The outcomes of the eight pregnancies were healthy babies (4), unknown (2), hypospadias (1), and therapeutic abortion (1).

Of the remaining 60 dropouts, 31 develop symptoms consistent with pharmacologic effect. Twenty-nine subjects in the LCTZ treatment group reported somnolence/fatigue/asthenia compared to only 5 subjects in the placebo group and 2 patients on LTCZ reported dry mouth compared to 0 in the placebo group. Analysis of the remaining 29 subjects dropping out shows no obvious worrisome clinical pattern and other reported events were of similar or lower frequency than in the placebo group. Seven subjects in the LCTZ group compared to 3 in the placebo group dropped out for headaches, however, the incidence of headache was similar between placebo and LCTZ groups for both short-term [≤ 6 weeks] (2.8% placebo; 3.0% LCTZ) and long-term [≥4 months] (19.1% placebo; 18.6% LCTZ) clinical studies.

7.1.3.1 Overall profile of dropouts

Table 15 and accompanying discussion (section 7.1) summarize subject numbers and reasons for study discontinuation in the ISS population.

Table 18 (below) summarizes reasons for dropouts by LCTZ dose (2.5, 5, and 10 mg; the placebo group is included in Table 4). Of note is that a higher percentage of subjects (5.6%) in the lowest LCTZ dose group dropout for lack of efficacy than in the higher dose groups (2.7% [5 mg] and 3.9% [10 mg]). Conversely, the LCTZ group with highest percentage of dropouts for adverse events is the 10 mg group, and somnolence/fatigue/asthenia is more likely in this group. The percent of subjects discontinued for protocol violations is small, and similar, across all LCTZ groups. Only 18 subjects (of 4,056) in the LCTZ groups are lost to follow-up.
Reviewer comment: the applicant did not account for 11 patients.

Table 18. Summary of subject discontinuation and reason, by LCTZ dose, ISS population

	LCTZ 2.5 mg (N = 484) n (%)	**LCTZ 5 mg (N = 3134) n (%)**	**LCTZ 10 mg (N = 438) n (%)**
Completed studies	442 (91.3%)	2905 (92.7%)	405 (92.5%)
Discontinued from studies	42 (8.7%)	226 (7.2%)	33 (7.5%)
Reason for Discontinuation			
Adverse event	9 (1.9%)	51 (1.6%)	11 (2.5%)
Lack of efficacy	27 (5.6%)	85 (2.7%)	17 (3.9%)
Protocol violation	2 (0.4%)	8 (0.3%)	1 (0.2%)
Lost to follow-up	0	18 (0.6%)	0
Withdrawal of consent for personal reasons unrelated to AE or efficacy	2 (0.4%)	30 (1.0%)	2 (0.5%)
Other reason	2 (0.4%)	34 (1.1%)	2 (0.5%)
Unknown	0	3 (0.1%)	0
Missing	0	0	0

Table 19 (below) provides the same information (plus addition of the placebo group for comparison) from the ISS pediatric population 6 to 12 years old. Of note is that the pediatric development program for this NDA exposes all subjects to LCTZ 5 mg, the same dose as most of the adult (18 years and older) study population. The study completion percentage is similar, across groups, to the entire ISS population; percent discontinuation for adverse events is lower, however. Discontinuations for lack of efficacy are higher in the placebo group (4.6%) than the LCTZ group (2.5%), and no unusual pattern for reason for discontinuations is noted.

Table 19. Summary of pediatric subject (6-12 years) discontinuation and reason ISS population

	Placebo (N = 240) n (%)	**LCTZ 5 mg (N = 243) n (%)**
Completed studies	216 (90.0%)	226 (93.0%)
Discontinued from studies	22 (9.2%)	14 (5.8%)
Reason for discontinuation		
Adverse event	3 (1.3%)	2 (0.8%)
Lack of efficacy	11 (4.6%)	6 (2.5%)
Protocol violation	0	0
Lost to follow-up	0	0
Withdrawal of consent for personal reasons unrelated to AE or efficacy	2 (0.8%)	0
Other reason	6 (2.5%)	6 (2.5%)
Unknown	0	0
Missing	2 (0.8%)	3 (1.2%)

7.1.3.2 Adverse events associated with dropouts

Refer to section 7.1, Table 5 and related discussion, and section 7.1.3.

7.1.3.3 Other significant adverse events

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

The only other potentially clinically significant adverse event that occurred at a rate of at least 1% higher in the LCTZ groups than placebo, that has not been previously discussed, is weight gain in adults (LCTZ 1.1% , placebo 0%) in the long-term studies. The UCB post-marketing database does not report any incidence of weight gain however.

There are no reports of seizure, syncope, or cardiac arrhythmia in the ISS database or in the UCB post-marketing database.

7.1.4 Other Search Strategies

No additional search strategies, other than those previously discussed are undertaken.

7.1.5 Common Adverse Events

The most common, clinically relevant, treatment-emergent adverse events in the LCTZ groups, with an incidence of ≥ 1%, and greater than placebo, in the adult (subjects 12 years and older) double-blind, placebo-controlled, confirmatory and dose-ranging Phase 2 and 3 studies are somnolence/fatigue/asthenia, dry mouth, and weight gain. Using the same criteria, the pediatric (6-11years) safety database, which is from two confirmatory efficacy trials (A00303, SAR; A00304, PAR), shows somnolence/fatigue, pyrexia, cough, and epistaxis to be more common in the LCTZ than placebo group. Of note is that while five cases of epistaxis occur in the two-week pediatric SAR trial (four in the LCTZ group), only one case occurs in the LCTZ group of the four-week pediatric PAR trial (A00304). It is difficult, therefore, to link epistaxis in the pediatric population (age 6-12 years) to extent of LCTZ exposure. Similarly, it is difficult to link either cough or pyrexia with LCTZ exposure, given that these symptoms are common manifestations of childhood illnesses, and occur in small enough raw numbers in each pediatric study for the difference to plausibly be attributed to chance alone.
Results are summarized in Tables 20, 21, and 22 in section 7.1.5.4, below.

7.1.5.1. Eliciting adverse events data in the development program

A summary of safety assessments performed in confirmatory efficacy and supporting studies is found in Table 3, above. The safety assessments are appropriate and consistent across the adult confirmatory trials for the SAR (A00268), PAR (A00266), and CIU (A00269, A00270) studies. Similarly, there is consistency in safety assessments across the two pediatric allergic rhinitis studies (A00303, A00304). The primary difference in safety assessment between the adult and pediatric programs is the absence of CBC and blood chemistry data in the pediatric confirmatory efficacy trials. (The applicant presents data in the ISS referencing safety laboratory assessments in 6-12 year olds presented in the NDA for cetirizine [20-346], and from open-label, single-arm studies of children less than 6 years of age, which is below the age-range the applicant seeks in this NDA [six years and older]).

The protocol review for the studies in Table 3 indicates that subjects recorded AE's in the DRC, and that the investigator reviewed these with the subject at scheduled visits. Investigators also instructed subjects to call with AE's, that the subject deemed significant between visits.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The most common reasons for study discontinuation are linked in this review under the rubric "somnolence/fatigue/asthenia" (the MedDRA preferred terms) which reflects the clinical significance of this side effect as well as the biologic plausibility that these terms, when used individually, usually describe the same (somnolence), or similar manifest symptom(s). A review

of the 64 subjects in the pooled safety database dropping out for AE's show 31 for reasons other than pregnancy or somnolence/asthenia/fatigue. There is no evidence to suggest a systematic mis-categorization of subject complaints by investigator use of the MedDRA preferred term.

7.1.5.3 Incidence of common adverse events

Common adverse events (those occurring in at least one LCTZ – exposed subject and pertinent negatives, compared to placebo) are summarized (by MedDRA system organ class and preferred term) from the adult confirmatory efficacy trials, adult dose-ranging studies, and the pediatric clinical development program. Table 20 summarizes common AE's from the adult, single-dose (LCTZ 5 mg) confirmatory studies for SAR (A00268), PAR (A00266), and CIU (A00269); and Table 21 summarizes common AE's from three adult dose-ranging studies (LCTZ 2.5, 5, and 10 mg; A219 and A00265 [PAR], and A00270 [CIU]). (A fourth dose-ranging study [A217, completed 10 years ago] lists adverse events by organ system only and is not included in the table).The NDA contains no pediatric dose-ranging or CIU studies. Table 24 (section 7.1.5.4, below) summarizes common AE's from pediatric (age 6-12 years) allergic rhinitis PC, DB study safety database.

Tables 20 and 21 summarize treatment-emergent adverse events with an incidence of at least 2% in a LCTZ treatment arm. (Study A217 [Table 20], completed in 1996, reports AE's by organ system class only).

Noteworthy observations are the consistency of common adverse events across the various studies, and the dose-related increase in somnolence seen in the dose-ranging studies. In aggregate, Tables 20 and 21 show that the most commonly occurring clinically significant AE is the combination of somnolence/fatigue/asthenia. Headache is the second most common AE, and its incidence is slightly higher in the treatment than in the group.

Table 20. Common adverse events: adult LCTZ 5 mg confirmatory studies (A00266, A00268, A00269)

MedDRA System Organ Class Preferred Term	**Placebo N = 346 n (%)**	**LCTZ 5 mg/day N = 350 n (%)**
Autonomic Nervous System Disorders		
Mouth dry	4 (1.2%)	11 (3.2%)
Body as a Whole-general Disorders		
Back pain	5 (1.5%)	7 (2.0%)
Fatigue	8 (2.3%)	21 (6.0%)
Headache	77 (22.3%)	85 (25.3%)
Influenza-like syndrome	21 (6.1%)	27 (7.7%)
Central & Peripheral Nervous System Disorders		
Dizziness	7 (2.0%)	10 (2.9%)

Gastro-intestinal Disorders		
Abdominal pain	12 (3.5%)	8 (2.3%)
Nausea	10 (2.9%)	8 (2.3%)
Musculo-Skeletal System Disorders		
Back pain	5 (1.5%)	7 (2.0%)
Respiratory System Disorders		
Epistaxis	5 (1.5%)	4 (1.2%)
Pharyngitis	10 (2.9%)	18 (5.1%)
Rhinitis	6 (1.8%)	7 (2.0%)
URI	15 (4.1%)	15 (4.1%)

Table 21. Common adverse events: adult dose-ranging studies (A219, A00265, A00270)

MedDRA System Organ Class Preferred Term	Placebo N = 295 n (%)	LCTZ 2.5 mg N = 308 n (%)	LCTZ 5 mg N = 303 n (%)	LCTZ 10 mg N = 296 n (%)
Autonomic Nervous System Disorders				
Mouth dry	3 (1.0%)	8 (2.6%)	5 (1.7%)	7 (2.4%)
Body as a Whole-general Disorders				
Abdominal pain	8 (2.7%)	5 (1.6%)	4 (1.3%)	4 (1.4%)
Asthenia	1 (0.3%)	5 (1.6%)	1 (0.3%)	14 (4.7%)
Back pain	4 (1.4%)	3 (1.0%)	6 (2.0%)	2 (0.7%)
Fatigue	9 (3.0%)	3 (1.0%)	14 (4.6%)	4 (1.4%)
Fever	0	1 (0.3%)	0	4 (1.4%)
Headache	30 (10.2%)	33 (10.7%)	29 (9.6%)	28 (9.5%)
Influenza-like syndrome	8 (2.7%)	15 (4.9)	10 (3.3%)	12 (4.0%)
Gastro-intestinal Disorders				
Abdominal pain	8 (2.7%)	5 (1.6%)	4 (1.3%)	4 (1.4%)
Gastroenteritis	3 (1.0%)	4 (1.3%)	8 (2.6%)	5 (1.7 %)
Metabolic & Nutritional Disorders				
Thirst	2 (0.7%)	0	4 (1.3%)	0
Musculo-Skeletal System Disorders				
Back pain	4 (1.4%)	3 (1.0%)	6 (2.0%)	2 (0.7%)
Psychiatric Disorders				
Insomnia	0	0	4 (1.3%)	1 (0.3%)
Sleep disorder	0	4 (1.3%)	3 (1.0%)	2 (0.7%)
Somnolence	**5 (1.7%)**	**19 (6.2%)**	**19 (6.3%)**	**25 (8.5%)**
Respiratory System Disorders				
Bronchitis	10 (3.4%)	5 (1.6%)	2 (0.7%)	3 (1.0%)

Coughing	4 (1.4%)	3 (1.0%)	6 (2.0%)	6 (2.0%)
Pharyngitis	23 (7.8%)	26 (8.4%)	14 (4.6%)	19 (6.4%)
Rhinitis	7 (2.4%)	15 (4.9%)	14 (4.6%)	9 (3.0%)
URI	2 (0.7%)	7 (2.3%)	2 (0.7%)	2 (0.7%)

7.1.5.4 Common adverse event tables

Common adverse events occurring in at least 2% (except for pertinent class effect AE's, such as asthenia) of LCTZ subjects are further characterized (by MedDRA system organ class and preferred term) for the adult, short-term (2 weeks of LCTZ exposure) PC, DB studies (Table 22), the adult long-term (4 weeks or greater LCTZ exposure) PC, DB studies (Table 23), and for the pediatric (2-6 weeks of LCTZ exposure) PC, DB database (Table 24). Noteworthy is the incidence of the combination of somnolence/fatigue/asthenia AE's: for the short-term adult studies the aggregate incidence is 11.4%, and for the adult long-term studies, 12.9%. This finding suggests that tolerance to somnolence does not develop with sustained LCTZ use. The pediatric study shows a lesser incidence of somnolence/fatigue/asthenia which is likely a function of the constraints of symptom reporting in pediatric studies generally.

Table 22. Common adverse events: adult, short-term (2 weeks), PC, DB studies

MedDRA System Organ Class Preferred Term	**Placebo N = 1137 n (%)**	**LCTZ 2.5/5 mg/day N = 1705 n (%)**	**LCTZ Pooled N = 2114 n (%)**
Total No. Subjects with TEAE	**477 (42.0%)**	**726 (42.6%)**	**910 (43.0%)**
Gastrointestinal Disorders			
Dry Mouth	12 (1.1%)	43 (2.5%)	54 (2.6%)
General Disorders & Administrative Site Conditions			
Asthenia	12 (1.1%)	21 (1.2%)	37 (1.8%)
Fatigue	21 (1.8%)	56 (3.3%)	65 (3.1%)
Infections/Infestations			
Nasopharyngitis	37 (3.3%)	75 (4.4%)	87 (4.1%)
Nervous System Disorders			
Headache	155 (13.6%)	215 (12.6%)	254 (12.0%)
Somnolence	18 (1.6%)	100 (5.9%)	137 (6.5%)
Respiratory, Thoracic and Mediastinal Disorders			
Epistaxis	15 (1.3%)	21 (1.2%)	23 (1.1%)
Pharyngolaryngeal pain	16 (1.4%)	35 (2.1%)	44 (2.1%)

Table 23. Common adverse events: adult, long-term (≥ 4 weeks), PC, DB studies

MedDRA System Organ Class Preferred Term	**Placebo N = 580**	**LCTZ 5 mg/day N = 560**

	n (%)	n (%)
Total No. Subjects with TEAE	**344 (59.3%)**	**323 (57.7%)**
Gastrointestinal Disorders		
Abdominal Pain	14 (2.4%)	14 (2.5%)
Diarrhea	13 (2.2%)	12 (2.1%)
Dry Mouth	8 (1.4%)	15 (2.7%)
Nausea	8 (1.4%)	12 (2.1%)
General Disorders & Administrative Site Conditions		
Asthenia	9 (1.6%)	12 (2.1%)
Fatigue	27 (4.7%)	35 (6.3%)
Influenza-like illness	8 (1.4%)	13 (2.3%)
Pyrexia	13 (2.2%)	15 (2.7%)
Infections/Infestations		
Bronchitis	13 (2.2%)	17 (3.0%)
Gastroenteritis	20 (3.4%)	16 (2.9%)
Nasopharyngitis	51 (8.8%)	51 (9.1%)
Pharyngitis	25 (4.3%)	24 (4.3%)
Sinusitis	15 (2.6%)	18 (3.2%)
URI	11 (1.9%)	12 (2.1%)
Musculoskeletal & Connective Tissue Disorders		
Back pain	22 (3.8%)	19 (3.4%)
Nervous System Disorders		
Headache	111 (19.1%)	104 (18.6%)
Somnolence	10 (1.7%)	25 (4.5%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	22 (3.8%)	16 (2.9%)
Epistaxis	12 (2.1%)	7 (1.3%)
Pharyngolaryngeal pain	48 (8.3%)	49 (8.8%)
Rhinitis	11 (1.9%)	12 (2.1%)

Table 24. Common adverse events: pediatric (6-12 years), PC, DB studies

MedDRA System Organ Class Preferred Term	**Placebo N = 240 n (%)**	**LCTZ 5 mg/day N = 243 n (%)**
Total No. Subjects with TEAE	**107 (44.6%)**	**115 (47.3%)**
General Disorders & Administrative Site Conditions		
Asthenia	3 (1.3%)	2 (0.8%)
Fatigue	0	4 (1.6%)
Pyrexia	5 (2.1%)	10 (4.1%)
Infections/Infestations		
Bronchitis	5 (2.1%)	5 (2.1%)
Influenza	14 (5.8%)	8 (3.3%)
Pharyngitis	5 (2.1%)	5 (2.1%)
URI	19 (7.9%)	13 (5.3%)
Injury, Poisoning, Procedural Complications		
Excoriations	4 (1.7%)	0

Nervous System Disorders		
Headache	25 (10.4%)	23 (9.5%)
Somnolence	1 (0.4%)	7 (2.9%)
Respiratory, Thoracic and Mediastinal Disorders		
Bronchospasm	4 (1.7%)	5 (2.1%)
Cough	2 (0.8%)	8 (3.3%)
Epistaxis	1 (0.4%)	6 (2.5%)

7.1.5.5 Identifying common and drug-related adverse events

The most common and clinically relevant drug-related adverse event is the combination of somnolence/fatigue/asthenia. This combination occurs consistently across adult studies, and is not unexpected, given that LCTZ is the R-enantiomer of the racemate cetirizine, which also caused sedation-related effects in placebo-controlled clinical trials (19.6% of ceterizine-exposed subjects reported somnolence or fatigue vs. 8.9 % for placebo). Dry mouth is the only other AE present across studies that is reasonably likely to be drug-related.

7.1.5.6 Additional analyses and explorations

For somnolence/fatigue/asthenia, there is no evidence of adaptation over time, using data from the adult short-term (2-week) (incidence =11.4%) and long-term [≥ 4 weeks] (incidence = 12.9%) clinical trials. The dose-ranging studies show a direct correlation between increasing LCTZ dose and somnolence/fatigue/asthenia.

The applicant did not perform subgroup analyses in the product development program.

The ISS tabulation of AE's for PC, DB studies shows that approximately 10% more females (age 12 and over) than males (50.8% versus 39.9%) reported AEs, although there is no evidence of gender-specific differences in incidence for a specific AE. For both sexes, the most common TEAE's are somnolence/fatigue/asthenia and headache.

No comments regarding subjects 65 years and older can be made, since the exposed cohort only numbers 43.

Pediatric data are presented in Table 13.

The ISS presents AE data from short-term controlled trials in Asian subjects, and compares this to analogous data from European subjects. The Asian cohort with LCTZ exposure numbers only 166 subjects. The same percent of Asian and European subjects completed the short-term trials (92.5%) and the AE incidence is similar (1.2% Asian, and 1.5% European).

7.1.6 Less Common Adverse Events

The safety review identified no rare AE's of significant concern in the clinical studies database.

7.1.7 Laboratory Findings

The pediatric clinical development program for 6-12 year-olds (studies A00303 and A00304) did not contain laboratory assessments. (The applicant is relying on this information from cetirizine for this population).

The discussion of clinical laboratory data is from analyses on the pooled safety database and a review of individual study reports. The review references the UCB Global Drug Safety database where specified.

Laboratory tests from the clinical pharmacology and clinical efficacy programs include hematology (CBC with differential) and biochemistry profiles. Within the biochemistry profile, no clinically significant changes in sodium or potassium occur. The discussion includes potentially clinically significant changes in liver and renal function tests. There are no hematologic SAE's and no hematology-related drop-outs. There is no evidence in the ISS of renal-related adverse effects. Regarding hepato-biliary SAE's, there is one drop-out for cholecystitis (discussed below).

Hematology:
A review of the pooled safety database notes no consistent LCTZ effect on RBC's: 15 non-serious RBC-related AE's are reported 1,960 LCTZ –exposed subjects, 12 years and older : 12 are mild decreases in hematocrit, one a mild increase in hematocrit, and two unspecified, mild RBC abnormalities.

