visits
A00333	3 visits: 1 wk selection v. and 30d of treatment	Monitored throughout	Not done	Not done	Not done	At all visits
Safety Assessments in Long-term SAR and PAR Studies in Subjects ≥ 12 years						
A00264	8 visits: 3 visits at 7d intervals, then 3-wk, 8-wk, 6-wk, and 8-wk periods; final visit 1 wk later	Monitored throughout	Screening and end of treatment	Screening and end of treatment	Not done	At all visits
A00306	5 visits: 4-wk intervals (~ 3d)	Monitored throughout	Monitored throughout	Not done	Not done	At all visits
Safety Assessments in Short-term Asian SAR, PAR, CIU Studies in Subjects ≥ 12 years						
A00299	4 visits: screening, randomization, 2x14d on	Monitored throughout	Monitored throughout	Screening; randomization; end of treatment	Not done	At all visits

	treatment					
A00334	3 visits: screening, randomization, end-of-treatment (14d)	Monitored throughout	Monitored throughout	Each visit	Each visit	At all visits
A00348	3 visits: screening, randomization, end-of-treatment (14d)	Monitored throughout	Monitored throughout	Each visit	Each visit	At all visits
A00349	3 visits: screening, randomization, end-of-treatment (14d)	Monitored throughout	Monitored throughout	Each visit	Each visit	At all visits
Safety Assessments in Pediatric Studies (≤ 12 years)						
A00303	5 visits: Initial, randomization, Control (V 3 & 4), End of Treatment v (separated by 1 & 32 wks, respectively)	Monitored throughout	Monitored throughout	Not done	Not done	At all visits
A00304	5 visits: Initial, randomization, Control (V 3 & 4), End of Treatment v (separated by 3x1 wk and 2 wks respectively)	Monitored throughout	Monitored throughout	Not done	Not done	At all visits
A00385	4 visits: Seletion, Start of Treatment, Control and end of treatment visit (separated by 3-7d and 2x2wks, respectively)	Monitored throughout	Monitored throughout	Not done	Not done	At all visits
A00315	6 visits: Screening (V 0-D-10-1), Treatment (V 1-4-D3-6, D30, D60), Final Eval (V 5, D90)	Monitored throughout	Monitored throughout	Visits 0-5	Not done	At all visits

Appendix 2B: Summary Tables of Demographics by Phase and Subject Age Group

Table 30. Baseline demographics for Phase 1 studies: healthy volunteers

Characteristic	Single-dose studies			Multiple-dose studies		
	Placeb0 N = 141	LCTZ N = 267	Comparator N = 186	Placebo N = 102	LCTZ N = 124	Comparator N = 69
Age (years)						
Mean +/-	30.4 +/- 7.4	32.7 +/- 9.5	30.5 +/- 7.8	32.3 +/-	31.2 +/-	24.2 +/- 2.9

				14.7	13.7	
Range	19-51	18-63	18-55	20-74	20-74	20-39
Category						
16 < 65	141 (100%)	267 (100%)	186 (100%)	93 (91.2%)	115 (92.7%)	69 (100%)
≥ 65	0	0	0	9 (8.8%)	9 (7.3%)	0
Sex n (%)						
M	108 (76.6%)	182 (68.2%)	141 (75.8%)	59 (57.8%)	69 (55.6%)	44 (63.8%)
F	33 (23.4%)	85 (31.8%)	45 (24.2%)	43 (42.2%)	55 (44.4%)	25 (36.2%)
Race n (%)						
Caucasian	126 (89.4%)	252 (94.4%)	171 (91.9%)	98 (96.1%)	120 (96.8%)	66 (5.7%)
Asian	15 (10.6%)	15 (5.6%)	15 (8.1%)	1 (1.0%)	1 (0.8%)	1 (1.4%)
Black	0	0	0	2 (0.2%)	2 (1.6%)	1 (1.4%)
Other	0	0	0	1 (1.0%)	1 (0.8%)	1 (1.4%)

Table 31. Baseline demographics for Phase 2 PD studies: allergic volunteers

Characteristic	Placebo N = 380	LCTZ N = 554	Comparator N = 532
Age (years)			
Mean +/- S.D.	28.5 +/- 8.9	30.0 +/- 10.3	31.1 +/-11.6
Range	16-69	16-74	16-69
Category			
16 < 65	378 (99.5%)	552 (99.6%)	524 (98.5%)
≥ 65	2 (0.5%)	2 (0.4%)	8 (1.5%)
Sex n (%)			
M	153 (40.3%)	237 (42.8%)	226 (42.5%)
F	227 (59.7%)	317 (57.2%)	306 (57.5%)
Race n (%)			
Caucasian	369 (97.1%)	543 (98.0%)	512 (96.2%)
Asian	5 (1.3%)	7 (1.3%)	10 (1.9%)
Black	5 (1.3%)	3 (0.5%)	8 (1.5%)
Other	1 (0.3%)	1 (0.2%)	2 (0.4%)

