CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

Statistical Review

NDA:	22,064
Drug Name :	Levocetirizine 5 mg tablets
Indications:	Seasonal Allergic Rhinitis, Perennial Allergic Rhinitis, and Chronic Idiopathic Urticaria in Adults and children 6 years of age and older
Applicant:	UCB, Inc.
Dates:	Electronic submission dated 07/24/2006, 8/29/2006, 8/31/2006, 9/19/2006, 10/24/2006, and 10/31/2006. Paper volume dated 12/05/2006.
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Keywords:	Analysis of Covariance, Clinical Studies, NDA Review

Table of Contents

1. Executive Summary

1.1 Conclusions and Recommendations

A dose-ranging study a217 showed 2.5 mg levocetirizine, 5 mg levocetirizine, and 10 mg levocetirizine to be more effective than placebo in patient assessed T4SS/24 (total of sneezing, runny nose, nasal pruritus, and ocular pruritus assessed over the last 24 hours) averaged over the two-week treatment period in adults and adolescents with seasonal allergic rhinitis. Study a00268 demonstrated efficacy of 5 mg levocetirizine over placebo in patient assessed T3SS/24 (total of sneezing, runny nose and nasal pruritus severity assessments) averaged over the first week and over the total six week treatment period in adults and adolescents with seasonal allergic rhinitis.

Study a222 demonstrated efficacy of both levocetirizine 5mg and cetirizine 10 mg over placebo in patient assessed T4SS/24 averaged over the total one week treatment period. levocetirizine 5 mg was numerically equivalent to cetirizine 10mg in patient assessed T4SS/24 but investigator assessed T4SS/24 numerically favored cetirizine. The patient assessed measure is considered more relevant.

Study a00266 demonstrated efficacy of 5 mg levocetirizine over placebo in patient assessed T3SS/24 averaged over the first week and over the first four weeks of the treatment period in adults and adolescents with perennial allergic rhinitis due to dust mites. Study a00304 demonstrated efficacy of 5 mg levocetirizine over placebo in patient assessed T3SS/24 averaged over the first week and over the first two weeks of the treatment period in children with perennial allergic rhinitis due to dust mites.

Study a00269 demonstrated efficacy of 5 mg levocetirizine over placebo in patient assessed pruritus, and number and size of wheals averaged over the first week and averaged over the whole treatment period in adults with Chronic Idiopathic Urticaria (CIU). Study a00270 demonstrated efficacy of 2.5 mg levocetirizine, 5 mg levocetirizine, and 10 mg levocetirizine over placebo in patient assessed pruritus, and number and size of wheals averaged over the first week and averaged over the whole treatment period in adults with CIU.

That levocetirizine 5mg, similarly to cetirizine 10mg, can be dosed once a day is supported by pruritus, size and number of wheals, evaluated at the moment in CIU Study a00270, mean size and number of wheals evaluated at the moment in CIU Study 00269, and T3SS/1 (evaluated over the last hour) in SAR Study a00268

The doses of levocetirizine (2.5 mg, 5 mg, and 10 mg) all showed efficacy and usually with dose response ordering. The appropriate dose is not obvious from efficacy considerations only. The 10 mg dose causes more somulance than the other two doses. If a subject cuts the scored 5 mg tablet in half, they should have an effective dose at 2.5 mg q.d.

1.2 Brief Overview of Clinical Studies

This review will mainly discuss Studies a00270 and a00269 for Chronic Idiopathic Urticaria, Study a00268 for Seasonal Allergic Rhinitis, and Studies a00266 and a00304 for Perennial Allergic Rhinitis. These were the studies the medical division considered pivotal for this submission. The medical division also requested a review of supportive Study a217. This reviewer chose also to review Study a222 because it was the only clinical study comparing levocetirizine 5mg and cetirizine 10mg.

1.3 Statistical Issues and Findings

There were no statistical issues with this submission. The reviewer was able to duplicate the sponsor's results from derived data files provided by the sponsor.

2. Introduction

Levocetirizine is the R-enantiomer of the racemate cetirizine and has been found to be, according to the sponsor, solely responsible for the therapeutic antihistaminic activity of cetirizine. Cetirizine under the trade name Zyrtec tablets was approved in 1995. Zyrtec tablets are approved in 5 mg and 10 mg strengths which contain 2.5 mg and 5 mg of levocetirizine, respectively. The recommended initial dose of Zyrtec is 5 mg or 10 mg per day in adults and children 12 years and older, depending upon symptom severity. The recommended initial dose of Zyrtec in children 6 to 11 years is identically 5 mg or 10 mg once daily depending upon symptom severity. The time of administration of Zyrtec may be varied to suit individual patient needs. In patients 12 years of age and older with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a Zyrtec dose of 5 mg once daily is recommended. Similarly, pediatric patients aged 6 to 11 years with impaired renal or hepatic function should use the lower recommended dose. Zyrtec syrup is also approved for these indications.

The Zyrtec label contains the following information in the Indication and Usage section.
Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens in adults and children 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing, and redness of the eyes.

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds in adults and children 6 months of age and older. Symptoms treated effectively include sneezing, rhinorrhea, postnasal discharge, nasal pruritus, ocular pruritus, and tearing.

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus.

This NDA for levocetirizine is being submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act. The current submission is only for the 5 mg tablet. The tablet is scored so that it can be cut in half.