Six platelet-related non-serious AE's were reported: four subjects had mild-to-moderate thrombocytopenia, and one subject had thrombocytosis all of which resolved. One subject had an unspecified platelet disorder.

The database notes no consistent effect on eosinophil counts. Two reports of mild eosinophilia in two subjects were reported as non-serious AE's.

Fourteen LCTZ-exposed subjects report WBC or lymphatic AE's: none were SAE's and there were no associated drop-outs. Six subjects had mild leukocytosis, four had mild leucopenia, one had an unspecified WBC count abnormality, and three had mild lymphadenopathy.

Renal:
Six subjects have mild, resolving increases in blood urea nitrogen. No SAE's occur and there are no renal-related drop-outs.

Hepatobiliary:

The baseline and worst mean values for ALT, AST, total bilirubin, and alkaline phosphatase were within normal limits. Analysis shows no evidence of a treatment effect on liver function, as the mean change from baseline to the worst post-treatment value was similar between placebo and LCTZ-exposed groups.

The pooled safety database shows 36 subjects with hepatobiliary-related AE's. One (cholecystitis) is a SAE, with subject withdrawal. The incidence of hepatobiliary dysfunction is < 1% for the database. Table 25 summarizes the review of the 35 other AE's, none of which led to study drop-out.

The hepatobiliary findings are not inconsistent with those of the racemate cetirizine, for which the proportions of cetirizine-treated subjects with abnormal values in the cumulative database of all studies is 2% for ALT (52/2932) and 1% for AST (27/2926.

Table 25. Summary of hepatobiliary-related AE's from pooled database

MedDRA Preferred Term	Daily mg Dose	Onset (days)	Outcome	Intensity
Hepatic pain	5	39	Resolved	Mild
Hepatic pain	5	76	Resolced	Moderate
Blood bilirubin incr.	5	15	Resolved	Mild
Blood bilirubin incr.	5	28	Ongoing	Mild
Blood bilirubin incr.	5	1	Ongoing	Mild
Blood bilirubin incr.	10	15	Resolved	Moderate
Blood bilirubin incr.	5	1	Ongoing	Mild
Blood bilirubin incr.	5	1	Resolved	Mild
Enzyme abnl.	5	10	Resolved	Mild
LFT abnl	30	7	Resolved	Moderate
LFT abnl	10	15	Resolved	Moderate
Hepatic enzyme inc.	30	7	Resolved	Moderate
Hepatic enzyme inc.	2.5	29	Resolved	Mild
Hepatic enzyme inc.	5	28	Resolved	Mild
Hepatic enzyme inc.	5	15	Ongoing	Moderate
Hepatic enzyme inc	5	190	Ongoing	Mild
Hepatic enzyme inc	5	24	Resolved	Moderate
Hepatic enzyme inc	5	1	Ongoing	Mild
ALT incr.	30	7	Resolved	Moderate
ALT incr.	5	44	Resolved	Mild
ALT incr.	2.5	16	Resolved	Mild
ALT incr.	10	15	Resolved	Moderate
ALT incr.	2.5	14	Resolved	Moderate
ALT incr.	10	15	Ongoing	Mild
ALT incr.	5	16	Ongoing	Mild
ALT incr.	5	29	Resolved	Mild
ALT incr.	5	10	Resolved	Moderate
ALT incr.	5	6	Resolved	Mild
ALT incr.	5	181	Ongoing	Moderate
AST incr.	5	2	Resolved	Mild
ALT, AST incr.	5	29	Resolved	Mild
ALT, AST incr.	5	33	Resolved	Moderate

ALT, AST incr.	5	30	Resolved	Mild
ALT, AST incr.	2.5	2	Ongoing	Moderate
ALT, AST incr.	5	11	Resolved	Moderate

The UCB Global Drug Safety Database contains 16 cases which include 19 events of hepatobiliary disorders, seven of which are hepatitis, five are jaundice, and three cholestasis. The seven hepatitis cases include hepatitis (unspecified, 3), cytolytic hepatitis (2), and cholestatic hepatitis (2), with an onset from five days to two years after start of LCTZ therapy. Five cases describe a positive dechallenge. None of the cases resulted in death or liver transplantation. Of the five cases of jaundice, one had cholestasis, one subject was on multiple medications that could have contributed to the enzyme abnormality, one case had a pre-treatment diagnosis of diabetes mellitus and chronic renal insufficiency, one subject was taking LCTZ and erythromycin, and one subject was diagnosed with acute Ebstein-Barr viral infection. All cases resolved after discontinuation of LCTZ, and, in some cases, the additional medications. The Global Safety database also contains 21 events of abnormal transaminase, LFT, and bilirubin increases. In all cases except one, the abnormalities resolved with LCTZ dechallenge, usually in association with discontinuation of other medications. The exceptional case was that of a 71-year-old poly-medicated male with diabetes mellitus and hyperthyroidism who developed increased transaminases two years after initiation of LCTZ therapy. Levocetirizine was discontinued, but up to the time of reporting the liver enzymes had not returned to normal.

7.1.7.1 Overview of laboratory testing in the development program

The clinical pharmacology section of the development program collects laboratory data in 15 of 25 studies, but these results are not analyzed since subjects receive limited dosing.

The primary database for overview of laboratory testing is from short- and long-term PC, DB controlled studies in the adult (12 years and older) development program. This database shows more than 2,000 subjects exposed to LCTZ from two weeks to six months. Eleven studies comprise the core database population; nine are short-term exposure (two-four weeks: A217, A219, A222, A00265, A00266, A00268, A00269, A00270, and A00333), and two are long-term exposure (A00264; six months; N exposed = 276, and A00306; 12 weeks; N exposed = 303). Table 26 summarizes laboratory parameters assessed, number of subjects exposed, mean baseline and worst on-treatment values.

Table 26. Summary of laboratory parameters assessed and p-values For baseline-to-worst changes, placebo compared to LCTZ-Exposed subjects in adult PC, DB, controlled studies

Parameter (Units)	Placebo (n = 1728)		LCTZ (N = 2709)	
	Baseline	Worst	Baseline	Worst
RBC (10^6 cells/μL)				
Mean	4.70	4.69	4.70	4.69
Hematocrit (5 Ercs vol)				
Mean	42.98	42.72	43.05	42.68
Hemoglobin (g/dL)				

Mean	14.12	13.99	14.04	13.94
WBC (10^3 cells/μL)				
Mean	7.24	7.01	7.10	7.01
Neutrophils (10^3 cells/μL)				
Mean	4.14	3.94	4.04	3.92
Lymphocytes (10^3 cells/μL)				
Mean	2.31	2.29	2.29	2.31
Monocytes (10^3 cells/μL)				
Mean	0.43	0.43	0.42	0.43
Basophils (10^3 cells/μL)				
Mean	0.03	0.03	0.03	0.04
Eosinophils (10^3 cells/μL)				
Mean	0.32	0.22	0.30	0.32
Platelets (10^3 cells/μL)				
Mean	258.6	255.0	254.9	253.7
ALT (U/L)				
Mean	21.0	21.0	20.7	21.3
AST (U/L)				
Mean	21.4	22.0	21.1	21.5
Total bilirubin (mg/dL)				
Mean	0.62	0.61	0.62	0.60
Alkaline phosphatase (U/L)				
Mean	77.0	74.9	70.5	69.2
Urea (mg/dL)				
Mean	30.0	30.0	30.0	30.2
Creatinine (mg/dL)				
Mean	0.97	0.98	0.97	0.97

(a) Wilcoxon Rank Sum Test

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Refer to section 7.1.7.1 and Table 26, above. Two PC, DB, controlled studies are the basis for the development program's long-term exposure assessments in subjects over 12 years old (A00264 and A00306), and are included in Table 26, and discussed above.

7.1.7.3 Standard analyses and explorations of laboratory data

The central tendency analysis is found in section 7.1.7.1.

Discussion of outliers is in section 7.1.7. Of note is that there is only one clinical study drop-out for a laboratory AE (cholecystitis with abnormal LFT's, discussed above).

7.1.7.4 Additional analyses and explorations

Analysis of laboratory parameters for dose-dependency is limited by the relatively small number of laboratory-related AE's and the fact that most subjects receive 5 mg per day of LCTZ. For example, in assessing changes in hepatic enzymes (Table 25), there are not enough subjects receiving more than LCTZ 5 mg daily to permit inferences to be made regarding potential dose dependency for a given abnormality. Of note, all of the hepatic enzyme changes are mild to moderate, most are documented as resolving (regardless of LCTZ dose), and only one is associated with study discontinuation.

An analysis of time dependency in the ISS (assessed by estimate of the hazard function by treatment group) shows risk of somnolence, fatigue, asthenia, and dry mouth are time dependent. The cumulative risk of somnolence increases from 5.7% to 6.5% over two to 16 weeks of treatment (compared to 1.4% to 1.7% for placebo).

Limited or no laboratory data are available for a substantive discussion of drug-demographic effect. Specifically, no laboratory parameters are assessed in the pediatric (6-12 years of age) clinical program, and the geriatric database (ages 65 and older) contains only 43 LCTZ-exposed subjects (although descriptive statistics suggest percent changes from baseline for ALT, AST, BUN, and creatinine are less than for subjects under age 65).

The review finds no evidence for gender-related laboratory differences. Approximately 90% of pooled database subjects are Caucasian; in four short-term, single- or double-blinded, active-controlled studies in 166 Asian subjects, 18 years and older, no differences in laboratory parameters is found.

For drug-disease laboratory assessments, the ISS discusses renal and hepatic disease. Pharmacokinetic studies show subjects with mild to severe renal impairment with a prolonged LCTZ half-life, necessitating dose-adjustment. Two studies in subjects with renal impairment (A230 and A234) show no significant change in laboratory parameters with appropriate dose adjustment. For hepatic disease, the ISS presents no specific laboratory assessments. Hepatic metabolism of LCTZ is less than 20%. The ISS notes however, that dose adjustment is necessary for subjects with combined hepato-renal dysfunction, and references a cetirizine study showing that 16 subjects with chronic liver disease had a 50% increase in drug half-life compared to 16 healthy subjects, resulting in labeling that dose-adjustment in chronic hepatic disease *may* be necessary.

The NDA contains no formal studies assessing drug-drug interactions with LCTZ. The applicant states that LCTZ does not inhibit cytochrome P450 isoenzymes and has a similar profile to cetirizine, for which no significant drug interactions have been found in several *in vivo* drug interaction studies.

7.1.7.5 Special assessments

Laboratory assessments of areas of special concern (hepatotoxicity) are described in above sections.

7.1.8 Vital Signs

The ISS states that vital signs data (systolic and diastolic blood pressure, pulse rate, and body weight) are not analyzed from the pooled database. The applicant references cetirizine, and states that, based on clinical experience with cetirizine, no effects on VS are anticipated. Descriptive data from the LCTZ clinical pharmacology program do not suggest an effect on VS.

7.1.8.1 Overview of vital signs testing in the development program

Refer to section 7.1.8.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.8.

7.1.8.3 Standard analyses and explorations of vital signs data

Refer to section 7.1.8.

7.1.8.4 Additional analyses and explorations

Other than those discussed above, this review conducts no additional analyses or explorations.

7.1.9 Electrocardiograms (ECG's)

Data for assessment of ECG's comes from four sources:

1) Study A00263 is a six-day, multiple dose (30 mg/day of LCTZ, five times the label dose of LCTZ) pharmacology study that analyzes ECG's on Days 0 thru 6 in 36 male and female subjects (age range 21 to 74 years). In the study, standard 12-lead ECG's at baseline and post-dosing intervals 0.5, 1, 1.5, 2, 4, 6, and 12 hours on Days 0, 1, and 6 were taken. On days 2 thru 5, ECG's are obtained pre-dose and 1 hour post-dose. A final ECG is obtained on Day 7, 24 hours after last dosing. Results show no apparent difference between lower and higher risk subjects. No QTcF change from baseline > 60 msec was observed and no ECG showed a QTc value ≥ 500 msec, regardless of correction method used (Fridericia, Bazett, and Framingham).

2) Study A00266, a randomized, PC, DB, adult PAR confirmatory efficacy trial comparing LCTZ 5 mg/day with placebo, in which ECG data was collected at baseline and during

expected peak plasma concentration of LCTZ (1 hour after intake). Analysis for 111 LCTZ-exposed subjects showed no difference between placebo and LCTZ groups (using Bazett and Fridericia correction), and no gender differences.

3) Two single-dose (LCTZ 5 mg) clinical pharmacology studies (A232 and A238) show no significant ECG changes at multiple post-dosing intervals (1, 2, and 24 hours).

4) Study A00419, submitted with the safety update, is a randomized, PC cardiac repolarization study of LCTZ on 52 healthy adult subjects. In this study design (four-way crossover) all subjects were exposed to LCTZ 5 mg, LCTZ 30 mg, moxifloxacin 400 mg, and placebo for three days each. Correction of QT interval by gender and study-specific heart rate correction, Fridericia's, and Bazette's methods did not demonstrate a difference from baseline in QTc change.

The applicant also references the cetirizine clinical development program which concludes that no clinically significant mean changes in QTc occur in four studies when CTZ is given in daily doses up to 60 mg, six times the label dose. From this study it can be concluded that LCTZ does not have an effect on QT.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Refer to section 7.1.9.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.9.

7.1.9.3 Standard analyses and explorations of ECG data

Refer to section 7.1.9.

7.1.9.4 Additional analyses and explorations

Based on findings discussed in section 7.1.9, data from the cetirizine clinical development program, and absence of clinically significant post-marketing events for LCTZ, this review conducts no additional analyses or explorations. Note is made of limited single studies for cognitive function (A00260, N =18 healthy volunteers) and driving performance (A246, N = 51 healthy volunteers). The results of A00260 suggest LCTZ 5 mg does not affect cognitive or psychometric functions and the results of A246 suggest that LCTZ 5 mg/day is equivalent to placebo regarding standard deviation of lateral position, a measure of driving ability. The results

of both studies are limited, not replicated, and insufficient to make a valid determination of effect.

7.1.10 Immunogenicity

The pooled safety database contains no reports of LCTZ-associated hypersensitivity. However, several reports of hypersensitivity were reported in the post marketing safety database. Refer to section 7.1.2 for reports of hypersensitivity from the UCB Global Drug Safety database.

7.1.11 Human Carcinogenicity

The development program has no human carcinogenicity studies. No pre-clinical carcinogenicity studies were conducted. The applicant references cetirizine which is not shown to have carcinogenic potential.

7.1.12 Special Safety Studies

There are no special safety studies, and no indication that any are warranted at this time.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

From the ISS and post-marketing global database there is no evidence of LCTZ abuse potential or significant withdrawal phenomena. The post-marketing database contains nine reports that may reflect withdrawal symptoms: antepartum drug dependence (1 case), drug withdrawal headache (2 cases), and drug withdrawal syndrome (6 cases, which lump together withdrawal pruritus, malaise, restlessness, and insomnia). However, these 9 cases in such an extensive database do not suggest a signal for abuse potential or withdrawal phenomena.

7.1.14 Human Reproduction and Pregnancy Data

Section 7.1.3 discusses the outcomes of eight pregnancies from the pooled database occurring in LCTZ-exposed subjects. No pregnancies occur in the non-pooled studies. The post-marketing safety database contains 30 reports of pregnancy on LCTZ treatment: there is one spontaneous abortion, one missed abortion, and one unspecified congenital anomaly, for which a therapeutic abortion was performed.

7.1.15 Assessment of Effect on Growth

The development program did not assess effect on growth. This is acceptable as this molecule is not expected to have an effect on growth velocity.

7.1.16 Overdose Experience

The ISS does not cite cases of LCTZ overdose in either the clinical development program or from the post-marketing database. (Pre-clinical data show changes in motor activity, posture,

respiratory effort, and gastrointestinal erosion in rats at doses greater than 240 mg/kg. In dogs LCTZ at 32 to 320 mg/kg doses elicits vomiting. The median lethal doses for mice and rats are 804 mg/kg and 472 mg/kg, respectively).

7.1.17 Postmarketing Experience

Post-marketing experience comments occur, as indicated, throughout the safety review. The applicant states that LCTZ has not been withdrawn from any foreign market (more than 80 countries) for reasons of safety or efficacy.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Refer to sections 4.1 and 7.1 for additional clinical data source discussion. The primary clinical data source for the safety review is the pooled safety database of 44 completed studies that contains data on a total of 4,067 unique, LCTZ-exposed subjects (243 of whom are children 6-12 years of age). Thirty-five of the studies are from Europe, three from South Africa, three from China, two from Canada, and one from Taiwan. An additional data source are four non-pooled completed studies, which include an additional 688 LCTZ-exposed subjects. (Six studies are on-going at the time of data closure [March, 2006]). Narratives for SAE's and dropouts as well as summary tables for safety data, and individual laboratory measurements by patient, are provided in studies included in the pooled database. Case report forms are not provided for all subjects in any study, although specific CRF's of all AE's leading to study drop-out are provided.

Tables 28 and 29 (Appendix 2A) summarize the clinical development program by phase, database (pooled and non-pooled studies) and safety assessments by study.

7.2.1.1 Study type and design/patient enumeration

Refer to Table 28 (Appendix 2A) for summary of the clinical development program. The summary table includes individual study descriptive information, dose, number of subjects exposed to LCTZ, and special studies.

7.2.1.2 Demographics

Refer to Appendix 2B for the following demographic tables: Phase 1 Healthy Volunteers (Table 30); Phase 2 Allergic Volunteers (Table 31); Phase 3 PAR, SAR, and CIU Subjects $\geq$ 12 years of age (Table 32); and Phase 3 Pediatric (6-12 years) SAR and PAR subjects (Table 33).

Of note in these tables are the following: 1) the program exposes only 206 children age 6-12 to LCTZ 5 mg (the age range the applicant seeks SAR, PAR, and CIU indications for), 2) only 42 subjects older than age 65 years are exposed to LCTZ, and 3) the vast majority of LCTZ-exposed subjects are Caucasian (> 90% across all studies); in the adult studies, blacks compose less than 2% of the LCTZ-exposed population.

7.2.1.3 Extent of exposure (dose/duration)

Most LCTZ exposure to subjects in the clinical development program is 5 mg per day. In the safety database of pooled 4,067 subjects, 3,134 (77.1%) receive 5 mg/day; 484 (11.9%) 2.5 mg/day; 438 (10.8%) 10 mg/day; and 36 (0.9%), 30 mg as a single dose. Most subjects receive LCTZ for two to six weeks, and a total of 154 subjects receive LCTZ for more than 26 weeks at 5 mg/day.

The following comments address ICH-E1A guidance on extent of exposure for the LCTZ clinical development program: for drugs with potentially chronic exposure, the number of LCTZ-exposed subjects to the proposed label dose is satisfactory (over 3,000), although the duration of exposure is less so (ICH guidance is for 300-600 subjects exposed for six months; 154 subjects are exposed for this duration in the LCTZ program. Notwithstanding the relatively small numbers in the six month cohort, LCTZ is not a new molecular entity, there is no evidence from the 15 year development program, or the post-marketing database, that there is a likelihood that the rate of AE's increases over time, and LCTZ is chemically related to cetirizine, the AE and safety profiles for which are well-described. Therefore, the exposure, and extent of exposure data for LCTZ, in these contexts, is satisfactory.

The LCTZ development program presents no substantial subgroup analyses; the limited data for renally-impaired subjects, however, again in conjunction with what is known about the racemate, is not cause for concern.

The applicant references the cetirizine database regarding age and ethnic sub-population exposure. This approach seems reasonable given the molecular, PK, and PD similarities between LCTZ and CTZ.

Table 27 summarizes LCTZ exposure data for all placebo-controlled clinical trials.

Table 27. Summary of Duration of Exposure to LCTZ in PC Trials

Study Grouping/Subject Category	N	Duration (Weeks)						
		0 -≤ 1	0 -≤ 2	0 -≤ 4	0 -≤ 6	0 -≤ 13	0 -≤ 26	> 26
Children ≥ 6-≤ 12 years								
Short-term LCTZ	243	1	4	114	89	35	0	0
Children and Adults ≥ 12 years								
Short-term LCTZ	2114	293	448	741	566	59	0	0
Long-term LCTZ	560	5	7	11	19	147	209	154

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Virtually all clinical studies of LCTZ are by the applicant and included in the ISS database. Comments on pertinent post-marketing data appear throughout the review. Literature review for LCTZ-related safety issues shows 10 articles, six of case series and four case reports, that reference safety. The most salient observation in the case series involves sedation and drowsiness (consistent with what appears in the ISS). Four case reports describe three patients with dermatologic AE's including exfoliation and fixed drug eruption.