Table 32. Baseline demographics for Phase 2 and 3 adult studies: SAR, PAR, and CIU subjects ≥ 12 years of age

Characteristic	Short-term Studies (≤ 6 weeks)			Long-Term Studies (4—6 months)	
	Placebo N = 1137	LCTZ N = 2114	Comparator N = 318	Placebo N = 580	LCTZ N = 560
Age (years)					
Mean +/- S.D.	31.5 +/- 12.8	32.2 +/- 13.0	29.8 +/- 11.5	30.7 +/- 10.3	30.8 +/- 10.7
Range	12-76	12-85	12-66	12-70	12-68
Category					
12 - < 16	89 (7.8%)	160 (7.6%)	24 (7.5%)	29 (5.0%)	20 (3.6%)

16 - < 65	1025 (90.1%)	1916 (90.6%)	293 (92.1%)	548 (94.5%)	536 (95.7%)
≥ 65	23 (2.0%)	38 (1.8%)	1 (0.3%)	3 (0.5%)	4 (0.7%)
Sex n (%)					
M	498 (43.8%)	899 (42.5%)	150 (47.2%)	254 (43.8%)	241 (43.0%)
F	639 (56.2%)	1215 (57.5%)	168 (52.8%)	326 (56.2%)	319 (57.0%)
Race n (%)					
Caucasian	655 (57.6%)	1014 (48.0%)	0	562 (96.9%)	542 (96.8%)
Asian	45 (4.0%)	48 (2.3%)	0	4 (0.7%)	6 (1.1%)
Black	14 (1.2%)	33 (1.6%)	0	12 (2.1%)	12 (2.1%)
Other	43 (3.8%)	47 (2.2%)	0	2 (0.3%)	0
Not requested	380 (33.4%)	972 (46.0%)	318 (100%)	0	0

Table 33. Baseline demographics for Phase 3 pediatric studies: SAR and PAR in subjects 6 – 12 years of age

Characteristic	Placebo N = 240	LCTZ N = 243
Mean age +/- S.D. (years)	9.9 +/- 1.9	9.9 +/-1.9
Age Range (years)	6-13	6-12
Category (years)		
6-< 12	198 (82.5%)	206 (84.8%)
12-< 16	42 (17.5%)	37 (15.2%)
Sex n (%)		
M	141 (58.8%)	162 (66.7%)
F	99 (41.3%)	81 (33.3%)
Race n (%)		
Caucasian	127 (52.9%)	121 (49.9%)
Asian	30 (12.5%)	40 (16.5%)
Black	14 (5.8%)	14 (5.8%)
Other	69 (28.8%)	68 (28.0%)

10.2 Line-by-Line Labeling Review

A line-by-line labeling review is in progress as this review is filed.

REFERENCES

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Layton D, Wilton LW, Boshier A, Cornelius V, Harris S, Shakir S. Drowsiness and sedation: A comparison between levocetirizine and desloratadine using post-marketing observational data. J Allergy Clin Immunol Feb-2006, 117(2 suppl.1): S262.

Simons FE and Simons KJ. Levocetirizine: Pharmacokinetics and pharmacodynamics in children age 6 to 11 years. J Allergy Clin Immunol. Aug-2005, 116: 355-361.

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/s/

Robert M Boucher
4/3/2007 02:10:26 PM
MEDICAL OFFICER

Lydia McClain
4/3/2007 04:15:32 PM
MEDICAL OFFICER
I concur. See Team Leader memo

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA # 22-064	TRADE NAME:	Xyzal®(proposed); backup option: _____
APPLICANT/SPONSOR:	UCB Inc.	USAN NAME:	Levocetirizine dihydrochloride
MEDICAL OFFICER:	Robert Boucher, MD, MPH		
TEAM LEADER:	Lydia Gilbert-McClain, MD	CATEGORY:	Anti-histamine
DUE DATE:	September 8, 2006	ROUTE:	Oral (5 mg tablet)

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
July 24, 2006	July 25, 2006	N-000	Original, electronic NDA with 5 pivotal Phase III clinical trials in patients with SAR, PAR, and CIU

RELATED APPLICATIONS

Document Date	Application Type	Comments
April 14, 2005	PIND 072,233, N-000	preIND meeting package to discuss sponsor's proposal for 505(b)(2) submission
January 4, 2006	PIND 072,233, N-006	Meeting package to discuss approval as prescription vs OTC product
	NDA 19-835	NDA for Zyrtec® 5mg and 10 mg tablets, referenced by applicant
	NDA 20-346	NDA for Zyrtec® oral syrup (5mg/ml), referenced by applicant
	NDA 21-621	NDA for Zyrtec® chewable tablets (5mg and 10mg), referenced by applicant

REVIEW SUMMARY:

This is a 45-day Filing Review of the original NDA 22-064 submitted by UCB, Inc., for the prescription use of once-daily levocetirizine dihydrochloride oral tablets. The proposed indications are the treatment of symptoms due to seasonal and perennial allergic rhinitis (SAR, PAR) in patients 6 years of age and older, and the treatment of pruritus and urticaria associated with chronic idiopathic urticaria (CIU) in adults.