The sponsor has submitted studies of levocetirizine for the Seasonal Allergic Rhinitis indication, the Perennial Allergic Rhinitis indication, and the Chronic Idiopathic Urticaria indication. All the studies of levocetirizine discussed in this review dosed once a day in the evening although the label of Zyrtec allows for both morning and evening dosing.

In reviewing the submission, this reviewer noticed that the sponsor had not supplied derived (analysis) data sets for the studies. Derived data sets were requested and supplied in the sponsor's 2006-10-24 submission. Subsequent to the request for derived data sets, the medical division found that the sponsor's total symptom score contained sneezing, nasal pruritus, runny nose and ocular pruritus. The medical division requested that ocular pruritus be excluded and the analysis results of the T3SS be provided. This reviewer then requested that the sponsor provide derived data sets containing the T3SS. These new derived data sets came in the sponsor's 2006-10-31 submission.

Levocetirizine will be denoted as Lctz in some of the tables in this review. T3SS/1 is total nasal symptom score assessed over the last hour (a more instantaneous assessment). T3SS/24 is total nasal symptom score assessed over the last 24 hours (a reflective assessment). In studies a00266 and a00304, the sponsor denoted the reflective assessment of the total of the four symptoms and total nasal symptom score by T4SS and T3SS, respectively. In this review for those studies this reviewer will denote them as T4SS/24 and T3SS/24 for consistency and emphasizing the assessment was over 24 hours.

This review will only discuss Studies a00270 and a00269 for Chronic Idiopathic Urticaria; Studies a217, a222, and a00268 for Seasonal Allergic Rhinitis; and Studies a00266 and a00304 for Perennial Allergic Rhinitis. Study a222, which is only one week, will be discussed because it is the only clinical study in

Allergic Rhinitis patients which compared 5 mg levocetirizine and 10 mg. cetirizine. This study was only considered supportive by the medical division.

This review will not discuss Biopharm and PK studies supplied in the submission. It will also not discuss environmental chamber studies (a00412, a00414, a004415), clinical studies against loratadine or desloratadine (a00299, a00334, a00348, a00349, a00391, a00394, and a00401), clinical studies for other indications (a00264, a00306, a00315,a00333, a00384, a00392, a00410, and a00419), clinical studies of oral solution (a00309 and a00385), and a few studies for the SAR and PAR indication that the medical division thought were only supportive (a219, a00265 and a00303). The latter three studies, taking the study summaries on face value, demonstrated efficacy for the 5 mg dose of levocetirizine for T4SS/24 that was seen in the other studies discussed in this review.

This reviewer found that the sponsor in their 2006-10-31 submission gave the T3SS/1 analyses results rather than the T3SS/24 analysis results for Study a00268. This reviewer requested the T3SS/24 analysis results and these were provided in the sponsor's 2006-12-05 submission.

2.1 Study Descriptions

2.1.1 CIU Studies

2.1.1.1 Study a00270

This was a randomized, double blind, placebo-controlled, multi-center, parallel group study, comparing levocetirizine 2.5 mg, levocetirizine 5 mg, levocetirizine 10 mg and placebo, administered once daily in the evening for four weeks, in adult subjects suffering from chronic idiopathic urticaria.

Clinic Visits were:
Visit 1: initial visit
Visit 2: randomization visit, one week after visit 1
Visit 3: control visit [sponsor's terminology], one week after visit 2
Visit 4: end of treatment visit, three weeks after visit 3
Visit 5: final visit, one week after visit 4

On a daily record card (DRC) the patients evaluated the following items once a day in the evening using a 4-point scale:

Severity of pruritus at the moment of evaluation:
0 = absent
1 = mild (present but not disturbing)
2 = moderate (disturbing but not hampering daytime activities and/or sleep)
3 = severe (hampering daytime activities and/or sleep).

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

Size of wheals (diameter of the greatest wheal)
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.

Severity of pruritus over the last 24 hours:
0 = absent
1 = mild (present but not disturbing)
2 = moderate (disturbing but not hampering daytime activities and/or sleep)
3 = severe (hampering daytime activities and/or sleep).

Duration of pruritus over the last 24 hours:
0 = no pruritus
1 = less than 1 hour
2 = 1 to 6 hours
3 = more than 6 hours.

The duration of the selection period (initial visit to date of randomization) could be reduced to up to three days or increased up to nine days.

The Investigator was to collect the DRC at the randomization visit and verify that the severity of pruritus score for the last 24 hours was ≥ 2 and the number of wheals score was ≥ 1 for at least 3 distinct days. Eligible subjects were randomized into the study.

Baseline period was from the day of the Initial Visit until Day 0 inclusive.

Of note: Efficacy evaluation at Day 1 was not used for the analysis (either in baseline or in on-treatment averages). According to the protocol, subjects were allowed to take one tablet in the evening of the randomization day (Day 1) after having filled in their daily record cards. This evaluation at Day 1 was intended to be a baseline evaluation. However, previous experience indicated that some subjects took their Day 1 treatment before having completed the daily record card. As a result, and to be consistent with previous similar studies, it was decided to exclude Day 1 from the baseline and from the total treatment period. This non-inclusion of Day 1 was given in the Statistical Analysis Plan (SAP) (Section 4.4.1).