7.2.2.1 Other studies

Refer to 7.2.2.

7.2.2.2 Postmarketing experience

The UCB Global Drug Safety database contains post-marketing safety data for LCTZ. Discussion of salient post-marketing events occurs in review sections of AE's.

7.2.2.3 Literature

Refer to 7.2.2. and the Reference section at the end of this document.

7.2.3 Adequacy of Overall Clinical Experience

Refer to 7.2.1.3 for discussion of demographic subsets and populations with pertinent risk factors.

Notwithstanding the limitations commented upon in section 7.2.1.3, the doses and duration of exposure are adequate to appropriately assess safety in the adult (ages 12 and older) and pediatric (ages 6-11 years) development programs (SAR, PAR, and CIU). Similarly, the design of the clinical trials supporting the adult and pediatric indications is satisfactory for safety assessments, and there are no significant unanswered safety questions. It is reasonable to reference cetirizine for most subgroup analyses not addressed in this NDA (specifically, those 65 years and older, and blacks).

The applicant did not conduct PK or dose-ranging studies in the pediatric population (ages 6-11 years) for which it is proposing a dose of 2.5 to 5 mg once daily. Rather, UCB references available literature which shows that pediatric exposure to LCTZ 5 mg is twice that of adults (refer to Section 5.1). The literature-derived data supports a dose of 2.5 mg once daily, rather than the proposed 2.5 to 5 mg, in the 6-11 year age group. Additionally, given the relatively high incidence of sedation-related effects of LCTZ in adult subjects, it is unlikely that the same milligram per day dose in children will not have the same, or, indeed, greater effect, irrespective of the findings regarding sedation in the pediatric trials. It is also important to note that LCTZ is given once in the evening in all of the DB, PC trials, thus making it likely that the true incidence

of sedation is under-reported in all age groups. For these reasons, the preponderance of the evidence suggests that LCTZ 2.5 mg, but not 5 mg, is the appropriate dose in children 6-11 years old. The pediatric safety data is otherwise satisfactory to support the 2.5 mg dose.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The pre-clinical program was adequate to explore potential adverse events. Refer to section 3.2 for a complete discussion.

7.2.5 Adequacy of Routine Clinical Testing

Refer to Table 13 (section 7.1) and Table 29 (Appendix 2A) for summaries of routine clinical testing. The extent of clinical testing is generally adequate across the clinical development program. Of note is the absence of LCTZ laboratory data for the pediatric population. However, availability of adequate pediatric laboratory safety data from the racemate CTZ, which supports the safety of CTZ use in children, is a satisfactory surrogate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Based on the minimal hepatic metabolism of LCTZ as well as the known lack of significant drug interactions for CTZ, the applicant did not conduct formal drug interaction studies. (Ketoconazole, erythromycin, azithromycin, cimetidine, and pseudoephedrine do not interact with CTZ pharmacokinetics, and vice-versa).

In vitro interaction studies of LCTZ on CYP expression indicate that LCTZ is unlikely to induce drug metabolizing enzymes in humans.

Levocetirizine excretion is by both glomerular filtration and tubular secretion. Although not formally studied, the applicant expects agents that affect renal excretion, such as probenicid, to reduce renal clearance by about 50%.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant's efforts to detect specific adverse events are adequate. As the R-enantiomer of the racemate cetirizine, the safety review expects to see certain class-specific adverse effects for LCTZ, such as sedation and dry mouth, as well as occasional, mild, transient hepatic transaminase elevations. Routine clinical laboratory testing in the development program is adequate to assess these events, and confirm that it is reasonable (by comparison of AE incidence rates for the two drugs) to reference CTZ in the discussion of AE's. Similarly, ECG monitoring and specific studies for LCTZ effect on QTc prolongation are satisfactory, and reflect the data from the CTZ development program showing lack of any significant effect. Conversely, there are

no expected AE's for CTZ that do not appear in the LCTZ ISS. The safety profiles for the two drugs are similar, and without any obvious exceptions.

7.2.8 Assessment of Quality and Completeness of Data

The overall LCTZ clinical development program is extensive, as measured by time (14 years) and by number of clinical trials in the safety database (54). The conduct of the trials, which occur in many different countries, appears quite consistent over time, and the confirmatory and supporting efficacy trials are generally adequate and well-controlled. There is no evidence from the safety review that systematic study design problems are present that affect the overall assessment that LCTZ is generally safe in the adult population. The quality and completeness of the safety data is satisfactory and without obvious shortcomings (notwithstanding concerns discussed in sections 7.2.3 and 7.2.4 regarding pediatric development).

7.2.9 Additional Submissions, Including Safety Update

In addition to the 120-Day Safety Update, the applicant submitted three submissions in response to clinical IR's during the review cycle. The IR's addressed the following issues, all of which were satisfactorily resolved: location of pollen count data for Study A00303, clarification of reasons for discontinuation of two subjects in study A00266, clarification of the definition of the intent-to-treat population in study A00269, and clarification of the baseline entry criteria for study A00412.

The 120-Day Safety Update identifies no new safety issues apart from those already addressed in this safety review. Specific items in the update not found in the original ISS include:
1) Safety results from three recently completed studies (A00410: Korean study 5 mg LCTZ compared with 10 mg CTZ in 423 subjects with dermatitis/eczema; A00419: a 52-subject four-way crossover study of cardiac repolarization [discussed in section 7.1.9]; A00392: a failed (due to lack of enrollment) study of continuous versus on-demand LCTZ treatment over six months in PAR subjects). The AE profiles for these three studies mirror those seen in the ISS.
2) New post-marketing reports to the UCB Global Drug Safety database which, upon review, do not raise new concerns about the safety of LCTZ. One death (unrelated to LCTZ) was reported and is discussed in section 7.1.1).
Except for study A00419, there were no new clinical laboratory, vital signs, or ECG data to report (except study A00419). The safety update did not contain any new reports of SAEs, drug-drug interactions, or overdose.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Two LCTZ-related AE's merit discussion as the most potentially clinically significant: sedation-related events (somnolence/fatigue/asthenia) and hepatobiliary changes.

Sedation-related AE's: Although these effects are expected (based upon class-effect and the chemical relationship of LCTZ to CTZ), sedation is the most common reason, except for lack of

efficacy, for subjects to drop out of clinical studies. The overall incidence of sedation-related AE's among subjects 12 years and older receiving 2.5 or 5 mg LCTZ daily is 10.4%. Dose-ranging studies show a higher incidence of sedation in cohorts receiving the 10 mg daily dose. Of note is that all of these studies administer LCTZ once daily in the evening. The incidence of sedation would likely be higher if LCTZ dosing is in the morning. The applicant, in the proposed label, [redacted] For the reasons cited above, the label should [redacted] reflect dosing as it occurs in the clinical studies. In this particular instance, the applicant should not reference cetirizine (for which dosing is once daily without regard to time of day).

Sedation in the pediatric development program is likely under-reported. Given the sedation concerns raised in the adult program, the fact that no dose-ranging studies are performed in children, the fact that key bridging studies of LCTZ and CTZ do not clearly show that the appropriate LCTZ dose (as the R-enantiomer of cetirizine) is half the CTZ dose, and the fact that the pediatric confirmatory studies for the NDA give the same 5 mg/day dose to children as well as adults, this safety review cannot endorse either the 2.5 or 5 mg dose of LCTZ as the safest dose in the pediatric population.

Hepatobiliary changes: The safety review shows data that suggest a roughly 1% incidence of transient elevation of hepatic transaminases, which is similar to the 1-2% reported for CTZ. Although alone it is not necessarily clinically relevant, it may become so depending upon potential concomitant medical therapy that patients might be receiving when LCTZ is prescribed. Additionally, hepatobiliary effects in the pediatric population are not adequately characterized in the clinical development program.

7.4 General Methodology

Specific methodologic concerns and data limitations are discussed as needed in various sections of the safety review. Overall, there are no systematic methodologic flaws identified in the safety review that influence the safety findings. The database is extensive and generally based on a satisfactory number of adequate and well-controlled clinical trials. Replicate studies show consistent and plausible findings from adequate safety assessments that do not raise concerns for any specific safety signal that would lead to a determination that LCTZ is generally unsafe to market.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Analysis of the pooled safety database is generally consistent with the findings of the individual controlled clinical trials. The pooled database is 44 of the 54 clinical studies in support of the NDA and includes safety assessments for all of the clinical confirmatory, supporting, and dose-ranging studies (covering the vast majority [85%] of LCTZ-exposed subjects in the development

program: 4,067, versus 688 in the non-pooled database), for all label indications. Issues of adequacy of exposure previously discussed (in the pediatric and geriatric populations, specifically) aside, the pooled safety database is extensive and an adequate reflection of LCTZ-exposure risk in adult study populations.

7.4.1.2 Combining data

Refer to section 7.4.1.1

7.4.2 Explorations for Predictive Factors

The review finds sedation-related AE's to be the most clinically meaningful that are drug- and dose-related, and, lack of subgroup analyses aside, likely present in all demographic categories. The review discusses this issue in depth in various sections.

7.4.2.1 Explorations for dose dependency for adverse findings

Cross-study comparisons show that LCTZ exposure increases proportionally with dose over the range of doses, which is consistent with the finding of increased sedation at higher doses during the clinical dose-ranging trials.

Regarding hepatobiliary changes, there is no clear evidence in the safety review of a LCTZ dose-dependent effect on transaminase elevation.

7.4.2.2 Explorations for time dependency for adverse findings

Sedation-related effects of LCTZ can occur after the first dose, and are reported at roughly the same incidence in the short-term (2-week) and long-term (≥ 4 weeks) studies.

A review of hepatobiliary changes (summarized in Table 25) does not clearly demonstrate a time-dependent exposure pattern.

7.4.2.3 Explorations for drug-demographic interactions

The ISS does not include adequate data to perform specific subgroup analyses for geriatric (older than 65 years) and black populations. The limitations of the pediatric data were also previously discussed.

7.4.2.4 Explorations for drug-disease interactions

Levocetirizine is primarily excreted renally. The ISS contains satisfactory data that are consistent with the findings for CTZ, and that support dose reduction in renally-impaired subjects. The applicant does not present specific data for assessment of LCTZ-exposure in subjects with hepatic dysfunction, but references CTZ, for which no dosage adjustment for hepatic dysfunction only is indicated. Given the similar metabolic profiles of LCTZ and CTZ, this reference seems

appropriate. (Subjects with combined hepato-renal syndromes require dose adjustments similar for renal insufficiency alone).

7.4.2.5 Explorations for drug-drug interactions

The applicant did not conduct formal drug-drug interaction studies, but references CTZ, which seems reasonable.

7.4.3 Causality Determination

No pattern of relatively rare SAE's is present in the safety review. Sedation-related effects are the most clinically relevant AE's for which LCTZ causality can be plausibly ascribed.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The LCTZ clinical development program exposes most pediatric and adult subjects to 5 mg given orally once daily. In the pooled safety database of 4,067 subjects, 3,134 (77.1%) receive 5 mg/day; 484 (11.9%) 2.5 mg/day; 438 (10.8%) 10 mg/day; and 36 (0.9%), 30 mg as a single dose. Most subjects receive LCTZ for two to six weeks, and a total of 154 subjects receive LCTZ for more than 26 weeks at 5 mg/day. With the exception of four dose-ranging studies (A217 and A00265 for adult allergic rhinitis [section 6.5]; A00270 for adult CIU [section 6.4]; and A00412 for multiple-dose comparative efficacy with CTZ [section 6.5]), all of the subjects in the adult and pediatric confirmatory efficacy trials receive LCTZ 5 mg once daily in the evening.

The applicant chose the 5 mg dose of LCTZ based on comparative PD studies of LCTZ, CTZ, and the S-enantiomer of CTZ (dextrocetirizine) which suggest that LCTZ is solely responsible for the *in vivo* pharmacologic activity of the racemate (CTZ). Comparison between dextrocetirizine and placebo showed no PD difference, while LCTZ and CTZ demonstrated similar, significant efficacy versus placebo.

The preponderance of data from PK, PD, and clinical trials supports once daily dosing of LCTZ.

The proposed label dose and regimen for children (ages 6-11 years), adolescents, and adults is [redacted] once daily in the evening. This is based on the cross-study comparison of PK exposure (AUC) in children and adults, and the extrapolation of efficacy of the 2.5 mg dose in adults and children 12 years of age and older.

8.1.1 Level of confidence for the dose/regimen

Although the dose-ranging study A217 shows evidence of a linear D-R effect, all three LCTZ doses (2.5, 5, and 10 mg) are statistically significantly more effective versus placebo for the primary endpoint and for many secondary endpoints. The other three dose-ranging studies

(named above) do not demonstrate a linear D-R; all three doses, once again, beat placebo significantly for the primary and many secondary endpoints, but the choice of 5 mg is made primarily due to the finding of a dose-dependent increase in sedation, worst at the 10 mg dose. In the adult short-term (two weeks) and long-term (≥ four weeks) clinical studies the difference in sedation-related side effects between the LCTZ 2.5 and 5 mg groups versus placebo is 5-6%. (The difference in sedation-related side effects for cetirizine [Zyrtec®] versus placebo at the maximum daily dose of 10 mg in adult placebo-controlled U.S. trials was 10.7%). While the difference for LCTZ is, therefore, less than for CTZ, it must be borne in mind that CTZ dosing is daytime, while LCTZ in clinical trials is given in the evening, which undoubtedly underestimates the incidence of sedation compared to CTZ.

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 LCTZ in the evening, and because of the likelihood of clinically relevant, increasing sedation with daytime dosing, the recommendation should be for evening dosing only.

The pediatric dosing is more problematic. The NDA submission has no pediatric dose-ranging studies and the only pediatric PK study is literature-derived (PSM 1216) and shows that children (ages 6-11) receive roughly twice the exposure from a single oral 5 mg LCTZ dose as adults (the applicant understates the extent of pediatric exposure demonstrated in this study). (Division clinical pharmacologists Dr.Tayo Fadiran and Dr. Partha Roy report that study PSM 1216 appears to be well-conducted with biologically plausible results). Given the results of the adult dose-ranging studies showing similar efficacy for LCTZ 2.5 and 5 mg, the failure to adequately characterize dosing of LCTZ viz-à-viz CTZ (study A00412), the lack of pediatric D-R studies, and the pediatric PK findings, it is difficult to justify the 5 mg dose for children ages 6-11 years. The preponderance of evidence suggests that the safest and most effective dose in 6 to 11 year old children is 2.5 mg. Therefore, this review endorses LCTZ 2.5 mg once daily in the evening for children 6-11 years of age.

8.1.2 Dose-toxicity and dose-response relationships

The dose-toxicity and dose-relationships of LCTZ appear to be satisfactorily characterized in the clinical development program. There are no obvious safety signals at doses substantially higher than the recommended daily adult dose. Sedation-related symptoms, which are not unexpected given the pharmacologic class of LCTZ, are the single most clinically relevant adverse effects occurring more in LCTZ than in placebo groups. Therefore, dosing in the evening, which reflects the dosing regimen of the majority of adult and pediatric clinical trials, is recommended.

Laboratory safety assessments in adult clinical trials show a roughly 1% incidence of transient hepatic transaminase elevation not clearly dose-related, and of uncertain clinical significance. (A

similar incidence is reported with CTZ). There is no evidence of hepatic necrosis or hepatic insufficiency in the safety data base, and the post-marketing experience is consistent with this.

Multiple studies demonstrate no clinically relevant effect on the QTc intervals at doses several times the recommended daily adult LCTZ dose.

8.1.3 Dose modifications for special populations

Recommended dose adjustments for renal and hepato-renal insufficiency are discussed in section 5.1. Dose modifications for older populations are primarily dependent on renal function, rather than age. Data from the LCTZ development program and experience with CTZ suggests no dose adjustments are necessary for gender or ethnic and racial differences, which seems reasonable.

8.2 Drug-Drug Interactions

The LCTZ development program conducts no formal drug interaction studies and references CTZ based on the similar metabolic profiles of the two drugs. Experience with CTZ 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 LCTZ post-marketing database does not suggest that clinically relevant drug interactions occur.

The NDA's approach to drug-drug interactions appears reasonable and there is no evidence to suggest further specific studies of LCTZ are warranted at this time.

8.3 Special Populations

8.3.1 Special dosing considerations based on demographics

Dosing considerations for race, gender, and age are discussed in various sections of the review; the pediatric issue notwithstanding, there do not appear to be special considerations based on race, gender, or age.

8.3.2 Special dosing considerations for co-existing states
Refer to sections 5.1 and 5.2.

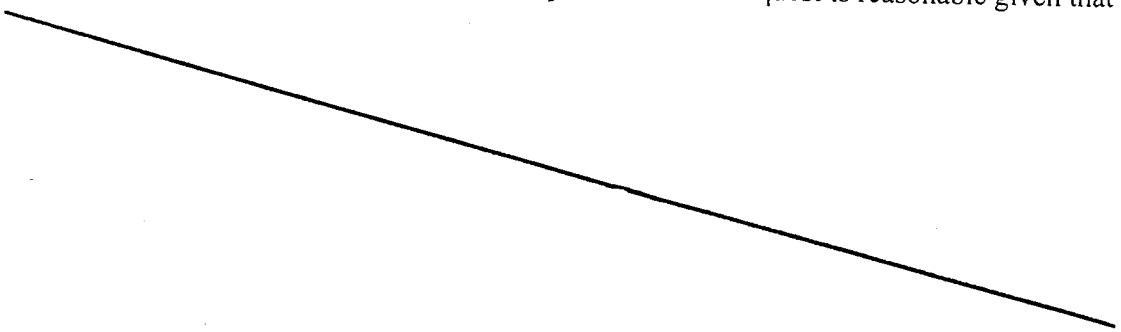
8.3.3 Special considerations for pregnancy or lactation.

Refer to sections 3.2 and 5.1. Levocetirizine is not recommended for pregnant or lactating women.

8.4 Pediatrics

Section 8.1.1 discusses the most salient issues regarding proposed pediatric dosing for the NDA.

In the NDA submission, UCB requests a deferral from PREA requirements for data submission supporting LCTZ use in children less than six years old. This request is reasonable given that



8.5 Advisory Committee Meeting

The clinical review does not identify issues that warrant advisory committee input.

8.6 Literature Review

A list of references is found after section 10.

8.7 Postmarketing Risk Management Plan

The applicant does not submit a postmarketing risk management plan, and the clinical review does not identify concerns that warrant such a plan at this time.

8.8 Other Relevant Materials

The clinical review does not indicate a need for actual use and labeling comprehension studies, marketing studies, or consultation with the Division of Drug Marketing, Advertising, and Communications or the Office of Surveillance and Epidemiology at this time.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.1.1 Adult (age 12 years and older) SAR and PAR

Levocetirizine 2.5 or 5 mg oral tablet, taken once daily in the evening, is safe and effective for the treatment of symptoms of seasonal and perennial allergic rhinitis in patients 12 years of older. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, and ocular pruritus. The replicate confirmatory studies supporting these findings are adequate and well-controlled; the results are biologically plausible, clinically relevant, and statistically consistent.

However, dose-ranging studies supporting the adult allergic rhinitis program are less robust. Statistically significant evidence of linear dose-response is found in only one of the two trials, and all three doses studied (2.5, 5, and 10 mg) show significant efficacy over placebo for the primary endpoints. Nonetheless, results show that the 10 mg dose produces more sedation than the two lower doses, of which the 5 mg dose is marginally more effective than 2.5 mg. The efficacy findings for LCTZ 2.5 mg versus placebo suggest it is unlikely that a lower LCTZ dose, for example, 1.25 mg, would be more effective than placebo in this age range. Additionally, comparative efficacy trials of multiple LCTZ and CTZ doses show similar efficacy for all four drug doses versus placebo, but do not characterize dose-response or effect-difference between LCTZ and CTZ. Notwithstanding the applicant's assertions to the contrary, the comparative LCTZ and CTZ trials cannot be used to support a LCTZ daily dose of 2.5 or 5 mg referencing CTZ's daily dose of 5 or 10 mg.

The proposed LCTZ label _____, but this review finds that dosing should be in the evening for the following reasons: 1) confirmatory efficacy and principal supporting studies all administer LCTZ in the evening, 2) sedation-related side effects are significantly more likely in LCTZ-exposed subjects than in placebo subjects, and 3) the extent to which sedation-related effects would be greater if LCTZ is used during the daytime is not characterized in the NDA.