Levocetirizine (LCTZ), the R-enantiomer of the racemate cetirizine, is a selective histamine H_1 receptor antagonist which has a two-fold greater affinity for the H_1 receptor than cetirizine. The applicant states that LCTZ is the enantiomer responsible the anti-histaminic effects of the racemate.

The submission contains information from multi-center (all outside the U.S.), controlled clinical studies in support of the safety and efficacy of LCTZ in patients 6 years of age and older with SAR and PAR, and in adults with CIU: three multi-center, randomized, double-blind, placebo-controlled Phase III trials (two adult, one pediatric) supporting SAR and PAR indications, one Phase IV pediatric SAR safety and efficacy trial, one Phase IV adult PAR efficacy trial, one Phase III adult CIU trial (superiority vs. placebo), and two adult SAR bridging studies (LCTZ and cetirizine vs. placebo). Three Phase II dose-ranging trials are also submitted. The applicant has not submitted clinical trials in support of a pediatric CIU indication.

This submission is adequate for in-depth review and, notwithstanding the absence of an ISE, is fileable. Audits of clinical centers will be requested from the Division of Scientific Investigations since all clinical studies were conducted outside of the U.S.

OUTSTANDING ISSUES:

1. The submission does not include an Integrated Summary of Efficacy (ISE).

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA # 22-064	**TRADE NAME:**	Xyzal®(proposed); backup option:
APPLICANT/SPONSOR:	UCB Inc.	**USAN NAME:**	Levocetirizine dihydrochloride
MEDICAL OFFICER:	Robert Boucher, MD, MPH		
TEAM LEADER:	Lydia Gilbert-McClain, MD	**CATEGORY:**	Anti-histamine
DUE DATE:	September 8, 2006	**ROUTE:**	Oral (5 mg tablet)

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	SAFE TO PROCEED	___	CLINICAL HOLD	
NDA/SUPPLEMENTS:	___	FILEABLE	X	NOT FILEABLE	
	___	APPROVAL	___	APPROVABLE	___ NOT APPROVABLE
OTHER ACTION:					

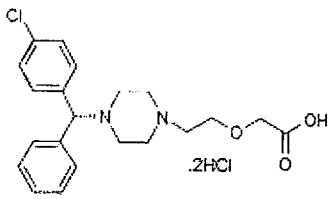
Appears This Way
On Original

I. General Information

Drug Substance:

Trade Name:	Xyzal
USAN:	Levocetirizine dihydrochloride
Molecular Formula:	$C_{21}H_{25}N_2O_3Cl.2HCl$

Structural Formula:



Molecular Weight:	461.8
Manufacturer:	UCB S.A. (Belgium), UCB Farchim SA (Switzerland)

This NDA is submitted for the prescription use of levocetirizine (LCTZ), the R-enantiomer of the racemate cetirizine, which is a selective H_1 receptor antagonist that has a two-fold greater affinity for the H_1 receptor than cetirizine. The applicant states that LCTZ is equivalent when given alone or as the racemate (cetirizine), its safety profile in humans is comparable to cetirizine, and it is responsible for most of the anti-histaminic effect of the racemate. These reported findings are offered by the applicant 1) to support the marketing of LCTZ under this NDA, and 2) to justify references to clinical and non-clinical studies of cetirizine in support of this NDA.

The applicant is seeking approval to market LCTZ 5mg oral tablets by prescription under Section 505(b)(2) of the FD&C Act 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" (see Cover Letter). The NDA references the approved prescription drug Zyrtec® (cetirizine hydrochloride), sponsored by Pfizer.

This NDA submission includes information from 54 clinical trials. Pivotal and supporting studies are summarized in section IV.

II. Regulatory and Foreign Marketing History

A. Regulatory History

Previous correspondence regarding levocetirizine dihydrochloride (LCTZ) has been submitted under P-IND 72,233 (meeting package date April 15, 2005; LCTZ has not been the subject of a U.S. IND application). Salient issues addressed during the P-IND phase include:

1. The applicant's rationale for NDA submission under 505(b)(2): The Division agreed with the applicant that such a submission may be appropriate for LCTZ (Source: MO review dated June 14, 2005, page 5 [Warner Carr, MD]).
2. The applicant's rationale for seeking prescription status for LCTZ: The Division indicated to UCB that "...such a decision cannot be made at this time. Note that the decision to consider your drug product for prescription or OTC marketing will be made at the time of the NDA submission. Provide your justification for initial prescription marketing at that time" (Source: MO review dated February 15, 2006, page 4 [Tejashri Purohit-Sheth, MD]).
3. Need for appropriate, multiple-dose bridging studies with the comparator cetirizine: The Division told UCB that "The clinical program is expected to demonstrate and support equal exposure and pharmacodynamic efficacy from LCTZ 2.5mg & 5mg, compared to cetirizine 5mg & 10mg, respectively" (Source: MO review dated June 14, 2005, page 5 [Warner Carr, MD]). (In the cover letter of this NDA submission UCB states that since the June 14, 2005 meeting with the Division a clinical efficacy study comparing two doses of LCTZ to two doses of cetirizine has been completed [EEU protocol, study A00412]).
4. The applicant's question regarding approval of LCTZ in the pediatric population 6 months to 5 years: The Division responded "Based on your submission, you appear to have adequate data and reasoning to support an application down to the age of 6 years. The extrapolation of efficacy and safety data for 6 months to 5 years will be a review issue" (Ibid, page 6). (In the cover letter of this NDA submission the applicant states that it is requesting a deferral for the submission of data supporting the use of LCTZ in the pediatric population below 6 years of age).

B. Foreign Marketing History

The foreign clinical development and marketing programs for LCTZ are extensive. The applicant began clinical development of LCTZ in Europe in 1992 and the product was first registered in the European Union in 2001 via the Mutual Recognition Procedure. Levocetirizine (5mg film-coated tablets), for use in adults and children 6 years of age and older, is currently approved in over 80 countries for SAR, PAR, and CIU indications. Fourteen countries where LCTZ is approved have a full 4 year period of marketing exposure, and exposure to LCTZ worldwide as of June 2006 is approximately 3.6 million patient years. The applicant states that LCTZ has not been withdrawn in any country for reasons related to safety or effectiveness. All 54 clinical trials supporting this NDA have been conducted in foreign countries. A liquid formulation of LCTZ intended for pediatric use down to age 2 years has recently been registered in multiple European countries. The tablets are manufactured at UCB Farchim SA in Switzerland. (Module 2, Section 2.2, CTD Introduction and 2.5, page 9)

III. Items Required for Filing and Reviewer Comments

A. Reviewer Comments

This NDA is submitted by UCB, Inc, of Smyrna, Georgia. UCB, Inc. is a branch of UCB Pharma, a publicly traded biopharmaceutical company based in Brussels, Belgium.

The structure of this electronic NDA is a Common Technical Document (CTD) hybrid provided as NDA items. Module 1 elements (administrative documents) are provided in both paper and electronic format. The electronic submission contains 2,270 files in 680 folders.

All LCTZ clinical studies were conducted outside of the U.S. and were not performed under an IND. The applicant states that financial disclosure information was routinely collected from investigators participating in covered studies initiated after the Financial Disclosure Rule became effective in February, 1999. The applicant, referencing 21 CFR 54.2, certified that: 1) it has not entered into any financial arrangements with investigators whereby the value of compensation to the investigator could be affected by the outcome of the study, 2) clinical investigators' disclosure documents revealed neither proprietary interests in LCTZ nor significant equity in the sponsor, and 3) no listed investigator was the recipient of significant payments of other sorts. Retrospective collection of financial disclosure information from investigators participating in studies which began *prior* to implementation of the Final Rule in 1999 was also done, although UCB states that it was unable to obtain information in every case, making up to three written requests of investigators. (A review of the non-responders shows a total of 46 investigators from 8 countries; of the 46, 39 were responsible for less than 5% of subjects in a given trial, and none were responsible for more than 10% of subjects in a given trial [Module 1, 1.3.1.6: *Financial Disclosure Information*]).

B. Necessary Elements (21 CFR 314.50)

Table 1. Necessary Elements

Item	Type	Status	Location (*electronic*)
	Application Form (FDA 356h)	Present	N22064\356h.pdf
	Formatting for Electronic Filing	Present	
	Format	Present	N22064\ctdmap.pdf
	Table of Contents / Indexes	Present	N22064\ndatoc.pdf
	Labeling	Present	N22064\labeling
1	Index / Table of Contents	Present	N22064\ndatoc.pdf
2	Samples and Labeling		
	Proposed Package Insert	Present	N22064\labeling\PLRannotated .pdf
	Proposed Label	Present	N22064\labeling\proposed.pdf