The first treatment week was therefore Days 2 to 8 inclusive. The total treatment period was Day 2 to the last evaluable day inclusive.

The sponsor stated that the primary efficacy variables were:
1. The mean DRC (Daily Record Card) pruritus severity score (over the last 24 hours evaluation) over the first treatment week.
2. The mean DRC pruritus severity score (over the last 24 hours evaluation) over the total 4-week treatment period.

Important secondary variables were the number of wheals and size of wheals. [Although the sponsor considered these as secondary efficacy variables, these variables would have to demonstrate efficacy to get a CIU indication.]

Each of the primary efficacy variables was analyzed using an analysis of covariance model (ANCOVA) including the mean DRC baseline pruritus severity score (over the last 24 hours evaluation) as covariate and treatment as a factor. [As stated in the protocol, centers was also to be included as a factor but was dropped as discussed later.] Each dose of levocetirizine was compared to placebo using a t-test at an alpha error of 2 % (Dunnett adjustment for multiple comparisons). A 98 % confidence interval of the difference in the adjusted means between placebo and each dose of levocetirizine was presented.

Due to the large number of small centers and due to the absence of a relevant way to pool them, the sponsor decided not to include the factor "center" in the analyses of covariance for this study. However, the consistency of treatment effect across centers was to be investigated by a sensitivity analysis of covariance including center and the interaction of center by treatment in the model where the centers with less than 8 subjects were to be grouped. This change to the protocol was detailed in an amendment to the SAP.

A sample size of 64 patients by group will have a power of 90% to detect a difference between placebo and one of the doses of levocetirizine of 0.5 in the mean DRC pruritus severity score (over the last 24 hours evaluation), assuming that each dose of levocetirizine will be compared to placebo at an alpha level of 2% to have an overall alpha error of 5% (Dunnett adjustment for multiple comparisons) and a common standard deviation of 0.77. The overall power to detect this difference for the first treatment week and for the 4 week treatment period will be at least 80%.

For the week 1 and total treatment period analyses all available data was used to calculate averages.

2.1.1.2 Study a00269

Study a00269 was similar to Study a00270 with the following exceptions:

- It compared only levocetirizine 5 mg to placebo.
- Pooled centers was included as a factor in the ANCOVA analyses of symptom scores.
- 95% confidence limits were used rather than 98% confidence limits.
- The targeted sample size was 77 patients per treatment group. This was chosen to have 95% power for a 0.5 difference in pruritus severity score (over the last 24 hours) at the 0.05 alpha level for an assumed standard deviation of 0.85. The overall power to detect this difference for the first week and for the 4 week treatment period will be at least 90%.

2.1.2 Seasonal Allergic Rhinitis Studies

2.1.2.1 Study a00268

This was a randomized, double blind, placebo controlled, multicenter, phase III study of the efficacy and safety of 5 mg levocetirizine tablets, administered once daily in the evening for two weeks, to adult and adolescent subjects suffering from grass pollen allergic rhinitis.

The total score of the four rhinitis symptoms (sneezing, rhinorrhea, nasal pruritus and ocular pruritus) was evaluated by the subject in the evening, before their next intake of study treatment, using the following 4-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).

T4SS/24 = T4SS evaluated **over the last 24 hours**
T4SS/1 = T4SS evaluated **over the hour preceding evaluation**

To be enrolled, the subject had to have sufficient histamine dependent rhinitis symptoms during the selection week. This meant that, over this period, the mean of T4SS/24 had to be ≥ 6 (this mean was calculated taking into account only the days on which the scores of the four symptoms were available) and the T4SS/24 had to be ≥ 6 on the day before the randomization visit. The selection (screening) week could be reduced to three days or increased up to nine days, if necessary.

The sponsor stated that the primary objectives were to confirm that 5 mg levocetirizine was superior to placebo in reducing rhinitis symptoms as measured by the Total 4 Symptoms Score (sneezing, rhinorrhea, nasal pruritus, ocular pruritus) evaluated in the evening over the last 24 hours (T4SS/24) when administered to subjects with grass pollen allergic rhinitis: (i) during the first treatment week; (ii) when administered over two weeks.

The medical division is of the opinion that T3SS/24, removing ocular pruritus, should be the primary efficacy assessment. The sponsor was asked to reanalyze the study using T3SS/24. They supplied the results of the analysis of T3SS/24 in their 2006-10-31 submission.

If an individual symptom in the T4SS/24 or T3SS/24 symptom complex was missing on a day, the T4SS/24 or T3SS/24 was missing on that day and hence not included in weekly averages or total treatment average.

As in the CIU trials the Day 1 assessment (day of randomization visit) was not included in the baseline or on-treatment averages.

The primary efficacy variables, the mean T4SS/24 over the first treatment week and the mean T4SS/24 over the total treatment period, were analyzed using an analysis of covariance (ANCOVA), including the mean baseline T4SS/24 score as covariate and treatment and pooled center as factors. A 95% confidence interval (CI) of the difference in the adjusted means between placebo and levocetirizine 5 mg was presented.

A sample size of 116 subjects per group has a power of 95% to detect a difference between placebo and levocetirizine 5 mg of 1.0 in the mean T4SS/24, assuming an overall alpha error of 5% and a common standard deviation of 2.1. The overall power to detect this difference for the first treatment week and for the two-week treatment period was at least 90%. A difference of 1 for the mean T4SS/24 corresponded to a 50% relative improvement from baseline over placebo, assuming a baseline score of 7.8 and an improvement from baseline for placebo of 25%. This was considered by the sponsor to be clinically relevant after one week of treatment.