No safety signal is observed in the safety review. The type and incidence of AE's more frequent than placebo are consistent with pharmacologic effect. Additional measures supporting confidence in the safety findings of the development program include: 1) no on-treatment deaths, 2) low number of AE study drop-outs *not* due to pharmacologic effect, 3) similar dropout rates between LCTZ and placebo groups 4) low number of clinical trial subjects lost to follow-up, 5) low number of subjects withdrawing consent, 6) satisfactory number of exposed subjects in the development program, 7) consistency of safety findings and satisfactory study conduct over several years, in many different countries, and 8) relatively small number of SAE's reported to the applicant's global post-marketing safety database from the 80 countries that market LCTZ.

The preponderance of the evidence, therefore, supports LCTZ, either 2.5 mg or 5 mg, once daily in the evening, for the treatment of allergic rhinitis symptoms in patients age 12 years and older.

9.1.2 Adult (ages 12 years and older) CIU

Levocetirizine 2.5 or 5 mg oral tablet, taken once daily in the evening, is safe and effective for the treatment of the symptoms and signs of chronic idiopathic urticaria in patients 12 years of older. Symptoms and signs treated effectively include pruritus, wheal number, and wheal size. The replicate studies supporting these findings are adequate and well-controlled; the results are biologically plausible, clinically relevant, and statistically consistent. A single, well-conducted dose-ranging study supports 5 mg as the optimum dose, although 2.5 mg is also satisfactory in many patients.

For the same reasons cited above, LCTZ dosing should be once daily in the evening.

9.1.3 Pediatric (ages 6-11 years) SAR, PAR, and CIU

While the 5 mg dose of LCTZ (the same dose used for adults) is shown to be effective versus placebo in the pediatric confirmatory studies, it is the only dose studied in the pediatric SAR and PAR confirmatory efficacy trials; the NDA does not contain pediatric CIU studies. Given that the characteristics of the diseases under study (allergic rhinitis and CIU) and the drug effects are expected to be similar in adults and children, extrapolation of efficacy from adults and adolescents to the younger age group is appropriate. The pediatric database for the proposed indications contains 243 subjects (79 age 6-8 years old) exposed to the highest recommended dose of LCTZ (5 mg) for four to six weeks. These data, along with the data from older pediatric patients (>12 years) are sufficient to assess the safety of LCTZ in the patients 6 to 12 years of age. The appropriate dose for the younger age group should be one that provides similar systemic exposure in adults. From the pharmacokinetic information provided, the 2.5 mg dose appears to be the most appropriate dose for the pediatric population 6 to 11 years of age.

9.1.4 Levocetirizine Prescription Status

The applicant seeks prescription status for LCTZ 5 mg tablets: "While the experience with levocetirizine is extensive, many of the approvals are relatively recent, within the last 5 years, and the majority are as a prescription product. In addition, no clinical studies have been performed in the United States with levocetirizine and the experience with reference product is as a prescription product. Therefore, marketing of levocetirizine is proposed as a prescription product" (Module 2, section 2.5, p 10).

This review concurs that LCTZ should be by prescription for the following reasons: 1) LCTZ is new to the U.S. market, 2) the efficacy link between LCTZ and the NDA reference drug CTZ is incompletely characterized in the application, 3) dose-finding data in the NDA are not robust, 4) there is uncertainty regarding extent of sedation-related side-effects if inadvertently used during the daytime, and 5) prescription status lessens the likelihood of use in patients less than 12 years old, which requires further study.

9.2 Recommendation on Regulatory Action

Adult (age 12 years and older) SAR, PAR, and CIU

The recommended regulatory action for Levocetirizine 2.5 mg or 5 mg oral tablet, once daily in the evening, is for approval, from a clinical standpoint, for the treatment of symptoms and signs of SAR, PAR, and CIU in patients 12 years and older. The lowest LCTZ should be used depending on symptom severity.

Pediatric (age 6-11 years) SAR, PAR, and CIU

The recommended regulatory action is for approval of Levocetirizine 2.5 mg oral tablet, once daily in the evening, from a clinical standpoint, for the treatment of symptoms and signs of SAR, PAR, and CIU in children age 6-11 years. This review does not recommend approval of LCTZ 5 mg in this age group primarily due to pediatric PK evidence showing that systemic exposure to LCTZ 5 mg is twice that of adults. Additionally, the pediatric development program did not conduct dose-finding and dose-ranging clinical trials.

Levocetirizine Prescription Status

Prescription status for LCTZ is recommended. Refer to section 9.1.4 for discussion.

9.3 Recommendation on Postmarketing Actions

The clinical review does not recognize a need for specific risk management activities or Phase 4 studies.

9.3.1 Risk Management Activity

Refer to section 9.3.

9.3.2 Required Phase 4 Commitments

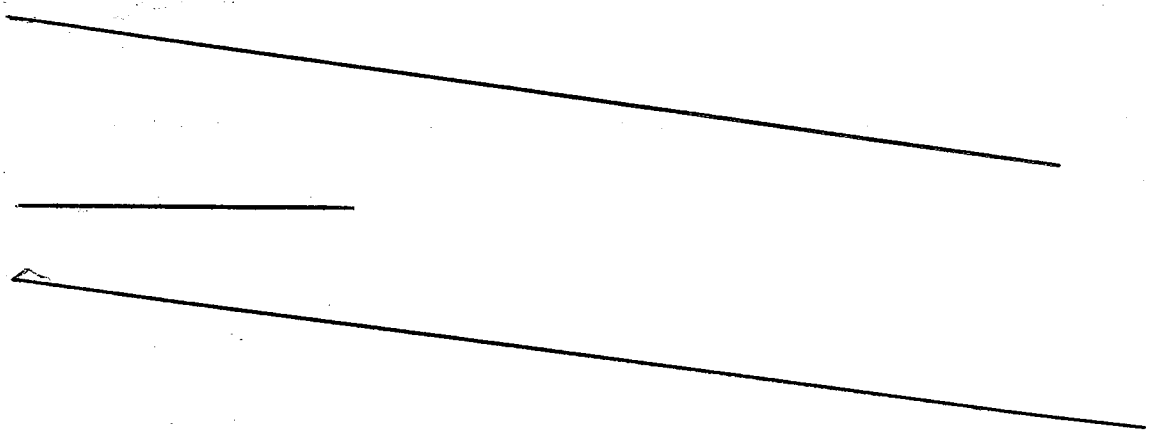
The clinical review does not identify concerns that require Phase 4 commitments.

9.3.3 Other Phase 4 Requests

Refer to section 9.3.2.

9.4 Labeling Review

The following is a summary, by label section, of the major changes needed in the LCTZ proposed label:



1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

9.5 Comments to Applicant

There are no comments from this review to be conveyed to the applicant. See Medical Team Leader Memo for labeling comments conveyed to the applicant during the labeling review.

10 APPENDICES

10.1 Review of Individual Study Reports

Appendix 1. A. 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."

** Page citations in this review refer to A00266.pdf unless otherwise specified.*

Overview

The purpose of this eight week study is to confirm the efficacy and safety, over placebo, of levocetirizine dihydrochloride (LCTZ) 5 mg oral tablets, taken once daily in the evening, to reduce rhinitis symptoms of subjects, 12 years and older, with perennial allergic rhinitis (PAR) to house dust mites. The primary efficacy analysis assesses the change from baseline in subject-recorded (reflective, over 24 hours), adjusted mean nasal symptom scores (T4SS: sneezing, rhinorrhea, nasal pruritus, and ocular pruritus*) over the first week of treatment, and over the first four treatment weeks.

** Refer to Study Procedure section for definition and discussion of nasal symptom score configurations*

Study Dates

June 17, 2000 – August 23, 2000

Investigators: Thirty investigators at 26 centers in South Africa enroll subjects in this study (p 2; pp 967-972). The study follows the ICH E6 note for guidance on Good Clinical Practices (GCP) and principles from the Declaration of Helsinki (p 1).

Reviewer comment: The June-August period is an appropriate season to conduct a PAR study in the southern hemisphere; it is winter, and subjects with SAR are very unlikely to have pollen-related rhinitis symptoms confounding the efficacy assessment.

Amendments

The study protocol has one amendment:
Amendment 1 (June 28, 1999) updates clinical contact information and the AE reporting form, enlarges the protocol limits for AST and ALT parameters, and corrects Investigator administrative information and units for AST and ALT (p 873).

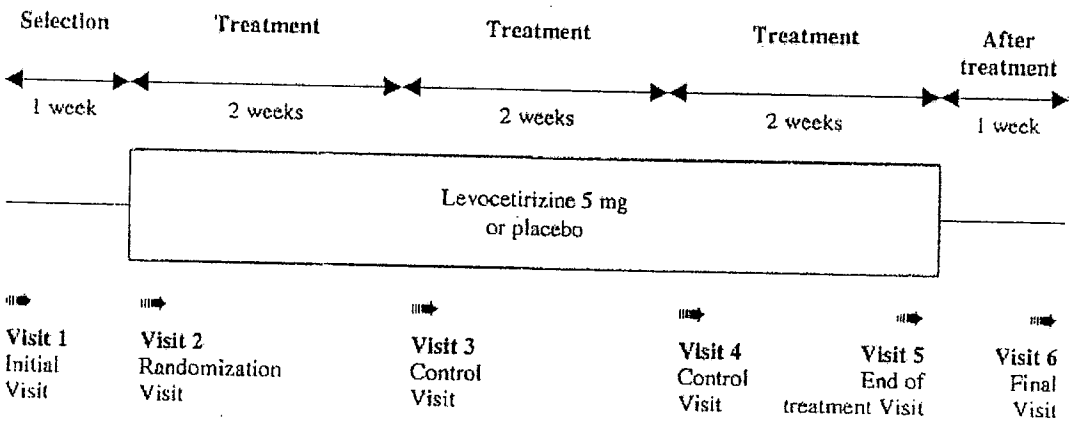
Protocol

The protocol describes a multi-center, randomized, double-blind, placebo-controlled study in subjects 12 years and older comparing LCTZ 5 mg oral tablets, once daily in the evening, with placebo for the treatment of house dust mite-related PAR symptoms. The primary objective is confirmation of superiority of LCTZ over placebo in reducing subject-recorded total nasal symptom scores, reflective over 24 hours [T4SS (R)], (defined in Study Procedure section, below), compared to baseline, for the first treatment week, and for the first four weeks of treatment. For the first week treatment week, the study aims to show an average relative improvement from baseline of 50% for LCTZ compared to placebo (p 19). The applicant chooses the 5 mg LCTZ dose because multiple studies in SAR subjects show efficacy, the 10 mg LCTZ dose causes more somnolence, and the 10 mg dose of the racemate cetirizine (of which LCTZ is the more active enantiomer) is effective (p 27, p 819).

The study period is eight weeks (six treatment weeks) and there are six visits (refer to schematic study diagram, below):
Visit 1 (V1) – Initial selection: includes eligibility screening (refer to Inclusion Criteria, below), obtaining informed consent, dietary and medical histories, and demographics. Subject undergoes a general physical examination (PE); Investigator records (in CRF) treatments during the previous three months, documents a positive skin test or RAST for house dust mites within the last 12 months (places a skin test if needed), and performs an ECG. Subject gives blood samples for hematology and chemistry profiles, and pregnancy testing (all females). Subject receives daily record card (DRC) for scoring daily symptom severity in the evening (for the last 24 hours), listing concomitant medications and AEs.
Visit 2 (V2) – Randomization: three to nine days after V1. Investigator checks laboratory results, excludes those with abnormal values, and questions subject about DRC details, AEs, and treatments taken since V1 (excluding those subjects taking prohibited medications). Subject undergoes PE. Investigator reviews DRC and assures eligible baseline symptom score. Eligible subject gets randomized to treatment, study medication, a new DRC, instructions to begin treatment that evening, and an appointment for Visit 3 (two weeks later).
Visit 3 (V3) – Control visit after two weeks of treatment: subject undergoes PE and returns medication container; Investigator collects DRC and records AEs and concomitant medications in CRF. Investigator counts and records tablets, has subject take one tablet and performs ECG one hour later, issues new DRC and treatment for next period, and makes appointment for V4 (two weeks later).
Visit 4 (V4) – Second control visit: follows same procedures as V3 except for ECG; Investigator makes appointment for V5 (two weeks).
Visit 5 (V5) – End of treatment: subject undergoes PE; Investigator collects DRC and records AEs and concomitant medications in CRF. Subject returns medication container, gives blood samples for hematology, chemistry, and pregnancy testing, and completes global assessment of efficacy scale (4 points: 0 = worsened to 3 = good). Investigator counts and records tablets, issues new DRC, and makes appointment for V6 (one week).
Visit 6 (V6) – Final visit: subject undergoes PE; Investigator collects DRC, records AEs and concomitant medications in CRF, and verifies blood test results from V5.

(pp 20-22)

Schematic Study Diagram



(Source: p 20)

Patient Population: Males or females 12 years and older who have perennial allergic rhinitis from house dust mites for at least the last two years.

Inclusion Criteria: The following criteria must be met at Visit1:

- Subject gives written informed consent (by parent or guardian if < 18 years)
- Investigator documents medically acceptable contraceptive method use in females of child-bearing potential
- Subject able to comprehend and complete DRC and communicate with Investigator
- Investigator confirms subject's dust mite PAR for at least the prior two years by positive skin test (≥ ++) or positive RAST (≥ class 3 or ≥ 3.5 U/ml); if allergy tests not done within preceding year, or unavailable, investigator performs skin test.

The following criteria must be met at Visit 2 (randomization):

- Subject records rhinitis symptoms in DRC; Investigator confirms mean daily total symptom score (T4SS, 24 hour reflective at bedtime) ≥ 5 between V1 and V2, and on the day before the randomization visit [V2] (Refer to Study Procedure, below)
- Subject laboratory data within protocol range
- Females have negative pregnancy test.

(pp 23-24)

Exclusion Criteria: V1 exclusion criteria:

- Seasonal AR that may change subject's symptoms during study

- Pregnancy, breast feeding, or sexually active females of child-bearing potential not using acceptable contraception
- Ear, nose, or throat infection in two weeks prior to V1
- Asthma requiring daily treatment other than prn β_2 agonist
- Dermatitis or urticaria requiring antihistamine or corticosteroid therapy (oral or topical)
- Vasomotor rhinitis or nasal obstruction from polyposis or septal deformity
- Clinically significant disease: cardiovascular, hepatic, renal, autoimmune, hematologic, neurologic, psychiatric, or others that affect ADME of study drug
- LCTZ or other piperazine-derivative allergy: hydroxyzine, cetirizine, cyclizine, meclozine, buclizine, or excipients (e.g., lactose)
- Subjects incapable of giving informed written consent
- Non-compliant subjects
- Alcoholism, drug addiction, mental instability
- Clinical trial participation during last three months
- Subjects intending to donate blood during study
- Investigators and their children, spouses, and colleagues.

The following are V1 to V5 prohibited medications (pre-study wash-out periods are in parentheses):

- Astemizole — 90 days
- Systemic corticosteroids — 30 days
- Ketotifen, nedocromil, cromoglicate, topical corticosteroids — 14 days
- H_1 antihistamines — 3 days
- Other nasal or ocular topicals, decongestants (oral or nasal) asthma treatments other than β_2 inhaled agonists prn, and ascending phase desensitization — no washout

V2 exclusion criteria:

- Laboratory results outside of protocol range; positive pregnancy test
- V1-V2 period less than three or greater than nine days
- Mean of total symptom scores not ≥ 5 between V1 and V2, or on day before V2
- Use of prohibited medication between V1 and V2

(pp 25-26, p 28, p 824)

Reviewer comment: Inclusion criteria are appropriate; Exclusion criteria are notable for absence of specific prohibitions against intranasal corticosteroids, loratadine, and anti-leukotrienes. (Interestingly, these three medications are specifically prohibited in the SAR study A00268, conducted by the same primary investigator). However, use of these medications is more likely to hinder than enhance efficacy assessments.

Study Procedure

Efficacy Parameter Scales: Subject records rhinitis symptoms each evening in the DRC (24 hour reflective), just prior to taking study medication. Subject grades symptoms (sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal congestion) on a four point scale:

0 = absent,
1 = mild (present but not disturbing),
2 = moderate (disturbing but not hampering day-time activities and/or sleep),
3 = severe (hampering day-time activities and/or sleep).

Sneezing, rhinorrhea, nasal pruritus, and ocular pruritus are the T4SS [R] (p 30).

Subject completes a four-point global assessment of efficacy scale at the end of treatment that compares current symptoms with V2 symptoms: 0 = worse, 1 = unchanged, 2 = slight – moderate improvement, 3 = good – excellent improvement (p 30).

Definition of baseline period and scores: Baseline period is between V1 and V2. The period is as short as three days, or as long as nine days. Eligibility for randomization at V2 requires three days (subject-recorded in the DRC) of a T4SS (R) $\geq$ 5, including the day prior to V2 (pp 23-24). (Subject also records component symptoms of T4SS and nasal congestion individually).

Reviewer comment:
*The primary study objective aims to confirm the superiority of LCTZ 5 mg, over placebo, in "reducing **rhinitis** symptoms" (p 2). The protocol uses the "Total 4 Symptoms Score (T4SS)" (sneezing, rhinorrhea, nasal pruritus, and ocular pruritus) to measure baseline and on-treatment symptoms. FDA does not recognize ocular pruritus as a symptom of allergic **rhinitis** and instructed the applicant to re-configure and re-analyze the nasal symptom score without ocular symptoms. The resulting "T3SS" (includes sneezing, rhinorrhea, nasal pruritus; omits ocular pruritus) is also analyzed in this review (refer to Primary Efficacy Results, below). T4SS to T3SS comparisons are made when considering ocular pruritus as a potential driver of efficacy.*

FDA guidance recommends moderate symptom severity for all or the majority of symptoms, using a scoring system analogous to this study's scale. A moderate score of 2 (out of 4) gives a T4SS baseline of 8. Although the protocol criterion of $\geq$ 5 allows subjects less than moderately symptomatic to enroll, a preponderance of low-scoring subjects is more likely to hinder rather than enhance efficacy determinations (Guidance for Industry, Allergic Rhinitis: Clinical Devlopment Programs for Drug Products, p 10).

Statistical and Analytical Plan

Efficacy Parameters: Primary efficacy variables are the adjusted mean T4SS (R), compared with baseline, for the first treatment week *and* for the first four treatment weeks in the LCTZ 5 mg arm versus the placebo arm.

Reviewer comment: The four week treatment period for a PAR study is appropriate (Guidance for Industry, Allergic Rhinitis: Clinical Devlopment Programs for Drug Products, p 9). The SAP

does not measure instantaneous scores; therefore, this study's results cannot be used support potential duration of effect claims.

Secondary endpoints, by protocol order, are 1) mean T4SS (R) 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 (p 33).

Safety Assessments: AEs (all visits), safety laboratory tests at V1 and V5 (complete blood count with differential, platelets, SGOT, SGPT, total bilirubin, direct bilirubin, urea, creatinine, pregnancy test) and ECG parameters at V1 and V3 [during expected peak plasma concentration] (p 34).

Medication Compliance: Subject returns all unused medication and containers at V3, V4, and V5. Drug accountability records include: number of container dispensed at V2, subject initials and CRF number, dates dispensed and returned, quantity remaining, and initials of container dispenser and collector (p 28).

Primary Efficacy Analysis: Primary efficacy analysis is on the ITT population (randomized subjects taking at least one dose of study medication). (A per protocol population analysis assesses the impact of protocol violations on study results). 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 (p 36).
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 (pp 36-37).
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 (p 37).

Secondary Efficacy Analysis: 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 (p 38).

Sample Size Determination: 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%] (p 39).

Results

Patient Disposition: The study screens 368 subjects, and randomizes 294, 144 in the placebo group and 150 in the LCTZ group. Two hundred seventy-six subjects complete the study (93.9%). The most common reason for early termination among the 18 subjects who do so is lack of efficacy, eight from the placebo group and two from the LCTZ group. No subject from the LCTZ group drops out due to an AE. Of the other eight drop outs, three withdraw consent (all placebo), two for AEs (placebo), one lost to follow-up (LCTZ), and two for unspecified reasons (LCTZ) [pp 41-42].

Investigators identify protocol deviations prior to unblinding and data analysis. Use of proscribed medications is the most common major protocol deviation during the treatment period (15%) and occurs more in the placebo group (20.1%) than the LCTZ group (10%). Table 1 summarizes major deviations.