Item	Type	Status	Location (*electronic*)
	Proposed Medication Guide	N/A	
3	Summary	Present	N22064\summary\ctdtoc.pdf
	Labeling	Present	N22064\labelingtoc.pdf
	Marketing History	Present	N22064\summary\ctdintro.pdf
	Chemistry, Manufacturing, & Controls (CMC)	Present	\N22064\summary\qos.pdf
	Nonclinical Pharmacology and Toxicology	Present	\N22064\summary\nonclin-sum.pdf
	Human Pharmacokinetics and Bioavailability	Present	\N22064\summary\clin-over.dpf
	Clinical	Present	\N22064\summary\clin-sum.pdf
	Benefits vs Risks	Present	\N22064\summary\clin-over.pdf
4	CMC	Present	\N22064\cmc\cmctoc.pdf
	Environmental Impact statement	Present	\N22064\other\environ.pdf
5	Nonclinical Pharmacology and Toxicology	Present	\N22064\pharmtox\pharmtoc.pdf
6	Human Pharmacokinetics and Bioavailability	Present	\N22064\hpbio\hpbiotoc.pdf
8	Clinical	Present	\N22064\clinstat\clintoc.dpf
8.5	Controlled studies	Present	\N22064\clinstat\listofstudies.pdf
8.7	Uncontrolled studies	Present	\N22064\clinstat\listofstudies.pdf
8.8	Integrated Summary of Effectiveness (subsets for age, gender, and race)	**NOT SUBMITTED**	
8.9	Integrated Summary of Safety	Present	\N22064\clinstat\iss\isstoc.pdf
	Potential for Abuse	Present	\N22064\summary\clin-over.pdf
8.11	Benefits vs Risks	Present	\N22064\summary\clin-over.pdf
8.12	Statements of Good Clinical Practice:	Present	\N22064\summary\clin-over.pdf
	Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures		
	Auditing information		
9	Safety Updates	120 update to be submitted	\N22064\summary\ctdintro.pdf
10	Statistics	Present	\N22064\clinstat
11	Case Report Tabulations	Present	\N22064\crt\crttoc.pdf
12	Case Report Forms (for patients who died or did not complete studies)	Present	\N22064\crf\crftoc.pdf
13	Patent Information	Present	\N22064\other\patinfo.pdf
14	Patent Certification	Present	\N22064\other\patcert.pdf

Item	Type	Status	Location (*electronic*)
16	Investigator Debarment Certification	Present	\N22064\other\debar.pdf
17	Field copy certification (if applicable)	Present	\N22064\other\fieldcopy.pdf
18	User Fee Cover Sheet	Present	\N22064\other\userfee.pdf
19	Financial Disclosure	Present	\N22064\other\financial.pdf
20	Other		
	Claimed Marketing Exclusivity	Present	\N22064\other\prescriptionstatus.pdf
	Pediatric Use	Request for deferral	N22064\other\pedsdeferral.pdf

C. Decision

Lack of an Integrated Summary of Efficacy is a filing issue. Reference is made to 21 CFR 314.50(5)(v): "An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications...The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also shall be presented."

IV. Clinical Studies

This submission includes data from 54 clinical studies sponsored by the applicant, 48 of which have been completed and six of which are ongoing (Module 2, Section 2, *CTD Introduction*, pages 2, 3). No clinical studies of levocetirizine have been performed in the U.S. (Module 2, Section 2.5, page 10). A pooled database for an analysis of safety from 44 of these studies (involving 3,824 adults and 243 children between 6 and 12 years of age) has been included in the submission [redacted]

Five pivotal and six supporting studies are summarized in Tables 2 and 3, respectively. All of these studies were randomized, controlled, double-blind clinical trials and include: 2 Phase III studies supporting adult SAR and PAR indications, one Phase III and one Phase IV study supporting pediatric (age 6-12 years) SAR and PAR indications, and one Phase II and one Phase III study supporting an adult CIU indication. (It is noted during the initial review of the three pivotal allergic rhinitis studies [A00268, A00266, and A00303] that the primary efficacy endpoint is mean change from baseline of the total of four symptom scores that include rhinorrhea, sneezing, nasal pruritus, and ocular pruritus ["T4SS"]. The "T4SS" is notable in that it does not include "nasal congestion," one of four symptoms recommended by the Division for inclusion in a composite symptom score when assessing efficacy [see Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products, page 12]. The Division includes rhinorrhea, sneezing, nasal pruritus, and nasal congestion, but not "ocular pruritus," in its allergic rhinitis symptom complex. In these three pivotal studies "nasal congestion" is one of several *secondary* endpoints assessed as an "individual symptom score"). The Agency guidance document also recommends assessment of both instantaneous

and reflective symptom scores (pages 12,13). Of the three pivotal allergic rhinitis trials, only one (A00268) includes an assessment of both instantaneous and reflective symptom scores.

No studies in support of a pediatric CIU indication have been submitted.

Reviewer Comment:

The inclusion of "ocular pruritus" rather than the Agency-preferred "nasal congestion" in the total symptom score ("T4SS") in the pivotal studies is problematic vis-à-vis assessment of primary efficacy as a change from baseline in the mean of the total *symptom score. Ideally, the mean total symptom score should* not *include "ocular pruritus" and* should *include "nasal congestion." Exclusion of the "ocular pruritus" component from the total symptom score ("T4SS") and its implications for re-assessment of the primary efficacy endpoint in these studies will be review issues.*

The assessment of "nasal congestion" by study investigators as a secondary rather than primary endpoint, as well as the absence of both instantaneous and reflective symptom scores in two of the three pivotal studies will also be a review issue.