This review will present the results of the analysis of T4SS/24 and T3SS/24 averaged over the first treatment week and T4SS/24 and T3SS/24 averaged over the whole treatment period.

2.1.2.2 Study a217

Study a217 was similar to Study a00268 with the following exceptions:

- This study did not have assessments over the last hour. It had only assessments over the last 24 hours.
- It was a phase 2 dose ranging study comparing levocetirizine 2.5 mg, levocetirizine 5 mg, levocetirizine 10 mg and placebo.
- The primary efficacy variable was T4SS/24 hours over the whole two week treatment period,
- Confidence limits were 98% reflecting the use of Dunnett's procedure.
- The target sample size was 130 per group. A sample size of 115 subjects per group has a power of 80% to detect a difference between placebo and any levocetirizine dose of 1.0 in the mean T4SS/24, assuming an overall alpha error of 5% (0.02 Dunnett's for individual comparison) and a common standard deviation of 2.4.

2.1.2.3 Study a222

This was a randomized, double blind, placebo controlled, multicenter, phase III study of the efficacy and safety of 5 mg levocetirizine tablets and 10 mg cetirizine administered once daily in the evening for one week, to adult and adolescent subjects suffering from grass pollen allergic rhinitis.

Randomization was 2:2:1 for levocetirizine, cetirizine and placebo, respectively. The targeted sample size was 274 for cetirizine and levoceterizine and 137 for placebo. The per-protocol population was to be used in the comparison of active treatments and the intent-to-treat population was to be used in the comparisons of active versus placebo.

In accordance to section 10.5 .A. 1 of the protocol, it was clarified that equivalence would be accepted if the 90% CI of the difference between the adjusted means of cetirizine and levocetirizine was fully contained within the following interval :[$-0.2(Cetiirizine_{mean}), 0.2(Cetirizine_{Mean})$]

2.1.3 Perennial Allergic Rhinitis Studies

2.1.3.1 Study a00266

Study a0266 was similar to Study a00268 with the following exceptions:

- It was in perennial allergic rhinitis, due to dust mites, adult and adolescent subjects rather than seasonal allergic rhinitis subjects.
- The score of T4SS/24 for inclusion was an average of ≥ 5 during baseline and a value ≥ 5 on the day before the randomization visit rather than ≥ 6 used for Study a00268.
- The treatment period was 6 weeks.
- This study did not have assessments over the last hour. It had only assessments over the last 24 hours.
- The co-primary assessment time for T4SS/24 was over the first 4 weeks rather than the whole 6 week treatment period.

With 125 subjects per group, the two-sided test was to have a power of about 95% to detect a difference between placebo and levocetirizine 5 mg of 1.0 for the first treatment week and a power of 85% to detect a difference of 0.8 between placebo and levocetirizine 5 mg over the first 4 weeks of treatment, assuming an overall alpha error of 5% and a common standard deviation of 2.1. A difference of 1 for the total four symptom score corresponds to a 50% relative improvement from baseline over placebo, assuming a baseline score of 6.8 and an improvement from baseline for placebo of 28%.

This review will present the results of the analysis of T4SS/24 and T3SS/24 averaged over the first treatment week and T4SS/24 and T3SS/24 averaged over the first 4 weeks.

2.1.3.2 Study a00304

Study a00304 was similar to Study a00268 with the following exceptions:

- It was in perennial allergic rhinitis, due to dust mites, children rather than seasonal allergic rhinitis subjects.
- The score of T4SS/24 for inclusion was an average of ≥ 5 during baseline and a value ≥ 5 on the day before the randomization visit rather than ≥ 6 used for Study a00268.
- The treatment period was 4 weeks.
- This study did not have assessments over the last hour. It had only assessments over the last 24 hours.
- The co-primary assessment time for T4SS/24 was over the first 2 weeks rather than the whole 4 week treatment period.

A sample size of 146 children per treatment group will have a power of 90% to detect a difference of 0.8 between placebo and levocetirizine 5 mg in the mean T4SS/24 over the first two weeks of treatment, assuming an overall alpha error of 5% and a common standard deviation of 2.1. A difference of 0.8 is deemed clinically relevant by the sponsor for studies in adults.

This review will present the results of the analysis of T4SS/24 and T3SS/24 averaged over the first treatment week and the T4SS/24 and T3SS/24 averaged over the first 2 weeks.

2.2 Data Sources

The study reports and data are contained in \\Cdsesub1\n22064\N_000\2006-07-24, \\Cdsesub1\n22052\N_000\2006-08-29, \\Cdsesub1\n22052\N_000\2006-10-24, and \\Cdsesub1\n22052\N_000\2006-10-31.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 CIU Studies

3.1.1.1 Study a00270

A total of 303 adult subjects were screened, of whom 258 subjects were randomized in the study, of which 1 subject did not take any study medication. The remaining 257 subjects were randomized as follows: 63 subjects in the placebo group, 70 subjects in the levocetirizine 2.5 mg group, 65 subjects in the levocetirizine 5 mg group and 59 subjects in the levocetirizine 10 mg group. It was conducted at 35 centers in France.