Table 1. Summary of Major Protocol Deviations (ITT Population)

Deviation	Placebo (N = 144)	LCTZ (N = 150)	Total (N = 294)
During Baseline	N (%)	N (%)	N (%)
Score out of range or baseline short/long	7 (4.9)	6 (4.0)	13 (4.4)
ENT infection before V1	1 (0.7)	0	1 (0.3)
General ineligibility	1 (0.7)	0	1 (0.3)
Prohibited med	6 (4.2)	4 (2.7)	10 (3.4)
Insufficient washout	0	2 (1.3)	2 (0.7)
During Treatment			
Compliance	16 (11.1)	9 (6.0)	25 (8.5)
DRC missing (V2-V3)	1 (0.7)	0	1 (0.3)
Prohibited med	29 (20.1)	15 (10.0)	44 (15.0)
Taste of medication discussed by subject	1 (0.7)	1 (0.7)	2 (0.7)

(Source: pp 42-43)

Treatment Compliance: Compliance is the ratio of the number of tablets actually taken by the subject over the number of tablets specified in the protocol and assessment is every two weeks of the treatment period. Mean daily compliance for the total treatment period is 98.5%. Five subjects (1.7%) in the ITT population have compliance below 80%, and none are over 120%. Three subjects do not have overall daily compliance data. Analysis shows no difference in overall compliance between study groups (p 49).

Demographics: Both groups have similar demographics (see Table 2). The average age of the 294 ITT subjects is 29.0 years (range 12.3 – 71.4 years). Mean duration dust mite PAR is 14.1 years (13.9 placebo group; 14.2 LCTZ group). Males and females distribute equally between groups; however, there are more females in the study (57% vs 43%). Most subjects are Caucasian (68%). All habit parameters (tobacco use, alcohol and caffeine consumption, illicit drug use) are equally distributed between groups.

Table 2. Summary of ITT Population Demographics

Characteristic	Placebo (N = 144)	LCTZ (N = 150)	Total (N = 294)
Age: Mean (Range)	28.76 (12.6-69.6)	29.18 (12.3-71.4)	29.98 (12.3-71.4)
Gender: N (%)	F 80 (55.6) M 64 (44.4)	F 88 (58.7) M 62 (41.3)	F 168 (57.1) M 126 (42.9)
Race: Origin (N; %)	Asian/Pacific Rim (20; 13.9) Black (2; 1.4) Caucasian (98; 68.1) Other (24; 16.7)	Asian/Pacific Rim (19; 12.7) Black (3; 2.0) Caucasian (102; 68.0) Other (26; 17.3)	Asian/Pacific Rim (39; 13.3) Black (5; 1.7) Caucasian (200; 68.0) Other (50; 17.0)
Mean Weight (kg) Range	69.2 33-130	67.9 34-117	68.5 33-130
Mean Height (cm) Range	168.4 141-193	168.9 147-197	168.7 141-197

(Source: pp 45-46)

Table 3 summarizes subjects' most common (with a prevalence of at least 10% in one group) additional medical conditions (p 47).

Table 3. Summary of Additional Medical Conditions ITT Population

Condition	Placebo (N = 144)	LCTZ (N = 150)	Total (N = 294)
Headache	15 (10.4%)	20 (13.3%)	35 (11.9%)
Asthma (unspecified)	50 (34.7%)	41 (27.3%)	91 (31.0%)
Acute sinusitis (unspecified)	40 (27.8%)	32 (21.3%)	72 (24.5%)
Acute URIs (unspecified)	31 (21.5%)	25 (16.7%)	56 (19.0%)
Influenza	22 (15.3%)	21 (14.0%)	43 (14.6%)
Atopic dermatitis	14 (9.7%)	20 (13.3%)	34 (11.6%)
Acute pharyngitis	20 (13.9%)	13 (8.7%)	33 (11.2%)
Bronchitis (unspecified)	19 (13.2%)	12 (8.0%)	31 (10.5%)
Acne	8 (5.6%)	15 (10.0%)	23 (7.8%)

(Source: p 47)

Concomitant Medications: About 76% of the placebo group and 65% of the LCTZ group take at least one concomitant medication during the study (p 48). Table 4 summarizes ITT population use of concomitant (non-proscribed) medications (by therapeutic class) by at least 10% of either treatment group. Other medication use by at least 3% (but less than 10%) of both groups includes: renin-angiotensin agents, anti-thrombotics, cough and cold preparations, endocrine therapy, ophthalmologicals, stomatologicals, topical joint and musculoskeletal preparations, and vitamins (pp 264-267).

Table 4. Concomitant Medication Use ITT Population (≥ 10% in either arm)

Therapeutic Class	Placebo (N = 144)	LCTZ (N = 150)	Total (N = 294)
Analgesics	58 (40.3%)	54 936.0%)	112 (38.1%)
Sex hormones	34 (23.6%)	33 (22.0%)	67 (22.8%)
Anti-asthmatics	36 (25.0%)	28 (18.7%	64 (21.8%)
Systemic anti-bacterials	24 (16.7%)	23 (15.3%)	47 (16.0%)
Other gynecologic	19 (13.2%)	10 (6.7%)	29 (9.9%)
Anti-inflammatory	14 (9.7%)	16 (10.7%)	30 (10.2%)

(Source: p 49)

Primary Efficacy Results

Change from baseline in adjusted mean T4SS (R) over Week 1 and over the first four week treatment period: LCTZ 5 mg produces a greater reduction in T4SS (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), $p < 0.001$ (p 17, Amendment to Pending Application, October 31, 2006). These results compare favorably to the T3SS (R) analysis (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), $p < 0.001$ (p 52). Summary of T4SS (R) and T3SS (R) comparisons are in Tables 5A and 5B, respectively.

Table 5A. 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
Week 1	Placebo LCTZ 5 mg	142 150	7.44 (1.80) 7.69 (1.82)	6.16 4.94	1.22 (0.73; 1.71)	< 0.001
First 4 Treatment weeks	Placebo LCTZ 5 mg	142 150	7.44 (1.80) 7.69 (1.82)	5.39 4.17	1.22 (0.76; 1.69)	< 0.001

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

Table 5B. 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
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"

(Source: p 17, Amendment to Pending Application, October 31, 2006)

The relative improvement of LCTZ 5 mg over placebo is 86% for the first week and 56% for the first four treatment weeks [per T4SS] (p 52).

A per protocol population analysis using T4SS (R) scores shows statistical significance favoring LCTZ 5 mg that is similar to the results of the T4SS analysis of the ITT population (p 52).

Reviewer comment: *The statistical significance present for either the T4SS or T3SS reflective scores strongly suggests that ocular pruritus is not driving the efficacy determination.*

Secondary Efficacy Results

1) 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) [p 19, Amendment to Pending Application, October 31, 2006]. These results compare favorably to the T3SS (R) analysis (without ocular pruritus). The relative improvement of LCTZ over placebo (T4SS) is 47% (p 54).
2) 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; none of the CIs contain zero (p 19, Amendment to Pending Application, October 31, 2006). The results compare favorably to the T3SS analysis, which also favors LCTZ over placebo for each treatment week.
3) 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. None of the CIs contain zero (pp 56-60).
4) 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 (p 61).

Multi-center Analysis

No evidence of a treatment by center interaction is found (p 62).

Subgroup Analysis

There is no subgroup analysis (p 63).

Safety Assessments

No deaths occur in the study. No SAEs or withdrawals due to AEs occur in the LCTZ group. Overall, 63.9% of subjects experience treatment-emergent AEs, 68.1% in the placebo group and 60.0% in the LCTZ group. Headache is the most common AE, with an equal incidence in the groups (34.7%). Treatment-emergent somnolence and fatigue are twice as common in the LCTZ group (N = 16, versus N = 8). Table 7 summarizes treatment-emergent AEs.

Table 7. Treatment-emergent AEs (at least 2% of subjects in either group)

Preferred term	Placebo (N = 144)		LCTZ 5 mg (N = 150)	
	n	(%)	n	(%)
Headache	50	(34.7%)	52	(34.7%)
Somnolence	4	(2.8%)	9	(6.0%)
Fatigue	4	(2.8%)	7	(4.7%)
Nausea	6	(4.2%)	5	(3.3%)
Abdominal Pain	9	(6.3%)	3	(2.0%)
Dry Mouth	2	(1.4%)	5	(3.3%)

Dizziness	6 (4.2%)	5 (3.3%)
URI	13 (9.0%)	10 (6.7%)
Pharyngitis	6 (4.2%)	13 (8.7%)
Back pain	5 (3.5%)	4 (2.7%)
Myalgia	1 (0.7%)	4 (2.7%)
Migraine	3 (2.1%)	0
Insomnia	3 (2.1%)	2 (1.3%)
Diarrhea	4 (2.8%)	2 (1.3%)
Asthma	4 (2.8%)	2 (1.3%)
Bronchitis	6 (4.2%)	5 (3.3%)
Bronchospasm	5 (3.5%)	5 (3.3%)
Cough	5 (3.5%)	3 (2.0%)
Epistaxis	4 (2.8%)	2 (1.3%)
Rhinitis	5 (3.5%)	4 (2.7%)
Sinusitis	10 (6.9%)	10 (6.7%)
Influenza-like sxs	20 (13.9%)	25 (16.7%)

(Source: pp 67-68)

Generally, no clinically relevant changes in laboratory values occur in the study. One subject in the LCTZ has a mild elevation in SGPT (66 IU/l; normal reference lab range 10-40 IU/l) at V5 (end of treatment assessment) that resolves (p 72).

ECG parameters do not change significantly during the study. Using Bazett's formula, 100% of placebo and 98.2% of LCTZ subjects have a normal post-treatment QTc (the change in the two LCTZ subjects is "borderline"). Using Fridericia's formula, all study subjects have a normal post-treatment QTc (pp 72-73).

Study Conclusions

Efficacy: Levocetirizine 5 mg oral tablet, taken daily, once in the evening, is statistically superior to placebo for reducing perennial allergic rhinitis nasal symptoms due to house dust mites, assessed as change from baseline in the reflective T4SS (sneezing, rhinorrhea, nasal pruritus, and ocular pruritus), for the first treatment week (adjusted mean difference 1.22 [95% CI 0.73; 1.71], $p < 0.001$), and for the first four weeks of treatment (adjusted mean difference 1.22 [95% CI 0.76; 1.69], $p < 0.001$).

Analysis favors LCTZ over placebo for all secondary endpoints: 1) T4SS (R) for the total six week treatment period, 2) T4SS (R) for each week of treatment period, 3) Reflective scores for the individual symptoms sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal obstruction for the first week, the first four weeks, and the total six week treatment periods, and 4) Subject global evaluation of treatment.

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

The results of this study support the use of LCTZ 5 mg tablets, taken once in the evening, for the treatment of nasal symptoms of dust mite-related perennial allergic rhinitis.

Safety: No deaths occur in the study. Somnolence and fatigue are more likely with LCTZ than placebo. There are no unusual AEs or safety signals in this study, and prolonged QTc interval did not occur in either group.

Reviewer comment: 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 study lacks instantaneous symptom scores and cannot support potential duration of effect claims.

Presentation of descriptive statistics without accompanying analysis for daily evolution of T4SS does not allow conclusions regarding time to maximal effect or onset of action.

Appendix 1. B. 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."

* *Page citations in this review refer to A00268.pdf unless otherwise specified.*

Overview

The purpose of this four-week study is to confirm the efficacy and safety, over placebo, of levocetirizine dihydrochloride (LCTZ) 5 mg oral tablets, taken once daily in the evening, to reduce rhinitis symptoms of subjects, 12 years and older, with seasonal allergic rhinitis (SAR) to grass pollen. Primary efficacy analysis assesses the change from baseline in subject-recorded (reflective, over 24 hours), adjusted mean nasal symptom scores (T4SS: sneezing, rhinorrhea, nasal pruritus, and ocular pruritus*) over the first week of treatment, and over the total two week treatment period.

* *Refer to Study Procedure section for definition and discussion of nasal symptom score configurations*

Study Dates

November 7, 2000 – March 19, 2001

Investigators: Twenty investigators at 20 centers in South Africa enroll subjects in this study (p 2; pp 780-784). The study follows the ICH E6 note for guidance on Good Clinical Practices (GCP), local regulations, and principles from the Declaration of Helsinki (p 15).

Amendments

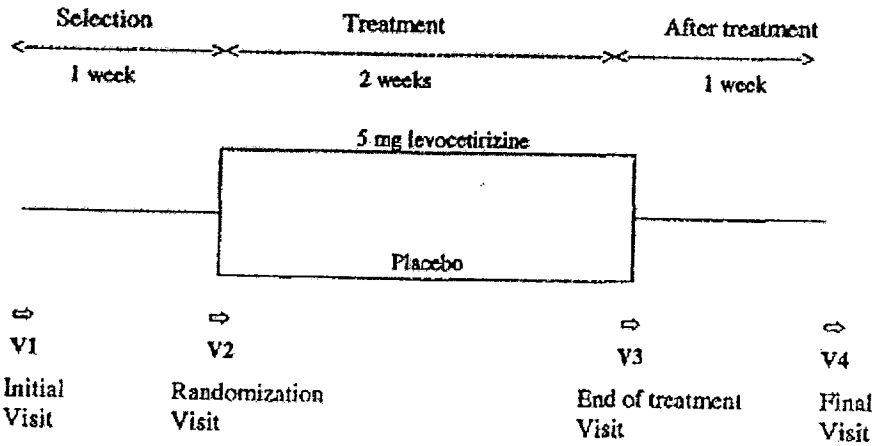
There are two amendments:
1) The applicant makes Amendment 1 to comply with the FDA draft guidance governing clinical development programs for drug products in allergic rhinitis that specifies recording of both *reflective* and *instantaneous* symptom scores (p 36). The amendment precedes subject enrollment by four months (Amendment date, July 14, 2000; Study commencement date, November 7, 2000).
2) Amendment 2 corrects an error in the laboratory range for hematocrit (p 867).

Protocol

The protocol describes a multi-center, randomized, double-blind, placebo-controlled study in subjects 12 years or older comparing LCTZ 5 mg oral tablets, once daily in the evening, with placebo, for the treatment of grass pollen SAR symptoms. The primary objective is confirmation of superiority of LCTZ over placebo in reducing subject-recorded total nasal symptom scores [T4SS] (defined in Study Procedure section, below), compared to baseline, for the first treatment week, and over the two week treatment period. The applicant chooses the 5 mg LCTZ dose because "Phase 2 and 3 studies (of LCTZ) in subjects suffering from SAR to grass and/or weed pollen suggest that LCTZ provides the best risk/benefit ratio at a dose of 5 mg once a day" (p 25). (Specific references are not cited).
The study period is four weeks and there are four visits (refer to schematic study diagram, below):
Visit 1 (V1) – Initial selection: includes eligibility screening (refer to Inclusion Criteria, below), and obtaining informed consent, dietary and medical histories, and demographics. Subject completes a "Rhinoconjunctivitis QoL" questionnaire (RQLQ) and undergoes a general physical examination (PE); Investigator records treatments during the previous three months in CRF, verifies positive skin test or RAST for grass pollen present, or performs skin test as needed. Subject gives blood samples for hematology and chemistry profiles, and pregnancy testing (all females). Subject receives daily record card (DRC) for scoring daily symptom severity in the evening (for the last 24 hours, and for the hour preceding self-assessment), listing concomitant medications and AEs.
Visit 2 (V2) – Randomization: (three to nine days after V1). Investigator checks laboratory results, excludes those with abnormal values, and questions subject about DRC details, AEs, and treatments taken since V1 (excluding those subjects taking prohibited medications). Subject undergoes PE and completes the RQLQ. Investigator reviews the DRC and assures eligible baseline symptom score. Eligible subject gets randomized to treatment, study medication, new DRC, instructions to begin treatment that evening, and an appointment for V3 (two weeks later).
Visit 3 (V3) – End of treatment: subject undergoes PE; Investigator collects DRC and records AEs and concomitant medications in CRF. Subject returns medication container, completes RQLQ and global assessment of efficacy scale, and gives blood samples for hematology, chemistry, and pregnancy testing. Investigator counts and records tablets in CRF, issues new DRC, and makes appointment for V4 (one week later).
Visit 4 (V4) – Final study visit. Investigator records AEs and concomitant medications, collects DRC, verifies blood test results from V3, and performs PE.
(pp 20-21)

Appears This Way
On Original

Schematic Study Diagram



(Source: p 794)

Patient Population: Males or females 12 years and older who have allergic rhinitis from grass pollen for at least the last two years.

Pollen Counts: Average daily grass pollen counts for the study period are 5-6 [Cape Town] and 16-17 [Pretoria] (pp 750-752).

Reviewer comment: A Division allergist (CEL) confirms these counts as satisfactory exposure for a SAR study.

Inclusion Criteria: The following criteria must be met at Visit1:

- Subject gives written informed consent (by parent or guardian if < 18 years)
- Investigator documents medically acceptable contraceptive method use in females of child-bearing potential
- Subject able to comprehend and complete DRCs and RQLQs

- Investigator confirms subject's grass pollen AR for at least the prior two years by positive skin test (≥ ++) or positive RAST (≥ class 3 or ≥ 3.5 U/ml); if allergy tests not done within preceding year, or unavailable, investigator performs skin test.

The following criteria must be met at Visit 2 (randomization):

- Subject records rhinitis symptoms on DRC (refer to Study Procedure, below); Investigator confirms mean total symptom score (T4SS) ≥ 6 between V1 and V2, and on the day before the randomization visit [V2] (Refer to Study Procedure, below)
- Subject's laboratory data within protocol range
- Females have negative pregnancy test.

(pp 21-22)

Exclusion Criteria: V1 exclusion criteria:

- Perennial AR
- Pregnancy, breast feeding, or sexually active females of child-bearing potential not using acceptable contraception
- Ear, nose, or throat infection in two weeks prior to V1
- Asthma requiring daily treatment other than prn $ß_2$ agonist
- Dermatitis or urticaria requiring antihistamine or corticosteroid therapy (oral or topical)
- Vasomotor rhinitis or nasal obstruction from polyposis or septal deformity
- Clinically significant disease: cardiovascular, hepatic, renal, autoimmune, hematologic, neurologic, psychiatric, or others that affect ADME of study drug
- LCTZ or other piperazine-derivative allergy: hydroxyzine, cetirizine, cyclizine, meclozine, buclizine, or excipients (e.g., lactose)
- Subject incapable of giving informed written consent
- Non-compliant subjects
- Alcoholism, drug addiction, mental instability
- Clinical trial participation during last three months
- Subject intending to donate blood during study
- Investigators and their children, spouses, and colleagues

The following are V1 to V3 prohibited medications (pre-study wash-out periods are in parentheses):

• Astemizole	90 days
• Intranasal or systemic corticosteroids	30 days
• Ketotifen, nedocromil, cromoglicate, topical corticosteroids	14 days
• Loratadine	10 days
• Anti-leukotrienes	7days
• Other antihistamines, decongestants	3 days
• Other nasal or ocular topicals, asthma treatments other than $ß_2$ inhaled agonists prn, and ascending phase desensitization	no washout

V2 exclusion criteria:

- Laboratory results outside of protocol range; positive pregnancy test
- V1-V2 period less than three or greater than nine days
- Mean of total symptom scores < 6 between V1 and V2, or on day before V2
- Use of prohibited medication between V1 and V2
- Occurrence of exclusion criterion checked at V1

(pp 22-24)

Reviewer comment: Inclusion and Exclusion criteria are appropriate.

Study Procedure

Efficacy Parameter Scales: Subject grades rhinitis symptoms (sneezing, rhinorrhea, nasal pruritus, ocular pruritus) on a four point scale –
0 = absent,
1 = mild (present but not disturbing),
2 = moderate (disturbing but not hampering day-time activities and/or sleep),
3 = severe (hampering day-time activities and/or sleep).
Subject grades total symptoms separately (over the last 24 hours [Reflective, "R"], and over the last hour [Instantaneous, "I"]), daily, in the evening, prior to taking the study drug, and records in the DRC. These scores are the T4SS (R or I).
Subject also records daily *individual* scores for the four symptoms above and "nasal congestion" in the same way. Therefore, a properly completed DRC has a T4SS (R and I) and five individual symptom scores (R and I) recorded daily, in the evening, prior to taking the study medication (pp 27-28).

Other parametric scales (for secondary endpoints) include 1) a four-point "Global Evaluation of efficacy" scale that compares subject symptoms at treatment completion with symptoms present at V2 (0 = worse, 1 = unchanged, 2 = slight – moderate improvement, 3 = good – excellent improvement), and 2) the Rhinitis Quality of Life Questionnaire (RQLQ), a disease-specific, seven-domain (ADLs, sleep, non-nasal and eye symptoms, practical problems, emotions, nasal symptoms, and eye symptoms), six-point scale (0 = untroubled, 6 = extremely troubled) recorded at V1-V3 (pp 28-29).