Table 2. Summary of Pivotal Studies

Study	Design	Dosage	Patients	Evaluations
A00268 (South Africa)	Phase III, 2 week, multi-center (20), randomized, double-blind, placebo-controlled trial in 236 adult patients with SAR	5mg LCTZ once daily	236	Primary Efficacy ΔT4SS/24 (i&r) over 1st treatment week and over the total 2-week treatment period (Safety assessment made; AEs recorded)
A00266 (South Africa)	Phase III, 6 week, multi-center (26), randomized, double-blind, placebo-controlled trial in 294 patients 12 years and older with PAR	5mg LCTZ once daily	294	Primary Efficacy Δ in mean T4SS over 1st treatment week and over 1st four treatment weeks (Safety assessment made; AEs recorded)

Study	Design	Dosage	Patients	Evaluations
A00303 (France, Germany)	Phase IV, 6 week, multi-center (30), randomized, double-blind, placebo-controlled trial in 177 pediatric patients, age 6-12 years, with SAR	5mg LCTZ once daily	177	Primary Efficacy Δ in mean T4SS over first 2 weeks of treatment (Safety assessment made; AEs recorded)
A00269 (Germany, Switzerland)	Phase III, 4 week, multi-center (19), randomized, double-blind, placebo-controlled trial in 166 adult patients with CIU	5mg LCTZ once daily	166	Primary Efficacy Superiority over placebo measured by pruritus severity score at week one and four (Safety assessment made; AEs recorded)
A00270 (France)	Phase II, 4 week, multi-center (35), randomized, double-blind, placebo-controlled trial in 257 adult patients with CIU	2.5mg, 5mg, or 10mg LCTZ once daily	257	Primary Efficacy Superiority of at least one dose of LCTZ over placebo measured by pruritus severity score at week one and four (Safety assessment made; AEs recorded)

Table 3. Summary of Supporting Studies

Study	Design	Dosage	Patients	Evaluations
A00304 (South Africa)	Phase III, 4 week, multi-center (25), randomized, double-blind, placebo-controlled trial in 306 pediatric patients (6-12 years) with PAR	5mg LCTZ once daily	306	Primary Efficacy Δ in mean T4SS over last 24 hrs/1st two wks of treatment (AEs were recorded)
A00412 (Canada)	Phase II, randomized, double-blind, double-dummy, placebo-controlled exploratory trial in EEU comparing 2 doses each of LCTZ and cetirizine with placebo in 551 patients 16 years and older with ragweed sensitivity	Once daily LCTZ 2.5mg or 5mg; Once daily Cetirizine 5mg or10mg	551	Primary Efficacy Reduction from baseline in Major Symptom Complex between each

Study	Design	Dosage	Patients	Evaluations
				active treatment group and placebo during Day 1 (Safety assessment made; AEs recorded)
A00265 (France, Germany)	Phase II, 4 week, multi-center (52) randomized, double-blind, placebo-controlled trial comparing 3 doses of LCTZ in 521 patients 12 years and older with PAR	Once daily LCTZ 2.5mg or 5mg or 10mg	521	Primary efficacy Δ in mean T4SS over 1st week and total treatment period (Safety assessment made; AEs recorded)
A00379 (Canada)	Phase IIIB, randomized, double-blind, double-dummy, placebo-controlled exploratory trial in EEU comparing single dose LCTZ and cetirizine with placebo in 570 patients 16 years and older with SAR (Re: Onset of Action)	Once daily LCTZ 5mg Once daily Cetirizine 10mg	570	Primary Efficacy Δ in mean Major Symptoms Complex score over Day 2 (Safety assessment made; AEs recorded)
A00264 (Belgium, France, Germany, Italy, Spain)	Phase II, 6 month, multi-center (57), randomized, double-blind, placebo-controlled QOL trial in 551 adults with PAR (Re: Persistence of Effect)	LCTZ 5mg once daily	551	Primary Efficacy Δ in overall QOL score after 4 weeks and mean T5SS over 24hrs, over 4 wks (Safety assessment made; AEs recorded)
A00373 (France)	Phase I randomized, double-blind, placebo-controlled clinical pharmacology study of wheal and flare reaction in 18 adult allergic volunteers	LCTZ 5mg single dose; desloratadine 5mg single dose	18	Primary Efficacy Activity of LCTZ, desloratadine on allergen-induced wheal and flare reaction (Safety assessment performed; AEs recorded)

V. DSI Review / Audit

If this application were to be filed, a Division of Scientific Investigation review and audit would be requested since none of the clinical studies in support of this NDA were conducted within the U.S.