A total of 202 subjects (78.6%) completed the study. Fifty-five subjects stopped the trial prematurely, 26 (41.3%) in the placebo group, 12 (17.1%) in the levocetirizine 2.5 mg group, 7 (10.8%) in the levocetirizine 5 mg group and 10 (16.9%) in the levocetirizine 10 mg group. The reasons of discontinuation are presented in Table 1. The most common reason for early termination was lack of efficacy (14.4% of the ITT subjects). More subjects terminated the study due to lack of efficacy in the placebo group (31.7%) than in the levocetirizine 2.5 mg group (14.3%), the levocetirizine 5 mg group (6.2%) and the levocetirizine 10 mg group (5.1%). Eighteen placebo and 8 levocetirizine 2.5 mg subjects dropped out during the first week.

Table 1 Number (%) of subjects who discontinued the treatment, by reason and Treatment (ITT Population)

Reasons of study discontinuation	**Placebo (N = 63)**	**Lctz 2.5 mg (N = 70)**	**Lctz 5 mg (N = 65)**	**Lctz 10 mg (N = 59)**	**Total (N = 257)**
Lack of efficacy	20 (31.7%)	10 (14.3%)	4 (6.2%)	3 (5.1%)	37 (14.4%)
Adverse event	2 (3.2%)	2 (2.9%)	1 (1.5%)	5 (8.5%)	10 (3.9%)
Other	2 (3.2%)	0	2 (3.1%)	1 (1.7%)	5 (1.9%)
Withdrawal of consent	1 (1.6%)	0	0	1 (1.7%)	2 (0.8%)
Lost to follow-up	1 (1.6%)	0	0	0	1 (0.4%)

The treatment groups were similar in demographic and baseline mean symptom assessments. Seventy-two percent of the subjects were female and 88% were Caucasian, 4% were Black, 5% were Asian/ Pacific Islander and 3% were other. Mean age was 41.4 years. (Age Range was 18-85 years.)

This review will mainly focus on the results over the whole treatment period. The results for pruritus severity over the previous 24 hours averaged over the first week of treatment will be presented as the sponsor stated it was a co-primary efficacy variable. For the other analyses the results at week 1 will be mentioned because the label discusses significance at week 1 also.

Table 2 below presents the results of the analysis of pruritus severity evaluated over the previous 24 hours averaged over the first week of treatment. All levocetirizine doses were significantly different from placebo.

Table 2 Mean pruritus severity evaluated over the previous 24 hours over the first week of treatment ITT population

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

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 2.5 mg/ Placebo minus levocetirizine 5 mg/ Placebo minus levocetirizine 10 mg
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment as factor.

Table 3 below presents the results of the analysis of pruritus severity evaluated over the previous 24 hours averaged over the total treatment period. All levocetirizine doses were significantly different from placebo.

Table 3 Mean pruritus severity evaluated over the previous 24 hours over the total treatment period -- ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [98% CI]	P-value [c]
Placebo	60	2.25	(0.50)	1.89	(0.74)	1.84	(0.09)		
Lctz 2.5 mg	69	2.08	(0.53)	1.00	(0.78)	1.02	(0.08)	0.82 [0.53, 1.11]	<0.001
Lctz 5 mg	62	2.07	(0.50)	0.91	(0.71)	0.92	(0.09)	0.91 [0.62, 1.21]	<0.001
Lctz 10 mg	55	2.04	(0.57)	0.70	(0.57)	0.73	(0.09)	1.11 [0.81, 1.41]	<0.001

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 2.5 mg/ Placebo minus levocetirizine 5 mg/ Placebo minus levocetirizine 10 mg
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment as factor.

Table 4 below presents the results of the analysis of assessment of pruritus severity at the moment averaged over the whole treatment period. All levocetirizine doses were significantly different from placebo. The results at Week 1 similarly showed efficacy for all levocetirizine doses. The significance of the pruritus severity at the moment of all doses provides evidence of the adequacy of once a day dosing.

Table 4 Mean pruritus severity evaluated at the moment (instantaneous) averaged over the total treatment period - ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [98% CI]	P-value [c]
Placebo	61	2.18	(0.62)	1.85	(0.73)	1.79	(0.09)		
Lctz 2.5 mg	69	2.01	(0.62)	0.98	(0.80)	0.99	(0.08)	0.80 [0.52, 1.09]	<0.001
Lctz 5 mg	64	1.97	(0.51)	0.88	(0.69)	0.91	(0.09)	0.88 [0.59, 1.17]	<0.001
Lctz 10 mg	57	1.99	(0.58)	0.72	(0.67)	0.75	(0.09)	1.05 [0.75, 1.35]	<0.001

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 2.5 mg/ Placebo minus levocetirizine 5 mg/ Placebo minus levocetirizine 10 mg
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment as factor.

Table 5 below presents the results of the analysis of duration of pruritus severity averaged over the whole treatment period. All levocetirizine doses were significantly different from placebo. The results at Week 1 similarly showed efficacy for all levocetirizine doses.