Definition of baseline period and scores: Baseline period is between V1 and V2. The period is as short as three days, or as long as nine days. Eligibility for randomization at V2 requires three days (subject-recorded in the DRC) of a T4SS (R) ≥ 6, including the day prior to V2. (Although the subject also records other scores, primary efficacy assessment is a function of T4SS (R); T4SS (I), individual symptom scores, global evaluation scores, and the RQLQ are used for secondary endpoints [pp 45-60]).

Subject records the T4SS (R and I) and individual symptom scores in the record card daily, in the evening, prior to taking study medication, between V2 and V3 (two weeks).
(Refer to Protocol section for specific details of V1-V4 activities).

Reviewer comment:
*The primary study objective aims to confirm the superiority of LCTZ 5 mg, over placebo, in "reducing **rhinitis** symptoms" (p 2). The protocol uses the "Total 4 Symptoms Score (T4SS)" (sneezing, rhinorrhea, nasal pruritus, and ocular pruritus) to measure baseline and on-treatment symptoms. FDA does not recognize ocular pruritus as a symptom of allergic **rhinitis** and instructed the applicant to re-configure and re-analyze the nasal symptom score without ocular symptoms. The resulting "T3SS" (includes sneezing, rhinorrhea, nasal pruritus; omits ocular pruritus) is also analyzed in this review (refer to Primary Efficacy Results, below). T4SS to T3SS comparisons are made when considering ocular pruritus as a potential driver of efficacy.*

Statistical and Analytical Plan

Efficacy Parameters: Primary efficacy variables are the adjusted mean T4SS (R), compared with baseline, for the first treatment week *and* for the total (two-week) treatment period in the LCTZ 5 mg arm versus the placebo arm.

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 (p 4).

Safety Assessments: AEs reporting occurs at V2-V4. Safety laboratory tests (drawn at V1 and V3) are: complete blood count with differential, platelets, SGOT, SGPT, total bilirubin, direct bilirubin, urea, creatinine, and pregnancy test. Investigator checks values (and negative pregnancy test) at V2 and V4 (pp 20-21, 802).

Medication Compliance: Subject returns all unused medication and containers at V3. Drug reconciliation occurs in the subject's presence. Drug accountability records include: number of container dispensed at V2, subject's initials and CRF number, dates dispensed and returned, quantity remaining, and initials of collector (p 26).

Primary Efficacy Analysis: 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.
Shapiro-Wilk test, a stem and leaf plot, and a normal probability plot verify underlying ANCOVA assumptions. Comparison of two nested ANCOVA models using a likelihood ratio test verifies homoscedasticity assumptions (p 35).

Efficacy analysis includes each subject in the ITT population with at least one DRC entry. The Last Observation Carried Forward method (LOCF) accounts for missing data (baseline scores are not carried forward) [p 61].

Secondary Efficacy Analysis: Analysis of secondary variables (except for global evaluation of efficacy) uses an ANCOVA model with baseline as covariate and treatment and center as factors (p 35).
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 (p 35).

Sample Size Determination: 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%] (p 36).

Reviewer comment: The SAP presents descriptive data for day-to-day evolution of mean T4SS differences (p 50). Lack of statistical analysis means this study cannot support potential time to maximal effect claims.
The Plan analyzes instantaneous scores (T4SS [I]) at the 24 hour mark (end of dosing interval), thereby addressing duration-of-effect (see Secondary Efficacy Results and Study Conclusion sections, below).
(Ideally, instantaneous total symptom scores are, along with reflective scores, primary endpoints, rather than secondary, as in this protocol. Notwithstanding that, efficacy results for T4SS (I) are sufficiently robust in this study to dispel concerns about primary versus secondary endpoint designation).

Results

Patient Disposition: The study screens 344 subjects, and randomizes 237, 118 in the placebo group and 119 in the LCTZ group. The ITT population numbers 236 (one exclusion for failure to take any medication from the placebo group), and each returns a DRC. Two hundred thirty-two subjects complete the study (98.3%). Four subjects do not complete the study: one withdraws consent, one each for headache and somnolence (both resolve spontaneously), and one unspecified (p 71, p 1587).

Investigators identify protocol deviations prior to unblinding and data analysis. Use of proscribed medications is the most common major protocol deviation during the treatment period (4.2%) and occurs more in the placebo group (6.0%) than the LCTZ group (2.5%). Table 1 summarizes major deviations.

Table 1. Summary of Major Protocol Deviations (ITT Population)

Deviation	Placebo (N = 117)	LCTZ (N = 119)	Total (N = 236)

During Baseline	N (%)	N (%)	N (%)
Score out of range	3 (2.6)	3 (2.6)	6 (2.5)
Baseline short/long	0	1 (0.8)	1 (0.4)
General	1 (0.9)	0	1 (0.4)
Prohibited med	4 (3.4)	2 (1.7)	6 (2.5)
Insufficient washout	2 (1.7)	3 (2.5)	5 (2.1)
During Treatment			
Unknown compliance	1 (0.9)	2 (1.7)	3 (1.3)
Compliance high	2 (1.7)	4 (3.4)	6 (2.5)
Compliance low	4 (3.4)	2 (1.7)	6 (2.5)
DRC missing	0	1 (0.8)	1 (0.4)
Prohibited med	7 (6.0)	3 (2.5)	10 (4.2)
Treatment period too long or short	2 (1.7)	1 (0.8)	3 (1.3)

(Source: pp 39-40)

Treatment Compliance: Compliance is the ratio of the number of tablets actually taken by the subject over the number of tablets specified in the protocol. Mean compliance for the total treatment period is 99.92%. Over- and under-compliance (120% and 80%, respectively) are 2.5% each, without significant difference between study arms (p 47-48).

Demographics: Both groups have similar demographics (see Table 2). The average age of the 236 ITT subjects is 30.3 years (range 12.1 – 71.4 years). Mean duration of grass pollen allergy is 15.2 years (15.0 placebo group; 15.3 LCTZ group). Males and females distribute equally between groups; however, there are more females in the study (62.3% versus 37.7%). Most subjects are Caucasian (70.8%). All habit parameters (tobacco use, alcohol and caffeine consumption, illicit drug use) are equally distributed between groups.

Table 2. Summary of ITT Population Demographics

Characteristic	**Placebo (N = 117)**	**LCTZ (N = 119)**	**Total (N = 236)**
Age: Mean (Range)	29.56 (12.1-66.4)	30.95 (12.6-71.4)	30.26 (12.1-71.4)
Gender: N (%)	F 71 (60.7) M 46 (39.3)	F 76 (63.9) M 43 (36.1)	F 147 (62.3) M 89 (37.7)
Race: Origin (N; %)	Asian/Pacific Rim (17; 14.5) Black (3; 2.6) Caucasian (81; 69.2) Other (16; 13.7)	Asian/Pacific Rim (15; 12.6) Black (7; 5.9) Caucasian (86; 72.3) Other (11; 9.2)	Asian/Pacific Rim (32; 13.6) Black (10; 4.2) Caucasian (167; 70.8) Other (27; 11.4)
Mean Weight (kg) Range	70.9 34-121	71.1 35-113	71.0 34-121
Mean Height (cm) Range	168.4 146-197	168.0 148-189	168.2 146-197

(Source: pp 42-43)

Table 3 summarizes the most common (with a prevalence of at least 10% in one group) additional medical conditions in subjects. Other conditions occurring in at least 3% (but less than 10%) of *both* groups include: acne, atopic conjunctivitis, acute pharyngitis, bronchitis, depression, HTN, hypothyroidism, influenza, menopause, migraine, and otitis media (pp 194-201).

Table 3. Summary of Additional Medical Conditions ITT Population

Condition	Placebo (N = 117)	LCTZ (N = 119)	Total (N = 236)
Headache	27 (23.1%)	39 (32.8%)	66 (28.0%)
Asthma (unspecified)	24 (20.5%)	21 (17.6%)	45 (19.1%)
Chronic sinusitis (unspecified)	15 (12.8%)	15 (12.6%)	30 (12.7%)
Acute tonsillitis (unspecified)	19 (16.2%)	10 (8.4%)	29 (12.3%)
Other AR	13 (11.1%)	7 (5.9%)	20 (8.5%)

(Source: p 44)

Concomitant Medications: About 75% of each treatment group takes at least one concomitant medication during the study (p 237). Table 4 summarizes ITT population use of concomitant (non-proscribed) medications (by therapeutic class) by at least 10% of either treatment group. Other medication use (therapeutic class) by at least 3% (but less than 10%) of both groups includes: systemic antibiotics, anti-cholinergics, thyroid-related, and stomatologic preparations (pp 238-244).

Table 4. Concomitant Medication Use ITT Population (≥ 10% in either arm)

Therapeutic Class	Placebo (N = 117)	LCTZ (N = 119)	Total (N = 236)
Analgesics	40 (34.2%)	44 (37.0%)	84 (35.6%)
Sex hormones	29 (24.8%)	34 (28.6%)	63 (26.7%)
Anti-asthmatics	16 (13.7%)	15 (12.6%)	31 (13.1%)
Ophthalmologics	11 (9.4%)	15 (12.6%)	25 (11.0%)
Other gynecologic	13 (11.1%)	13 (10.9%)	25 (11.0%)
Anti-inflammatory	10 (8.5%)	15 (12.6%)	25 (10.6%)
Topical joint/muscular	8 (6.8%)	14 (11.8%)	22 (9.3%)

(Source: p 47)

Primary Efficacy Results

Change from baseline in adjusted mean T4SS (R) over Week 1 and over the total (two week) treatment period: LCTZ 5 mg produces a greater reduction in T4SS (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 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 (p 7, Amendment N-000BM, December 26, 2006). These results compare favorably to the T3SS (R) analysis (without ocular pruritus): 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 (p 51). Summary of T4SS (R) and T3SS (R) comparisons are in Tables 5A and 5B, respectively.

Table 5A. 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
Week 1	Placebo LCTZ 5 mg	117 118	8.50 (1.68) 8.40 (1.66)	6.45 5.49	0.96 (0.39;	0.001

					1.53)	
Total Treatment	Placebo LCTZ 5 mg	117 118	8.50 (1.68) 8.40 (1.66)	6.09 5.20	0.89 (0.30; 1.47)	0.003

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

Table 5B. 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
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"

(Source: p 7, Amendment N-000BM, December 26, 2006)

For the T4SS (R) analysis the relative improvement for LCTZ over placebo for the first week is 48%, and 38% for the total treatment period (p 51).
Per protocol population analysis using T4SS (R) scores shows statistical significance favoring LCTZ 5 mg similar to the results of the ITT population T4SS analysis (p 52).

Reviewer comment: The statistical significance present for either the T4SS or T3SS reflective scores strongly suggests that ocular pruritus is not driving the efficacy determination.

Secondary Efficacy Results

1) Change from baseline in adjusted mean T4SS(R) for the second treatment week: LCTZ 5 mg produces a greater reduction in T4SS(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). The relative improvement of LCTZ over placebo is 27% (p 52).
2) Change from baseline in adjusted mean T4SS (I) over Week 1 and over the total two week treatment period: LCTZ 5 mg produces a greater reduction in T4SS (I) scores than placebo, compared to baseline scores, over Week 1, and over the total treatment period. The results are statistically significant. Table 6 summarizes.

Table 6. MeanT4SS (I) Comparisons for Week 1 and the Total Treatment Period (ITT)

Period	Treatment	N	Baseline Mean (SD)	On-treatment Adj. Mean	Diff vs Placebo Adj. Mean (95% CI)	p-value
Week 1	Placebo LCTZ 5mg	117 118	7.48 (2.21) 7.24 (2.23)	5.58 4.83	0.75 (0.20; 1.29)	0.007
Total Treatment	Placebo LCTZ 5 mg	117 118	7.48 (2.21) 7.24 (2.23)	5.30 4.58	0.73 (0.17; 1.28)	0.011

(Source: Amended datasets submitted by applicant October 31, 2006)

Reviewer comment: The statistical analysis for T4SS (I) scores shows significant differences, versus placebo, for LCTZ 5 mg for the first week and the total treatment period. This review includes the CIs and p-values for this secondary endpoint due to the implications for duration-of-effect claims the applicant makes. Additionally, A00268 is the only SAR or PAR study in this NDA that includes instantaneous total symptom scores.

3) Changes from baseline in adjusted mean individual symptom scores (R) for the first week and the total treatment period: The SAP analyzes five individual symptom scores (reflective): 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 (both treatment periods) [pp 54-58].

Reviewer comment: Nasal pruritus is a component of the T3SS (along with sneezing and rhinorrhea). Failure of LCTZ to beat placebo in the analysis for the ***individual*** *symptom score nasal pruritus suggests that LCTZ's reduction in sneezing and rhinorrhea is responsible for the efficacy demonstrated for LCTZ, versus placebo, as assessed by T3SS (R) scores. Analysis of the adjusted mean individual sneezing and rhinorrhea scores for LCTZ and placebo compared with baseline supports this (neither CI contains zero). Although, by this same assessment, LCTZ is favored over placebo for improvement in ocular pruritus, the findings are less robust than for sneezing or rhinorrhea. These findings suggest that LCTZ-related reductions in sneezing and rhinorrhea are the primary determinants of LCTZ efficacy in this study.*
The SAP indicates that analysis includes assessments of instantaneous individual symptom scores, but presents descriptive statistics only.

Multi-center Analysis

The analysis finds no evidence of a treatment by center interaction ($p = 0.824$ for the first week, and 0.929 for the total treatment period (p 61).

Subgroup Analysis

There is no subgroup analysis (p 62).

Safety Assessments

No deaths occur in the study. The only AE-related withdrawal in the LCTZ group is for somnolence (after five days of treatment). Roughly 50% of subjects experience treatment-emergent AEs, with a similar incidence between groups. Headache is the most common treatment-emergent AE and 20% of subjects in each group report this (28% of subjects report headache in baseline medical history). Somnolence is reported by seven subjects (6%) in the LCTZ group, and one (1%) in the placebo group. Notwithstanding the withdrawal for

somnolence in the LCTZ group (N = 1), no treatment-emergent SAEs occur due to LCTZ. Table 7 summarizes treatment-emergent AEs.
One subject in the LCTZ group develops an elevated bilirubin level that resolves without treatment. A non-parametric comparison of the treatments on the difference between baseline and post-treatment laboratory values shows a small, but statistically significant, decrease in median RBC values for the LCTZ group (-0.055 [-0.095; -0.015] x 10^{12}/L).

Reviewer comment: The applicant states variability in RBC is very low, resulting in small changes being detected statistically, which is plausible. The amount of decrease is not clinically relevant, and no other confirmatory efficacy or supporting studies submitted with this NDA report similar findings.

Table 7. Summary of Treatment-emergent AEs (at least 2% of subjects in either group)

Preferred term	Placebo (N = 117)		LCTZ 5 mg (N = 118)	
	n	(%)	n	(%)
Headache	23	(19.7%)	23	(19.3%)
Somnolence	1	(0.9%)	7	(5.9%)
Fatigue	3	(2.6%)	4	(3.4%)
Nausea	4	(3.4%)	3	(2.5%)
Abdominal Pain	2	(1.7%)	4	(3.4%)
Dry Mouth	2	(1.7%)	3	(2.5%)
Dizziness	1	(0.9%)	5	(4.2%)
URI	1	(0.9%)	5	(4.2%)
Pharyngitis	2	(1.7%)	3	(2.5%)
Skeletal pain	0		3	(2.5%)

(Source: p 65)

Study Conclusions

Efficacy: Levocetirizine 5 mg oral tablet, taken daily, once in the evening, is statistically superior to placebo for reducing grass pollen allergic rhinitis nasal symptoms, assessed as change from baseline in the reflective T4SS (sneezing, rhinorrhea, nasal pruritus, and ocular pruritus), for the first treatment week (adjusted mean difference 0.96 [95% CI 0.39; 1.53], p = 0.001), and over the two week treatment period (adjusted mean difference 0.89 [95% CI 0.30; 1.47], p = 0.003).

For secondary endpoints, analysis favors LCTZ over placebo for the following: 1)T4SS (R) for the second treatment week, 2) T4SS (I) for the first week and the total treatment period, and 3) for reflective sneezing, rhinorrhea, and ocular pruritus individual symptom scores for the first week and the total treatment period.

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

The results of this study support the use of LCTZ 5 mg tablets, taken once in the evening, for the treatment of nasal symptoms of grass pollen allergic rhinitis.

Safety: Somnolence is more likely with LCTZ than placebo. There are no unusual AEs or safety signals in this study.

Reviewer comment: 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 may improve on LCTZ (although not as greatly as sneezing and rhinorrhea), and 3) nasal pruritus, a core T3SS symptom, does not improve with LCTZ. Findings 2 and 3 may affect potential labeling claims.

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 grass pollen allergic rhinitis is appropriate.

Presentation of descriptive statistics without accompanying analysis for daily evolution of T4SSs does not allow conclusions regarding time to maximal effect or onset of action.

Appendix 1. C. Study A00303*

"A randomized, double-blind, placebo-controlled, multi-center, Phase 4 study of the efficacy and safety of 5 mg levocetirizine dihydrochloride tablets, administered once daily in the evening, for six weeks, to children from 6 to 12 years old suffering from seasonal allergic rhinitis due to grass and/or weed pollen."

* *Page citations in this review refer to A00303.pdf unless otherwise specified.*

Overview

The purpose of this seven week (six on-treatment) study is to confirm the efficacy and safety, over placebo, of levocetirizine dihydrochloride (LCTZ) 5 mg oral tablets, taken once daily in the evening, to reduce seasonal allergic rhinitis (SAR) symptoms due to grass and/or weed pollen of subjects 6 to 12 years old. The primary efficacy analysis assesses the change from baseline in subject-recorded (reflective, over 24 hours), adjusted mean nasal symptom scores (T4SS: sneezing, rhinorrhea, nasal pruritus, and ocular pruritus*) over the first two weeks of treatment.

* *Refer to Study Procedure section for definition and discussion of nasal symptom score configurations*

Study Dates

April 9, 2002 – September 4, 2002

Investigators: Forty-nine investigators at 28 centers in France (N = 22) and Germany (N = 6) enroll subjects in this study (p 82; pp 583-584). The study follows the ICH E6 note for guidance on Good Clinical Practices (GCP) and principles from the Declaration of Helsinki (p 20).

Amendments

The study protocol has one amendment:
Amendment 1 (December 20, 2001) adds new sites due to low recruitment (p 466).

Protocol

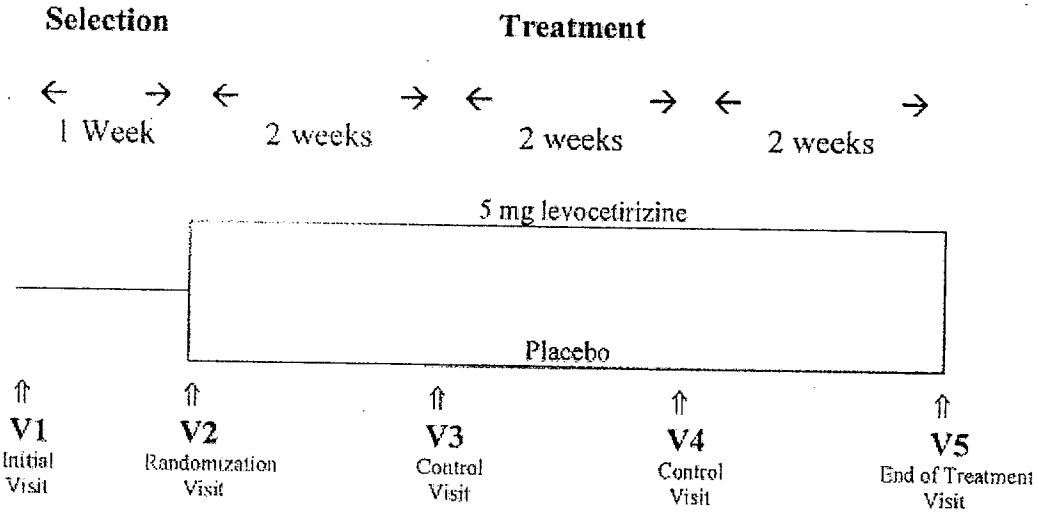
The protocol describes a multi-center, randomized, double-blind, placebo-controlled study in subjects 6 to12 years old comparing LCTZ 5 mg oral tablets, once daily in the evening, with placebo for the treatment of SAR symptoms due to grass and/or weed pollen. The primary objective is confirmation of superiority of LCTZ, over placebo, in reducing subject-recorded total nasal symptom scores, reflective over 24 hours [T4SS (R)], (defined in Study Procedure section, below), compared to baseline, for the first two weeks of treatment (p 21). The applicant chooses the 5 mg LCTZ dose because multiple studies in SAR subjects show efficacy, and the 10 mg dose of the racemate cetirizine (of which LCTZ is the more active enantiomer) is effective and used in children six years and older as well as adults (p 27).