The pivotal and supporting trials were conducted in several countries on three continents: Europe, Africa, and North America. Of these locations, South Africa stands out and will be the subject of the DSI request for the following reasons:

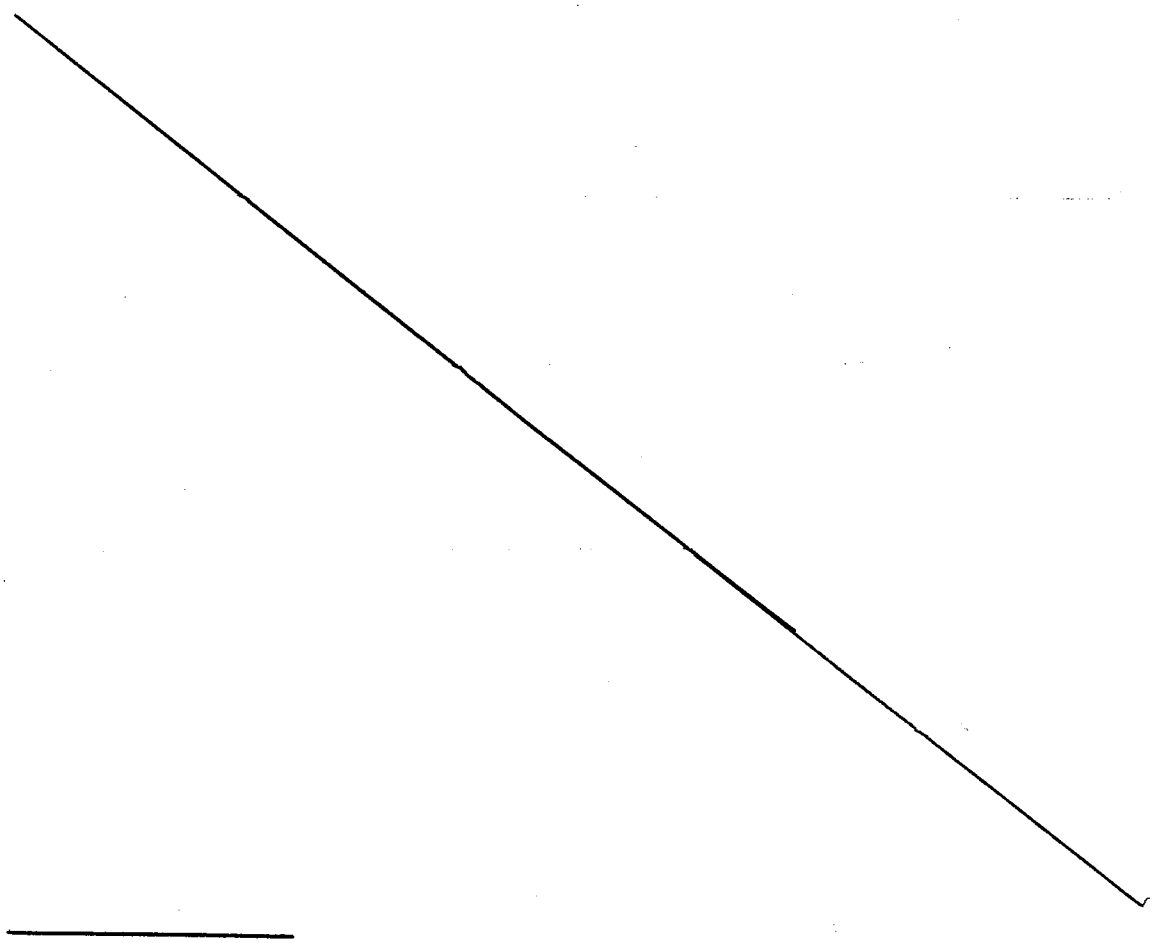
1) Three of the 11 pivotal and supporting trials (two adult SAR [A00268] and PAR [A00266]; one pediatric PAR [A00304]) were conducted at multiple centers in South Africa.

2) The three studies have the same principal/coordinating investigator.

3) Each study involved 20 or more centers.

3) The three trials comprise 48 percent of phase III/IV subjects (in the pivotal and supporting studies).

4) The three trials comprise 26 percent of all subjects in the pivotal and supporting studies investigating LCTZ's safety and efficacy in adult and pediatric subjects with allergic rhinitis.



VII. Summary

This NDA is submitted in support of levocetirizine, the R-enantiomer of the racemate cetirizine, indicated for treatment of the symptoms of SAR, PAR, and CIU, administered as 5mg oral tablets once daily in patients 6 years of age and older.

Outstanding issues include:

1) absence of an Integrated Summary of Efficacy (ISE)

2) reliance upon a scoring system which includes "ocular pruritus," a symptom not usedby the Division as a component of the total nasal symptom score most appropriate for assessing primary efficacy in subjects with allergic rhinitis (See Section IV, "Reviewer Comment")

VIII. Comments to Applicant

Refuse to File Comment:

1a) You did not submit an Integrated Summary of Efficacy (ISE).