Table 5 Mean pruritus duration (24-hour evaluation) over the total treatment period- ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [98% CI]	P-value [c]
Placebo	61	2.17	(0.66)	1.82	(0.75)	1.73	(0.10)		
Lctz 2.5 mg	69	1.86	(0.66)	1.05	(0.87)	1.13	(0.09)	0.60 [0.29, 0.91]	<0.001
Lctz 5 mg	61	2.00	(0.62)	1.01	(0.88)	1.02	(0.10)	0.71 [0.39, 1.03]	<0.001
Lctz 10 mg	54	2.02	(0.62)	0.80	(0.77)	0.80	(0.10)	0.93 [0.60, 1.26]	<0.001

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 2.5 mg/ Placebo minus levocetirizine 5 mg/ Placebo minus levocetirizine 10 mg
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment as factor.

Table 6 below presents the results of the analysis of number of wheals assessment averaged over the whole treatment period. All levocetirizine doses were significantly different from placebo. The results at Week 1 similarly showed efficacy for all levocetirizine doses.

Table 6 Mean number of wheals evaluated at the moment averaged over the total treatment period - ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [98% CI]	P-value [c]
Placebo	61	1.97	(0.78)	1.68	(0.89)	1.68	(0.10)		
Lctz 2.5 mg	69	1.98	(0.72)	1.08	(0.91)	1.07	(0.09)	0.61 [0.30, 0.93]	<0.001
Lctz 5 mg	64	1.91	(0.61)	0.96	(0.79)	0.99	(0.10)	0.69 [0.37, 1.01]	<0.001
Lctz 10 mg	56	1.98	(0.75)	0.81	(0.82)	0.80	(0.10)	0.88 [0.55, 1.21]	<0.001

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 2.5 mg/ Placebo minus levocetirizine 5 mg/ Placebo minus levocetirizine 10 mg.
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment as factor.

Table 7 below presents the results of the analysis of size of wheals assessment averaged over the whole treatment period. All levocetirizine doses were significantly different from placebo. The results at Week 1 similarly showed efficacy for all levocetirizine doses.

Table 7 Mean size of wheals evaluated at the moment averaged over the total treatment period - ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [98% CI]	P-value [c]
Placebo	60	2.10	(0.65)	1.69	(0.81)	1.61	(0.10)		
Lctz 2.5 mg	69	1.90	(0.70)	1.05	(0.94)	1.06	(0.09)	0.55 [0.23, 0.87]	<0.001
Lctz 5 mg	61	1.83	(0.71)	0.69	(0.83)	1.00	(0.10)	0.66 [0.28, 0.95]	<0.001
Lctz 10 mg	57	1.83	(0.75)	0.72	(0.70)	0.76	(0.10)	0.85 [0.51, 1.19]	<0.001

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 2.5 mg/ Placebo minus levocetirizine 5 mg/ Placebo minus levocetirizine 10 mg
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment as factor.

All of the above analyses show significance of all doses and dose response ordering. The judgment of the appropriate dose is not obvious from efficacy considerations only.

3.1.1.2 Study a00269

A total of 186 adult subjects were screened, of whom 166 subjects were randomized in the study. There were 85 subjects in the placebo group and 81 subjects in the levocetirizine 5 mg group. There were 16 university centers in Germany, 3 university centers in Switzerland, and 8 private clinics in Germany.

One hundred and twenty four (124) subjects completed the study (74.7 %). Forty-two (42) subjects discontinued the study prematurely, 33 in the placebo group (38.8 %) and 9 in the levocetirizine 5 mg group (11.1 %). The reasons of discontinuation are presented by category in Table 8 below. The most common reason for early termination was lack of efficacy (30.6 % in the placebo group and 4.9 % in the levocetirizine group). Seventeen placebo subjects dropped out in the first week.

Table 8 Number (%) of subjects who discontinued the treatment, by reason and treatment . ITT population

Reasons of study discontinuation	**Placebo (N = 85)**	**Lctz 5 mg (N = 81)**	**Total (N = 166)**
Lack of efficacy	26 (30.6%)	4 (4.9%)	30 (18.1%)
Other	6 (7.1%)	4 (4.9%)	10 (6.0%)
Lost to follow-up	1 (1.2%)	1 (1.2%)	2 (1.2%)

Centers of the same type (university or GP) were pooled within country. This resulted in three groups of centers: German university centers, German GPs, and Swiss university centers (No Swiss GPs were included in the study). This pooling was given in the sponsor's statistical analysis plan (section 5.4.2.4)

The treatment groups were similar in demographic and baseline mean symptom assessments. Fifty-nine percent of the subjects were female and 99 % were Caucasian. Mean age was 42 years. (Age Range was 18-79 years.)

Table 9 below presents the results of the analysis of pruritus severity evaluated over the previous 24 hours averaged over the first week and over the whole treatment period. The levocetirizine 5 mg dose was significantly different from placebo.

Table 9 Mean pruritus severity over the previous 24 hours during Week 1 and during the total treatment period- ITT Population

Period	Treatment	N	Mean	(SD)	Adjusted mean [(a)]	(SE)	Diff. vs. placebo [95 % CI]
Baseline	Placebo	82	2.06	(0.57)			
	Lctz 5 mg	79	2.07	(0.61)			
Week 1	Placebo	82	1.80	(0.84)	1.80	(0.09)	
	Lctz 5 mg	79	1.02	(0.85)	1.02	(0.09)	0.78[(b)] [0.53, 1.04]
Total treatment period	Placebo	82	1.54	(0.87)	1.56	(0.09)	
	Lctz 5 mg	80	0.93	(0.75)	0.94	(0.09)	0.62[(b)] [0.38, 0.86]

[(a)] From an ANCOVA model with baseline score as covariate and pooled center and treatments as factors.
[(b)] $p<0.001$

Table 10 below presents the results of the analysis of pruritus severity evaluated at the moment (instantaneous) averaged over the whole treatment period. The levocetirizine 5 mg dose was significantly different from placebo. Similar significant differences were seen at Week 1.