The study period is seven weeks (six treatment weeks) and there are five visits (refer to schematic study diagram, below):
Visit 1 (V1) – Initial selection: includes eligibility screening (refer to Inclusion Criteria, below), demographics, obtaining informed consent (subject and parents or guardian participate), dietary, allergy-specific, and medical histories. Subject undergoes a general physical examination (PE); Investigator records (in CRF) treatments during the previous three months and school absenteeism due to asthma or AR during the last four weeks, documents a positive skin test or RAST for grass or weeds within the last 12 months (places a skin test if needed). Subject completes Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) by interview, receives daily record card (DRC) for scoring daily symptom severity in the evening (for the last 24 hours; subject may be assisted by parent or guardian) and listing concomitant medications and AEs, and receives appointment for V2 (one week, although as short as three days, but not longer than nine days).
Visit 2 (V2) – Randomization: three to nine days after V1. Investigator verifies subject DRC details, AEs, and treatments taken since V1 (excluding those subjects taking prohibited medications). Subject undergoes PE and updates PRQLQ. Investigator reviews DRC, assures eligible baseline symptom score, randomizes eligible subject to treatment, and gives subject study medication, a new DRC, instructions to begin treatment that evening, and an appointment for Visit 3 (two weeks later).
Visit 3 (V3) – Control visit after two weeks of treatment: subject undergoes PE, updates PRQLQ, and returns medication container; Investigator verifies and collects DRC and records AEs and concomitant medications in CRF. Investigator counts and records tablets. At V3 only, subject, parent (or guardian) and Investigator complete seven-point Global Evaluation Scale.

Investigator dispenses next study medication container, a new DRC, and makes appointment for V4 (two weeks).
Visit 4 (V4) – Second control visit: follows same procedures as V3 except for Global Evaluation Scale; Investigator makes appointment for V5 (two weeks).
Visit 5 (V5) – End of treatment: same procedures as V3 and V4. Investigator records willingness of subject and parent (or guardian) to continue same treatment in future (pp 29-31).

Appears This Way
On Original

Schematic Study Diagram



(Source: p 389)

Patient Population: Males or females 6 to 12 years old who have seasonal allergic rhinitis to grass and/or weed pollen for at least the last year.

Pollen Counts: Pending (IR to applicant for data set, December 28, 2006).

Inclusion Criteria: The following criteria must be met at Visit1:

- Subject and parent (or guardian) gives written informed consent

- Investigator documents medically acceptable contraceptive method use in females of child-bearing potential
- Subject able to comprehend study information complete DRC and questionnaires, and communicate with Investigator
- Investigator confirms subject's allergy to grass and/or weed pollen by positive skin test (wheal ≥ 3 mm larger than control for prick test or ≥ 7 mm larger than control for intradermal test) or positive RAST (≥ class 3 or ≥ 3.5 U/ml); if allergy tests not done within preceding year, or unavailable, investigator performs skin test.

The following criteria must be met at Visit 2 (randomization):

- Subject records rhinitis symptoms in DRC; Investigator confirms mean daily total symptom score (T4SS, 24 hour reflective at bedtime) ≥ 6 between V1 and V2, and on the day before the randomization visit [V2] (Refer to Study Procedure, below).

(p 24)

Exclusion Criteria: V1 exclusion criteria:

- Perennial allergic rhinitis that may change subject's symptoms during study
- Ear, nose, or throat infection in two weeks prior to V1
- Temperature ≥ 38.5°
- Vasomotor rhinitis or nasal obstruction from polyposis or septal deformity
- Clinically significant disease: cardiovascular, hepatic, renal, autoimmune, hematologic, neurologic, psychiatric, or others that affect ADME of study drug
- LCTZ or other piperazine-derivative allergy: hydroxyzine, cetirizine, cyclizine, meclozine, buclizine, or excipients (e.g., lactose)
- Hypersensitivity to cromones
- Parent or guardian incapable of giving informed written consent
- Non-compliant subjects
- Clinical trial participation during last three months
- Subjects intending to donate blood during study
- Child of Investigators or other study collaborators.

The following are V1 to V5 prohibited medications (pre-study wash-out periods are in parentheses):

• Corticosteroids	30 days
• Ascending phase desensitization	30 days
• Ketotifen, nedocromil, cromoglicate	14 days
• Loratadine	10 days
• Leukotriene antagonists	7 days
• Other H_1 antihistamines, decongestants	3 days
• Other nasal or ocular topicals, asthma treatments other than $ß_2$ inhaled agonists prn	No washout

V2 exclusion criteria:

- V1-V2 period less than three or greater than nine days

- Occurrence of any non-inclusion criterion (e.g., fever, ENT infection) between V1 and V2
- Use of prohibited medication between V1 and V2.

(pp 24-25)

The protocol permits nasal sodium cromoglicate (1 puff in each nostril four times daily) as rescue medication if, after two weeks of treatment, subject requires additional treatment due to lack of therapeutic response (p 28).

Reviewer comment: *Inclusion criteria are appropriate. FDA guidance recommends exclusion of subjects with asthma (except mild intermittent asthma) to lessen confounding by asthma medications (Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, April 2000, p 10). Over the total treatment period 21.6% of placebo subjects and 18% of LCTZ subjects use short-acting β_2 drugs for asthma (Table 11:23, p 71). The study does not document use of other anti-asthma therapies nor does it provide data on concomitant on-treatment medication use. Notwithstanding this, it is unlikely that anti-asthma medications confound the results of this study: medications most likely to affect symptom scores (including all corticosteroids [except topical], other anti-histamines, and anti-leukotrienes) are prohibited. Use of cromoglicate as a rescue medication after two weeks is unlikely to affect primary outcome assessment (change in T4SS over first two treatment weeks).*

Study Procedure

Efficacy Parameter Scales: Subject records rhinitis symptoms each evening in the DRC (24 hour reflective), just prior to taking study medication. Subject grades symptoms (sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal congestion) on a four point scale:

0 = absent,
1 = mild (present but not disturbing),
2 = moderate (disturbing but not hampering day-time activities and/or sleep),
3 = severe (hampering day-time activities and/or sleep).

Sneezing, rhinorrhea, nasal pruritus, and ocular pruritus are the T4SS [R] (p 31).

Subject records (in DRC) each nocturnal cough event with sleep disturbance, each wheezing event (any time), use of short-acting β_2 drugs for asthma, and use of rescue cromoglicate for rhinitis symptoms. Investigator asks subject about willingness to continue same treatment in future (p 32).

Subject, parent (or guardian), and Investigator complete separate seven-point global evaluation of disease evolution scale (1 = marked improvement, 4 = no change, 7 = marked worsening) at V3, comparing to start of study medication (p 32).

Investigator interviews subject at beginning of all visits and completes PRQLQ, a five-domain, 23 item QOL questionnaire assessing nasal and ocular symptoms, practical problems, activity limitations, and other problems (p33).

Definition of baseline period and scores: Baseline period is between V1 and V2. The period is as short as three days, or as long as nine days. Eligibility for randomization at V2 requires three days (subject-recorded in the DRC) of a T4SS (R) ≥ 6, including the day prior to V2 (p 24). (Subject also records component symptoms of T4SS and nasal congestion individually).

Reviewer comment:
*The primary study objective aims to confirm the superiority of LCTZ 5 mg, over placebo, in "reducing **rhinitis** symptoms" (p 2). The protocol uses the "Total 4 Symptoms Score (T4SS)" (sneezing, rhinorrhea, nasal pruritus, and ocular pruritus) to measure baseline and on-treatment symptoms. FDA does not recognize ocular pruritus as a symptom of allergic **rhinitis** and instructed the applicant to re-configure and re-analyze the nasal symptom score without ocular symptoms. The resulting "T3SS" (includes sneezing, rhinorrhea, nasal pruritus; omits ocular pruritus) is also analyzed in this review (refer to Primary Efficacy Results, below). T4SS to T3SS comparisons are made when considering ocular pruritus as a potential driver of efficacy.*

Statistical and Analytical Plan

Efficacy Parameters: Primary efficacy variable is the adjusted mean T4SS (R), compared with baseline, for the first two weeks of treatment in the LCTZ 5 mg arm versus the placebo arm.

Reviewer comment: The four week treatment period for a SAR study is satisfactory; FDA guidance recommends at least two weeks (Guidance for Industry, Allergic Rhinitis: Clinical Devlopment Programs for Drug Products, p 9). The SAP does not measure instantaneous scores; therefore, this study's results cannot be used support potential duration of effect claims.

Secondary endpoints, by protocol order, are 1) mean T4SS (R) over the first four weeks of treatment, over the total six week treatment period, and over each week, 2) mean individual symptom score (sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal congestion) over two, four, and six weeks of treatment, and over each treatment week, 3) the percentage of days with asthma symptoms (nocturnal cough with sleep disturbance, wheezing) over the treatment period, 4) use of short-acting β_2 agonists over the treatment period, and 5) use of cromoglicate nasal spray and percentage of days of use for allergic rhinitis symptoms over the last four weeks of treatment (p 37).

Exploratory variables are: global evaluation of disease by subject, parent, and Investigator over the first two weeks of treatment, proportion of 50% and 70% responders over one, two, four, and six weeks of treatment, PRQLQ over each visit, subject and parent willingness to continue same treatment in future, SAR symptoms as a function of pollen counts and dry weather days, use of medical resources (e.g., physician, hospital, and ER visits), and school absenteeism (p 38).

Safety Assessments: AEs and physical examination data (p 39).

Medication Compliance: Subject returns all unused medication and containers at V3, V4, and V5. Drug reconciliation occurs in subject's presence to document discrepancies. Investigator records (in CRF) number of tablets returned (and date) and explanations of non-compliance (p 28).

Primary Efficacy Analysis: Primary efficacy analysis is on the ITT population (randomized subjects taking at least one dose of study medication and having a baseline measurement and at least one on-treatment score). (A per protocol population analysis assesses the impact of protocol violations on study results). 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 percent relative improvement from baseline of LCTZ over placebo (p 36).

Secondary Efficacy Analysis: Analyses are as follows: 1) DRC variables (T4SS-related and individual symptom scores) as per the primary efficacy variable (ANCOVA not performed if T4SS for a given period not statistically significant), 2) sensitivity analysis on mean six week T4SS taking into account use of rescue cromoglicate, 3) non-parametric analysis of variance for asthma-related symptoms, 4) logistic model for use of short-acting β_2 agonists, 5) chi-square for use of cromoglicate, and 6) Wilcoxon rank-sum for percentage of days using cromoglicate (pp 37-38).

Sample Size Determination: 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 for the first two weeks of treatment [assumptions: alpha 5% and SD 2.1] (p 39).

Results

Patient Disposition: The study screens 223 subjects, and randomizes 177, 88 to the placebo group and 89 to the LCTZ group. One hundred and forty-five subjects complete the study (81.9%) and 27 (15.3%) drop out. (The study classifies five subjects [two placebo and three LCTZ] as "missing" due to the death of the Investigator at center 0011). The most common reason for early termination is lack of efficacy, which occurs more in the placebo group (N = 9 [10.2%]) than the LCTZ group (N = 5 [5.6%]). No subject from the LCTZ group drops out due to AEs. Of the other 13 drop outs, one withdraws consent (placebo), one for AE (placebo), and 11 for other reasons (holidays, non-compliance), six in the placebo group and five in the LCTZ group [p 42].

Investigators identify protocol deviations prior to unblinding and data analysis. Use of proscribed medications is the most common major protocol deviation during the treatment period (13%), more in the placebo group (N = 13) than the LCTZ group (N = 10). Insufficient washout of pre-study drugs (11.3%) is higher in the placebo group (N = 13) than the LCTZ group (N = 7). Table 1 summarizes major deviations (pp 42-43).

Table 1. Summary of Major Protocol Deviations (ITT Population)

Deviation	Placebo (N = 88)	LCTZ (N = 89)	Total (N = 177)
During Baseline	N (%)	N (%)	N (%)
Score out of range or baseline short/long	9 (10.2)	7 (7.9)	16 (9.0)
Prohibited medication/treatment	4 (4.5)	6 (6.7)	10 (5.6)
General ineligibility	0	1 (1.1)	1 (0.6)
Prohibited med	6 (4.2)	4 (2.7)	10 (3.4)
Insufficient washout	13 (14.8)	7 (7.9)	20 (11.3)
During Treatment			
Compliance (high, low, unavailable)	9 (10.2)	8 (9.0)	17 (9.6)
DRC missing/unavailable	1 (1.1)	3 (3.4)	4 (2.3)
Prohibited med	13 (14.8)	10 (11.2)	23 (13.0)
Deviation (general, unspecified)	2 (2.3)	3 (3.4)	5 (2.8)

Treatment Compliance: Compliance is the ratio of the number of tablets actually taken by the subject over the number of tablets specified in the protocol and assessment is every two weeks of the treatment period. The mean compliance for the total treatment period is 96.5%. Four subjects (three placebo and one LCTZ) in the ITT population have compliance below 80%, and none are over 120%. Five subjects do not have overall compliance data (Investigator death at center 0011). Analysis shows no difference in overall compliance between study groups (p 48).

Demographics: Both groups have similar demographics (see Table 2). The average age of the 177 ITT subjects is 9.9 years (range 6.0 – 13.0 years). More than twice as many children are between 9 and 12 years (69.5%) than 6 to 8 years (29.9%). There are more boys (66.1%) than girls (33.9%) in the study (however, the placebo group has a higher percentage of girls [38.6%] than the LCTZ group [29.2%]). Most subjects are Caucasian (90.4%).

Table 2. Summary of ITT Population Demographics

Characteristic	Placebo (N = 88)	LCTZ (N = 89)	Total (N = 177)
Age: Mean (Range)	9.93 (6.1-13.0)	9.89 (6.0-12.8)	9.91 (6.0-13.0)
Age Category 6-8 yrs 9-12 yrs 13 yrs	28 (31.8%) 59 (67.0%) 1 (1.1%)	25 (28.1%) 64 (71.9%) 0	53 (29.9%) 123 (69.5%) 1 (0.6%)
Gender: N (%)	F 34 (38.6) M 54 (61.4)	F 26 (29.2) M 63 (70.8)	F 60 (33.9) M 117 (66.1)
Race: Origin (N; %)	Asian/Pacific Rim (0) Black (5; 5.7) Caucasian (82; 93.2) Other (1; 1.1)	Asian/Pacific Rim (4; 4.5) Black (6; 6.7) Caucasian (78; 87.6) Other (1; 1.1)	Asian/Pacific Rim (4; 2.3) Black (11; 6.2) Caucasian (160; 90.4) Other (2; 1.1)
Mean Weight (kg) Range	33.92 18-54.5	34.78 18.0-61.0	34.36 18.0-61.0
Mean Height (cm) Range	138.4 110-162	139.3 110-170	138.9 110-170

(Source: pp 45-46)

Reviewer comment: Only 25 subjects six to eight years old are exposed to LCTZ, which, depending upon exposure of this age group to LCTZ in supporting studies (e.g., A00304

[pediatric PAR study]) may have implications for potential approval for LCTZ down to six years old.

Table 3 summarizes subjects' most common (other than SAR, and with a prevalence of at least 5% in one group) additional medical conditions (pp 46-47).

Table 3. Summary of Additional Medical Conditions ITT Population

Condition	Placebo (N = 88)	LCTZ (N = 89)	Total (N = 177)
Asthma (unspecified)	30 (34.1%)	37 (41.6%)	67 (37.7%)
Atopic dermatitis	9 (10.2%)	11 (12.4%)	20 (11.3%)
Eczema	8 (9.1%)	12 (13.5%)	20 (11.3%)
URIs (unspecified)	6 (6.8%)	6 (6.7%)	12 (6.8%)
Perennial Rhinitis	6 (6.8%)	5 (5.6%)	11 (6.2%)
Bronchitis (unspecified)	3 (3.4%)	7 (7.9%)	10 (5.6%)
Cough	4 (4.5%)	5 (5.6%)	9 (5.1%)
Varicella	0	5 (5.6%)	5 (2.8%)

Concomitant Medications: The study presents data for subjects' use of nasal sodium cromoglicate, a permitted rhinitis rescue medication after two weeks of treatment, and short-acting β_2 agonists (pp 69-71). Over the total treatment period 69 placebo (78.4%) and 68 LCTZ (76.4%) subjects use cromoglicate. Those in the placebo group using it do so on 65% of treatment days, and in the LCTZ group, on 66.7% of treatment days.

Over the total treatment period the proportion of subjects using β_2 agonists is less for the LCTZ group (18.0%) than for the placebo group (21.6%).

Reviewer comment: The study does not specify actual use of cromoglicate (by either group) during the first two treatment weeks, the occurrence of which may affect efficacy findings. However, cromoglicate is prohibited during the first two treatment weeks, and, since only 13% of all subjects (13 placebo, and 10 LCTZ, [Table 10:2, p 43]) use prohibited medication during the total treatment period, it is likely that most usage occurs after the two week mark. Furthermore, since cromoglicate use equally distributes between groups, use becomes a potential issue only in the event of a marginal, rather than robust, efficacy finding favoring LCTZ (i.e., in the event of marginal primary efficacy favoring LCTZ, it would be important to review specific usage of cromoglicate by the LCTZ group during the first two treatment weeks).

Primary Efficacy Results

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. The results are statistically significant: adjusted mean difference is 1.29 (95% CI 0.66; 1.92), $p < 0.001$ (p 9, Amendment to Pending Application, October 31, 2006). These results compare favorably to the T3SS (R) analysis (without ocular pruritus): adjusted mean difference is 1.11 (95% CI 0.64; 1.59), $p < 0.001$. Summaries of T4SS (R) and T3SS (R) comparisons are in Tables 4A and 4B, respectively.

Table 4A. 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 4B. 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"

(Source: p 9, Amendment to Pending Application, October 31, 2006)

The relative improvement of LCTZ 5 mg over placebo is 94.1% [per T4SS] (p 50).

A per protocol population analysis using T4SS (R) scores shows statistical significance favoring LCTZ 5 mg that is similar to the results of the T4SS analysis of the ITT population (p 51).

For the primary efficacy analysis the SAP imputes maintenance of same T4SS for droputs and missing data. This results of this strategy compare favorably to analysis of subjects with available per day T4SS (p 81).

Reviewer comment: The statistical significance present for either the T4SS or T3SS reflective scores strongly suggests that ocular pruritus is not driving the efficacy determination. Additionally, the findings are satisfactorily robust to allay concerns regarding sample size (the original protocol was powered for 292 subjects, but the study randomizes only 177 [Division statisticians concur with this observation]) and cromoglicate use.

Secondary Efficacy Results

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 [p 11, Amendment to Pending Application, October 31, 2006]. These results compare favorably to the T3SS (R) analysis (without ocular pruritus). Analysis by treatment week favors LCTZ for all except the sixth week for both the T4SS and T3SS. (A sensitivity analysis of cromoglicate use on T4SS over six weeks of treatment for both groups shows treatment difference similar to the ITT analysis) [p 53].
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 (pp 55-64).
3) Global Evaluation of treatment: For the first two week treatment period, the Investigator rates 60.7% of the LCTZ group moderately to markedly improved compared to 30.7% of the placbo group; subjects favor LCTZ by 48.3% to 13.6%, and parents favor LCTZ by 57.3% to 28.4% (pp 72-74).

Multi-center Analysis

No evidence of a treatment by center interaction is found for the mean T4SS over the first two treatment weeks (p 83).

Subgroup Analysis

The study provides descriptive statistics by age category, but no formal subgroup analysis (p 83).

Safety Assessments

No deaths occur in the study. No SAEs or withdrawals due to AEs occur in the LCTZ group. Overall, 32.2% of subjects experience treatment-emergent AEs, 30.7% in the placebo group and 33.7% in the LCTZ group. Headache, bronchitis, and epistaxis are the most common treatment-emergent AEs. Table 5 summarizes treatment-emergent AEs. Additionally, in the LCTZ group, one subject complains of fatigue and one of somnolence (pp 87-89).