1b) Refer to the requirements for applications contained in 21 CFR 314.50(5)(v): "An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications...The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also shall be presented."

Non Refuse to File Comments:

2) Your pivotal and supporting allergic rhinitis studies (A00266, A00268, A00303, A00304, A00265) used the T4SS, which included "ocular pruritus," to assess the primary efficacy outcome. However, the Division's recommended total nasal symptom score (TNSS) does not include "ocular pruritus." Refer to the Agency's draft guidance for industry "Allergic Rhinitis: Clinical Development Programs for Drug Products."

Re-analyze the efficacy data for the studies A00266, A00268, A00303, A00304, and A00265 removing "ocular pruritus" from the total symptom score. Re-calculate the mean change from baseline using the revised total score (i.e., without the "ocular pruritus" symptom).

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/s/

Robert M Boucher
9/18/2006 06:00:47 PM
MEDICAL OFFICER

Lydia McClain
9/18/2006 06:09:57 PM
MEDICAL OFFICER
I concur

Medical Team Leader Memorandum

Date: September 18, 2006

To: NDA 22-064

From: Lydia I. Gilbert-McClain, MD, FCCP
Medical Team Leader, Division of Pulmonary and Allergy Products

Through: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Products

Product: Zyzal® (Levocetirizine dihydrochloride) 5 mg tablets

Applicant: UCB Inc.

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 filing date for this application is September 23, 2006. The application is submitted in electronic format in the structure of a Common Technical Document (CTD) hybrid. Levocetirizine, a selective 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 racemic 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 U.S. 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 a 505 (b)(2) NDA, and UCB's [redacted] 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 and not OTC.

A total of 54 clinical studies with levocetirizine have been submitted with the NDA. Most of these studies are over 10 years old dating back to 1992 when the first studies were initiated in Europe.

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. UCB also stated that their intent to not submit an ISE was mentioned in their Pre-IND briefing document. They indicated that they have submitted a summary of clinical findings in the Summary section (Module 2) of the NDA. Of note, neither at the Pre-IND meeting, nor at the follow up teleconference did the Applicant pose any questions to the Division regarding their intent to not submit an ISE. Whereas, there was a specific question posed about the Integrated Summary of Safety in their pre-IND meeting package.

The Integrated Summary of Efficacy is a required component of the clinical section of an NDA application (21CFR 314.50). The summary provided by the Applicant in Module 2 of the application is not an adequate substitute because critical information is lacking from this summary. This summary is a brief (14 page) overview of the efficacy of levocetirizine for the different indications. Effectiveness data presented by gender, age, and racial subgroups, modifications of dose or dosing interval for specific subgroups, and effectiveness data from other subgroups of the population such as patients with renal failure are not presented. The lack of an Integrated Summary of Efficacy is a Refuse to File Issue. Other standard filing elements and elements specific to a 505(b)(2) application – i.e. patent certification are present.

Apart from the lack of an ISE, there are several other serious deficiencies with this application that even if it were to be filed it would be extremely difficult or impossible to review within the review timelines. As noted earlier, the clinical studies conducted for this program began in the early 1990's and were conducted outside the U.S. without any input from the Agency. The clinical studies conducted to support the allergic rhinitis indication used a symptom score for the primary endpoint that would not be acceptable to the Division for evaluating efficacy. The Division uses a total nasal symptom score comprised of at least 3 of these 4 nasal symptoms: nasal congestion, runny nose, sneezing, and nasal itching as the primary efficacy measure. UCB's allergic rhinitis trials used a score comprised of runny nose, sneezing, nasal itching, and ocular pruritus. In order to assess efficacy, all the allergic rhinitis trials data would need to be reanalyzed removing ocular pruritus from the total symptom score. Because the Applicant did not submit any derived data files (i.e. the variables that were actually used in the analysis) with the application, it is very difficult for the biostatistics team to verify the Applicant's analyses done and to do the more appropriate analyses. The Applicant will need to re-analyze the efficacy data and submit them to the Division for review. The Applicant would also need to submit new derived datasets including the new total symptom score for the new analyses. In the spirit of the Good Review Management Practices (GRMP) guidance of having a complete application at the time of submission to allow for a substantive review with the goal of taking an approval action within the first review

cycle, the deficiencies with this application make the review untenable within this review cycle.

In summary, given that the Applicant has not submitted an Integrated Summary of Efficacy (required by regulation) and given that the deficiencies identified in the application make the review untenable during this review cycle, this application should be a Refuse to File.

Recommended Regulatory Action
Refuse to File.

Comments to the Applicant
The refuse to file comment and additional non-refuse to file comments that are to be sent to the Applicant are captured in the primary medical officer review and I concur with those comments.

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/s/

Lydia McClain
9/19/2006 08:16:52 PM
MEDICAL OFFICER

Badrul Chowdhury
9/20/2006 09:35:01 AM
MEDICAL OFFICER
I concur