Table 10 Mean pruritus severity evaluated at the moment averaged over the total treatment period - ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [95% CI]	P-value [c]
Placebo	82	2.00	(0.59)	1.52	(0.87)	1.55	(0.09)		
Lctz 5 mg	80	2.01	(0.61)	0.90	(0.75)	0.91	(0.09)	0.63 [0.39, 0.88]	<0.001

[a] Mean adjusted for baseline score.
[b] Placebo minus levocetirizine 5 mg.
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment and pooled centers as factors.

The consistency of the treatment effect across pooled centers was investigated for the primary efficacy variables including a term for center by treatment interaction in the model. No evidence of a treatment by center interaction was found ($p = 0.235$ over the first treatment week and $p = 0.190$ over the total treatment period).

Table 11 below presents the results of the analysis of pruritus duration (24-hour evaluation) averaged over the whole treatment period. The levocetirizine 5 mg dose was significantly different from placebo. Similar significant differences were seen at Week 1.

Table 11 Mean pruritus duration (24-hour evaluation) averaged over the total treatment period - ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [95% CI]	P-value [c]
Placebo	82	2.02	(0.66)	1.55	(0.88)	1.57	(0.09)		
Lctz 5 mg	79	2.03	(0.69)	0.96	(0.73)	0.98	(0.09)	0.60 [0.36, 0.84]	<0.001

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 5 mg
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment and pooled centers as factors.

Table 12 below presents the results of the analysis of mean size of wheals averaged over the whole treatment period. The levocetirizine 5 mg dose was significantly different from placebo. Similar significant differences were seen at Week 1.

Table 12 Mean size of wheals evaluated at the moment averaged over the total treatment period - ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [95% CI]	P-value [c]
Placebo	82	1.87	(0.75)	1.33	(0.92)	1.35	(0.09)		
Lctz 5 mg	78	1.74	(0.79)	0.89	(0.79)	0.96	(0.09)	0.38 [0.15, 0.62]	<0.001

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 5 mg
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment and pooled centers as factors.

Table 13 below presents the results of the analysis of mean number of wheals averaged over the whole treatment period. The levocetirizine 5 mg dose was significantly different from placebo. Similar significant differences were seen at Week 1.

Table 13 Mean number of wheals evaluated at the moment averaged over the total treatment period - ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [95% CI]	P-value [c]
Placebo	82	1.94	(0.72)	1.44	(0.97)	1.51	(0.10)		
Lctz 5 mg	80	1.95	(0.75)	0.99	(0.91)	1.04	(0.10)	0.46 [0.20, 0.73]	0.001

[a] Mean adjusted for baseline score
[b] Placebo minus levocetirizine 5 mg
[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment and pooled centers as factors.

3.1.2 Seasonal Allergic Rhinitis Studies

3.1.2.1 Study a00268

A total number of 344 adult and adolescent subjects were screened for the study, of which 107 subjects were screening failures. Consequently, 237 subjects at 20 centers in South Africa were randomized to treatment: 118 subjects in the placebo group and 119 subjects in the levocetirizine 5 mg group. There was evidence that one of the 237 randomized subjects (randomized to placebo) had not taken any study medication. As a result, 236 randomized subjects were included in the ITT population.

Two hundred and thirty-two (232) subjects completed the study (93.9%). Two subjects discontinued from the study due to an AE (one in the placebo group and one in the levocetirizine group). One placebo patient withdrew for personal reasons and one levocetirizine subject withdrew for other reasons.

Treatment groups were comparable in demographic and baseline symptom assessments. Sixty-two percent of the subjects were female and 71% were Caucasian, 14% were Asian/Pacific Islander, 4% were Black, and 11% were Other. Mean age was 30.3 years. (Age Range was 12-71 years.)

Centers 5 and 12 were pooled into pooled center 98. Center 9 and 11 were pooled into pooled center 99.

Tables 14 and 15 present the mean T4SS/24 and T3SS/24, respectively, evaluated in the evening during week 1 and during the total two week treatment period-ITT population. Both T4SS/24 and T3SS/24 showed significance at Week 1 and over the total 2 week treatment period.

Table 14 Mean T4SS/24 evaluated in the evening during Week 1 and during the total two week treatment period- ITT Population

Period	Treatment	N	Mean	(SD)	Adjusted mean [a]	(SE)	Diff. vs. placebo [95 % CI]	P-value
Baseline	Placebo	117	8.50	(1.68)				
	Lctz 5 mg	118	8.40	(1.66)				
Week 1	Placebo	117	6.59	(2.42)	6.45	(0.216)		
	Lctz 5 mg	118	5.56	(2.54)	5.49	(0.216)	0.96 [0.39, 1.53]	0.001
Total treatment period	Placebo	117	6.22	(2.43)	6.09	(0.221)		
	Lctz 5 mg	118	5.28	(2.53)	5.20	(0.222)	0.89 [0.30, 1.47]	0.003

[a] From an ANCOVA model with baseline score as covariate and pooled center and treatments as factors.