Table 5. Treatment-emergent AEs (at least 2% of subjects in either group)

Preferred term	Placebo (N = 88)		LCTZ 5 mg (N = 89)	
	n	(%)	n	(%)
Headache	8	(9.1%)	4	(4.5%)
Asthenia	3	(3.4%)	2	(2.2%)
Pyrexia	1	(1.1%)	3	(3.4%)
Gastroenteritis (NOS)	3	(3.4%)	2	(2.2%)
Tracheitis	0		2	(2.2%)
Irritability	2	(2.3%)	1	(1.1%)
Asthma	3	(3.4%)	2	(2.2%)
Bronchitis	3	(3.4%)	3	(3.4%)
Cough	0		2	(2.2%)
Epistaxis	1	(1.1%)	5	(5.6%)
Pharyngolaryngeal pain	3	(3.4%)	2	(2.2%)

Reviewer comment: Although the relative risk for epistaxis in the LCTZ group is 4.94 (p 88), causality is uncertain. The epistaxis episodes apparently resolved spontaneously, since none is reported as an SAE, and no subject withdrew from the study due to epistaxis. There is no obvious direct mechanism of action that explains epistaxis with LCTZ use. Furthermore, epistaxis is not reported with unusual frequency in another pediatric allergic rhinitis study (A00304), nor is it

an AE feature in adult LCTZ studies for PAR, SAR, and CIU indications (the applicant cites a range of occurrence in clinical trials [pediatric and adult] of 0.6% to 1.2%) [p 88]. A plausible explanation is that epistaxis by multiple mechanisms is common in children, and, by chance, is more common in the LCTZ group in this study.

Study Conclusions

Efficacy: Levocetirizine 5 mg oral tablet, taken daily, once in the evening, is statistically superior to placebo for reducing seasonal allergic rhinitis nasal symptoms in children 6 to 12 years old due to grass and/or weed pollen, assessed as change from baseline in the reflective T4SS (sneezing, rhinorrhea, nasal pruritus), for the first two treatment weeks (adjusted mean difference 1.29 [95% CI 0.66; 1.92], $p < 0.001$).

Analysis favors LCTZ over placebo for the following secondary endpoints: 1) T4SS (R) for the first four and six week treatment periods, and over each week, 2) Reflective scores for the individual symptoms sneezing, rhinorrhea, nasal pruritus for the first two week, four week, and the total six week treatment periods, and 3) Subject, Investigator, and parent (or guardian) global evaluation of treatment.

Indirect indicators of efficacy are more subjects using prohibited medications in the placebo than the LCTZ group, and premature study termination for lack of efficacy is twice as likely in the placebo as the LCTZ group.

The results of this study support the use of LCTZ 5 mg tablets, taken once in the evening, for the treatment of nasal symptoms of SAR due to grass and/or weed pollen in children 6 to 12 years old.

Safety: No deaths occur in the study. No LCTZ subject withdraws due to an AE. Two LCTZ subjects report somnolence or fatigue. Epistaxis occurs more frequently in LCTZ (N = 5, 5.6%) group than in placebo group (N = 1, 1.1%).

Reviewer comment: 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 lower than expected recruitment does not adversely affect the otherwise robust efficacy shown for the primary endpoint.

The study exposes only 25 subjects six to eight years old to LCTZ, which, depending upon exposure of this age group to LCTZ in supporting studies (e.g., A00304 [pediatric PAR study]) may have implications for potential approval for LCTZ down to six years old.

The study results cannot support potential claims for reduction in ocular pruritus or nasal obstructive symptoms in pediatric subjects.

Use of the rescue medication nasal sodium cromoglicate does not confound the finding of efficacy favoring LCTZ.

The study lacks instantaneous symptom scores and cannot support potential duration of effect claims.

Appendix 1.D. 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."

* *Page citations in this document refer to A00269.pdf, unless otherwise specified.*

Overview

The purpose of this study is to confirm the effectiveness, over placebo, of levocetirizine dihydrochloride (LCTZ) 5 mg oral tablets taken once daily in the evening in treating the signs and symptoms of chronic idiopathic urticaria (CIU) in adults 18 years of age and older. The primary efficacy analysis assesses change from baseline of adjusted mean subject-rated pruritus severity scores (reflective, prior 24 hours) for the first seven days, and over four weeks. 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

February 26, 2001 – September 12, 2001

Investigators: Forty-six investigators at 19 centers (16 in Germany, three in Switzerland) enroll subjects in the study. The study follows good clinical practice (GCP) guidelines (p 39).

Amendments

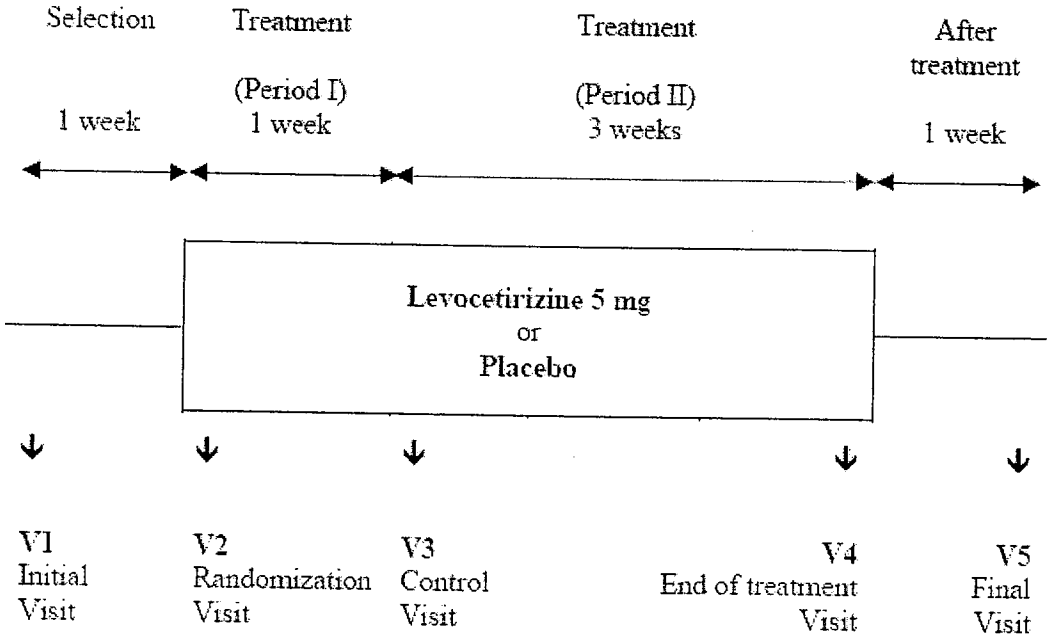
None

Protocol

The protocol describes a multi-center, randomized, double-blind, placebo-controlled study in adults (18 years of age and older) to demonstrate the superiority of LCTZ 5 mg once daily in the evening, over placebo, in treating the symptoms and signs of chronic idiopathic urticaria (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 5 mg once daily in the evening LCTZ dose is based on the results of Phase 2 and 3 rhinitis studies (not specified) finding this to be the most appropriate in terms of risk/benefit ratio (p 28).

The study period (see Study Diagram, below) spans six weeks; during four consecutive weeks (weeks two through five) subjects receive either LCTZ 5 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 study arm and onset of treatment begins at V2. Visit 3, one week after V2, 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 diagram of the study



(p 25)

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 (pp 28-29).

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 28-30).

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 (pp 29-30).

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 34-35)

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 26-29).

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 5 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 (pp 26-27).

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 (p 27).

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 completes global evaluation of treatment questionaire, comparing current disease state with baseline condition at V2 [using a seven-point scale, see below for details] (p 27).

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 (pp 27-28).

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 LCTZ 5 mg daily arm versus the placebo arm (pp 42-43). (See "Baseline period and scores," above, for definition of baseline).

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 43).

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 43).

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 38).

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 33).

Primary Efficacy Analysis: Primary efficacy variables analysis is on the ITT population (subjects with at least one measurement for the daily pruritus severity in the DRC during baseline and during the treatment period. The primary efficacy analysis uses an ANCOVA model that includes baseline score as covariate, and treatment and center as factors. The analysis presents p-value and 95% confidence interval for the difference in adjusted means between placebo and LCTZ.
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. A likelihood ratio test for homogeneity of variance allows different variances for the two treatment groups. Evaluation of interaction between treatment and baseline scores is by testing the equality of slopes of the treatment regression line of the predicted values versus the baseline scores; testing the consistency of the treatment effect across centers assesses the interaction between the treatment and center [after pooling] (pp 42-43).

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 p-value and confidence interval of the difference in adjusted means between placebo and LCTZ (p 43).
Investigator-observed secondary endpoint analyses uses a Cochran-Mantel-Haenszel test based on ranks, and stratified by baseline score. The Fisher's exact test assesses the presence of dermographism, Quincke's edema, and pressure association (p 43).

Sample Size Determination: 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] (p 44).

Results

Patient Disposition: The study screens 186 subjects and randomizes 166 (the ITT population, defined as the population of all randomized subjects taking at least one dose of study medication): 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] (see Table 1, below).

Table 1. Discontinuation of Treatment – ITT Population

Reasons for discontinuation	Placebo (N = 85)	LCTZ (N = 81)	Total (N = 166)
Lack of efficacy	26 (30.6%)	4 (4.9%)	30 (18.1%)
Other (unspecified)	6 (7.1%)	4 (4.9%)	10 (6.0%)
Lost to follow-up	1 (1.2%)	1 (1.2%)	2 (1.2%)
Total	33	9	42 (25.3%)

(p 47)

Reviewer comment:
An Information Request to the applicant November 7, 2006 seeks clarification of the ITT population. The applicant's response (November 14, 2006) indicates that two of the 166 randomized subjects did not have a baseline value recorded in the DRC; an additional three do not have a value recorded during the first week. Since the protocol requires at least one recording during baseline and Week 1 for inclusion in the primary efficacy analysis, the ITT population should be 161, not 166. However, this discrepancy does not appear to influence the assessment of the primary efficacy endpoint (see below).

Protocol Deviations: The Investigator identifies major and minor protocol violations prior to unblinding the database. After randomization (i.e., during the four week treatment period) 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%). Six subjects, three from each arm, have compliance in excess of 120%, and six subjects in the placebo group (compared to none in the LCTZ group) have treatment periods too short [< 3 days] (p 47).

Treatment Compliance: (See "Protocol Deviations," above). The compliance (%) calculation is the ratio of the number of tablets taken by the subject (determined by the number of tablets in the returned bottles) over the number of tablets the subject was instructed to take and is assessed at the end of the first and last treatment weeks. The mean compliance for the total treatment period is 97.4%. Thirteen subjects in the ITT population (7.8%) have compliance rates less than 80%, of whom 11 were in the placebo arm, and two were in the LCTZ arm. None of the study subjects discontinue study medication due to an adverse event (p 83).

Demographics: Males and females distribute equally between the treatment groups, although the study includes more females than males, 59% to 41% respectively. Age range for the 166 ITT subjects is 18.3 – 79.5 years, with a mean of 42.0 years. Minority populations are under- or unrepresented.
On average, both treatment groups have a diagnosis of CIU for a median of 5.8 years (range 0.2 to 34 years). The most common medical condition (other than the study condition) is essential hypertension (15.3% in the placebo group and 16.0% in the LCTZ group). All habit parameters (caffeine, alcohol, tobacco, illicit drug use by history) distribute equally among the groups except for tobacco (47.1% in the placebo group and 25.9% in the LCTZ group). Table 2 summarizes demographic characteristics.

Table 2. Summary of demographic characteristics – ITT population

Demographic Characteristic	Placebo (N = 85)	LCTZ (N = 81)	Total (N = 166)
Age (years) Mean Range	 39.7 18.3 – 76.5	 44.3 18.6 – 79.5	 42.0 18.3 – 79.5
Gender, N (%) Female Male	 51 (60) 34 (40)	 47 (58) 34 (42%)	 98 (59) 68 (41)
Race, N (%) White. Asian Other Black	 83 (97.6) 1 (1.2) 1 (1.2) 0	 81 (100) 0 0 0	 164 (98.8) 1 (0.6) 1 (0.6) 0
Weight (kg) Mean Range	 74.0 46 - 105	 73.0 39 - 128	 73.5 39 - 128
Height (cm) Mean Range	 170.8 148- 197	 169.6 150 - 196	 170.2 148 - 197

(p 50)

Concomitant Medications: One hundred fourteen subjects in the ITT population (68.7%) take concomitant medications, 60 in the placebo group, and 54 in the LCTZ group. Table 3 summarizes concomitant drugs by therapeutic class and lists medications taken by at least 3% or

more of subjects in either study arm. Systemic corticosteroids, antihistamines, and nasal preparations are all used more in the placebo than LCTZ group.

Table 3. Concomitant drug use (therapeutic class) by more than 3% of either arm

Therapeutic Class	Placebo Arm (N = 85) %	LCTZ Arm (N = 81) %
Angiotensin inhibitors	5.9	8.6
Analgesics	9.4	19.8
Antacids	7.1	3.7
Anti-asthmatics	5.9	4.9
Antibacterials, systemic	1.2	6.2
Antihistamines, systemic	12.9	2.5
Anti-inflammatories	1.2	6.2
Anti-pruritics	3.5	0
Antithrombotics	3.5	8.6
Beta blockers	7.1	6.2
Calcium channel blockers	2.4	3.7
Corticosteroids, systemic	4.7	0
Corticosteroids, topical	4.7	1.2
Diuretics	1.2	4.9
Nasal preparations	7.1	1.2
Ophthalmologicals	8.2	6.2
Gynecologicals	18.8	6.2
Psycholeptics	5.9	3.7
Serum lipid reducers	0	3.7
Sex hormones	29.4	30.9
Stomatologic preparations	3.5	7.4
Thyroid medications	4.7	3.7
Vasoprotectives	3.5	2.5

(pp 121-125)

Primary Efficacy Results

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

Pruritus severity decreases more in the LCTZ 5 mg group, compared to the placebo group, during the first week of treatment. The adjusted mean (ITT population) 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 ($p < 0.001$). (See Table 4, below).

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

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

(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

Change from baseline in mean pruritus severity over the previous 24 hours during the total treatment period (per subject DRC):
Pruritus severity decreases more in the LCTZ group compared to the placebo group. The adjusted mean (ITT population) 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 between the two groups is statistically significant ($p < 0.001$). (See table 5, below). 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 (p 59; p 80).

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

	Treatment	N	Mean (SD)	Adjusted Mean[(a)]	Diff. vs Placebo[(b)] [95% CI]	p-value[(c)]
Baseline	Placebo LCTZ 5 mg	82 80	2.06 (0.57) 2.07 (0.61)			
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 59)

(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

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, the majority of subjects (26 of 30) dropping out for lack of efficacy are in the placebo 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 points relate to subjects in the placebo group dropping out for lack of efficacy (26 in the placebo group versus 4 in the LCTZ group).

Secondary Efficacy Results

Change from baseline in mean pruritus severity over the previous 24 hours during Weeks 2, 3, and 4:
Analysis of mean pruritus severity scores for Weeks 2, 3, and 4 show a difference favoring LCTZ over placebo for Weeks 2 and 4, but not 3. The number of drop-outs for lack of efficacy in the placebo group may underestimate treatment effect. Application of LOCF methodology to the dataset suggests statistical differences between the LCTZ 5 mg and placebo groups supporting efficacy for LCTZ for all three weeks (pp 60-61).

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

Comparisons of difference from baseline in mean number of wheals between the LCTZ 5 mg group and placebo group in the ITT population by treatment week, and for the total treatment period, show 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. Results are summarized in Table 6, below.

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

Week	Treatment	N	Baseline Mean (SD)	Mean (SD)	Adjusted Mean[a]	Diff. vs placebo[b] [95% CI]	p-value[c]
1	Placebo LCTZ 5 mg	82 79	1.92 (0.72) 1.95 (0.76)	1.67 (0.96) 1.11 (1.02)	1.72 1.16	0.57 [0.29; 0.84]	< 0.001
2	Placebo LCTZ 5 mg	65 76	1.95 (0.72) 1.95 (0.74)	1.20 (1.01) 1.01 (0.98)	1.29 1.07	0.22 [-0.09; 0.53]	0.170
3	Placebo LCTZ 5 mg	56 73	1.86 (0.70) 1.92 (0.74)	0.96 (0.88) 0.83 (0.91)	1.10 0.89	0.21 [-0.09; 0.51]	0.167
4	Placebo LCTZ 5 mg	52 73	1.86 (0.70) 1.92 (0.74)	0.79 (0.79) 0.76 (0.85)	0.89 0.80	0.09 [-0.19; 0.37]	0.526
Total Treatment Period	Placebo LCTZ 5 mg	82 80	1.94 (0.72) 1.95 (0.75)	1.44 (0.97) 0.99 (0.91)	1.51 1.04	0.46 [0.20; 0.73]	0.001

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

(p 63)

(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

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

Comparisons of difference from baseline in mean size of wheals between the LCTZ 5 mg group and placebo group in the ITT population by treatment week, and for the total treatment period, also favor LCTZ for the first week, and for the total treatment period. 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. Results are summarized in Table 7, below.

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

Week	Treatment	N	Baseline Mean (SD)	Mean (SD)	Adjusted Mean[a]	Diff. vs placebo[b] [95% CI]	p-value[c]
1	Placebo LCTZ 5 mg	82 77	1.87 (0.75) 1.74 (0.80)	1.53 (0.91) 1.03 (0.92)	1.53 1.08	0.45 [0.19; 0.71]	0.001
2	Placebo LCTZ 5 mg	65 73	1.88 (0.71) 1.75 (0.79)	1.12 (0.96) 0.92 (0.86)	1.14 0.98	0.16 [-0.12; 0.45]	0.259
3	Placebo LCTZ 5 mg	55 69	1.79 (0.69) 1.74 (0.80)	0.93 (0.86) 0.74 (0.80)	1.00 0.80	0.20 [-0.07; 0.47]	0.144
4	Placebo LCTZ 5 mg	51 69	1.79 (0.68) 1.74 (0.80)	0.80 (0.80) 0.68 (0.72)	0.86 0.72	0.13 [-0.13; 0.39]	0.311
Total	Placebo	82	1.87 (0.75)	1.33 (0.92)	1.35	0.38	0.001

Treatment Period	LCTZ 5 mg	78	1.74 (0.79)	0.89 (0.79)	0.96	[0.15; 0.62]	

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

(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

(p 64)

Change from baseline in mean pruritus duration by treatment week and during the total treatment period:
The difference in adjusted means for pruritus duration between groups (ITT population) by treatment week, and for the total treatment period, favors LCTZ for every week, and for the total treatment period. The mean differences are greater for Week 1 and for the total treatment period, than for Weeks 2, 3, and 4 (p 65).

Multi-center Analysis

Factors determining pooling of centers are country and location (university or general practice [GP]), resulting in three groups: German university and GP centers, and Swiss university centers. There is no evidence of a treatment by center interaction for the primary variables [p = 0.235 over the first treatment week and p = 0.190 over the total treatment period] (p 78).

Subgroup Analysis

The study performs no subgroup analyses.

Safety Assessments

No deaths occur during the study. None of the subjects discontinue study medication due to an adverse event. Approximately one-third of the ITT population experience at least one AE; headache and fatigue are the most commonly reported AEs (pp 82-87).
Two subjects in the LCTZ group have elevated liver transaminases at the end-of-treatment evaluation. The Investigator does not attribute the transaminase elevation to LCTZ in either case, and both subjects have complete resolution to normal values after study completion. The relative risk of a treatment-emergent adverse event in the LCTZ group - the placebo group is 2.62 (CI 0.86; 8.03). See summary for ITT population in Table 8, below.

Reviewer comment:
The product label for the racemate cetirizine (Zyrtec®) states that occasional instances of transient, reversible hepatic transaminase elevations have been reported during cetirizine therapy (see label dated 10/21/02).

Table 8. Summary of treatment-emergent adverse events with incidence ≥ 2%

Preferred term	Placebo (N = 85)	LCTZ (N = 81)
Headache	4 (4.7%)	10 (12.3%)
Fatigue	1 (1.2%)	10 (12.3%)
Peripheral Edema	0	2 (2.5%)

Dry Mouth	0	3 (3.7%)
SGOT/SGPT Elevation	0	2 (2.5%)
Pharyngitis	2 (2.4%)	2 (2.5%)
Rhinitis	1 (1.2%)	2 (2.5%)
Injury	2 (2.4%)	0

(p 82)

Study Conclusions

Efficacy:
Levocetirizine 5 mg tablets, 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 the LCTZ arm 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.

The results of this study 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.

Safety:
There are no unusual adverse events or safety signals in this study. Levocetrizine may, like cetirizine, be associated with occasional episodes of transient, reversible hepatic transaminase levels.

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 A00269 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. The study population does not represent racial minorities; extrapolation of these study results to non-caucasian populations should be done with caution.