Table 15 Mean T3SS/24 evaluated in the evening during Week 1 and during the total two week treatment period- ITT Population

Period	Treatment	N	Mean	(SD)	Adjusted mean [(a)]	(SE)	Diff. vs. placebo [95 % CI]	P-value
Baseline	Placebo	117	6.47	(1.29)				
	Lctz 5 mg	118	6.53	(1.37)				
Week 1	Placebo	117	5.12	(1.92)	5.04	0.168		
	Lctz 5 mg	118	4.38	(1.97)	4.27	0.168	0.77[0.32, 1.21]	<0.001
Total treatment period	Placebo	117	4.86	(1.94)	4.79	0.174		
	Lctz 5 mg	118	4.19	(1.98)	4.09	0.173	0.69[0.23, 1.15]	0.003

[(a)] From an ANCOVA model with baseline score as covariate and pooled center and treatments as factors.

Table 16 presents the results of the analysis of Total Nasal Symptom Score evaluated over the last hour (T3SS/1) averaged over the first week and averaged over the total treatment period. These results are supportive of once a day dosing.

Table 16 Mean T3SS/1 evaluated in the evening during Week 1 and during the total two week treatment period- ITT Population

Period	Treatment	N	Mean	(SD)	Adjusted mean [(a)]	(SE)	Diff. vs. placebo [95 % CI]	P-value
Baseline	Placebo	117	5.60	(1.73)				
	Lctz 5 mg	118	5.54	(1.79)				
Week 1	Placebo	117	4.47	(2.09)	4.33	0.157		
	Lctz 5 mg	118	3.80	(2.11)	3.70	0.157	0.63[0.21, 1.04]	0.003
Total treatment period	Placebo	117	4.27	(2.07)	4.14	0.163		
	Lctz 5 mg	118	3.65	(2.09)	3.56	0.163	0.58[0.15, 1.01]	0.008

[a)] From an ANCOVA model with baseline score as covariate and pooled center and treatments as factors.

3.1.2.2 Study a217

A total of 470 subjects were randomized into the study, 266 at 16 centers in France and 204 at 14 centers in Germany. There were 119 subjects in the placebo group, 117 subjects in the levocetirizine 2. 5 mg group, 116 subjects in the levocetirizine 5 mg group, and 118 subjects in the levocetirizine 10 mg group. Two patients withdrew consent, one of whom took no medication, and had no on-treatment data.

Four hundred and five (405) subjects completed the study (86.2 %). Sixty-five (65) subjects discontinued the study prematurely, 29 in the placebo group (24.4 %), 11 in the levocetirizine 2.5 mg group (9.4 %), 14 in the levocetirizine 5 mg group (12.1 %), and 11 in the levocetirizine 10 mg group (9.3 %). The reasons of discontinuation are presented by category in Table 17 below. The most common reason for early termination was lack of efficacy with (19.3 %) in the placebo group and 6-7% % in the levocetirizine groups.

Table 17 Number (%) of subjects who discontinued the treatment, by reason and Treatment (ITT Population)

Reasons of study discontinuation	Placebo (N =119)	Lctz 2.5 mg (N = 117)	Lctz 5 mg (N =11 6)	Lctz 10 mg (N = 118)	Total (N = 470)
Lack of efficacy	23 (19.3%)	8 (6.8%)	8 (6.9%)	7 (5.9%)	46 (9.8%)
Adverse event	3 (2.5%)	0	2 (1.7%)	3 (2.5%)	8 (1.7%)
Withdrew Consent	1 (1.6%)	0	0	0	1 (0.2%)
Lab values outside Of protocol ranges	2 (1.7%)	2 (1.7%)	3 (2.6%)	1 (0.8%)	8 (1.7%)
Personal reason	0	1 (0.9%)	1 (0.9%)	0	2 (0.4%)

Treatment groups were comparable in demographic variables. Fifty percent of the subjects were female and mean age was 32 years. (Age Range was 17-72 years.) The study report did not specify race. Most were likely Caucasian. The treatment groups were significantly different at baseline in T4SS/24 assessment (p=0.015).

Table 18 presents the results of the analysis of T4SS/24 averaged over the total treatment period.

Table 18 Mean T4SS/24 averaged over the total treatment period - ITT population

Treatment	N	Baseline Mean	(SD)	Total Treatment Period Mean	(SD)	Adjusted Mean[a]	(SE)	Diff vs Placebo [b] [98% CI]	P-value [c]
Placebo	118	7.94	(2.06)	5.33	(2.46)	5.18	(0.19)		
Lctz 2.5 mg	116	7.83	(2.14)	4.37	(2.38)	4.27	(0.19)	0.91 [0.27, 1.55]	0.001
Lctz 5 mg	115	7.45	(2.07)	4.00	(2.14)	4.06	(0.20)	1.11 [0.47, 1.75]	<0.001
Lctz 10 mg	118	7.15	(2.08)	3.37	(2.16)	3.57	(0.19)	1.61 [0.96, 2.25]	<0.001

[a] Mean adjusted for baseline score

[b] Placebo minus levocetirizine 2.5 mg/ Placebo minus levocetirizine 5 mg/ Placebo minus levocetirizine 10 mg

[c] p-value was obtained from an ANCOVA with baseline score as covariate and treatment as factor.

In a supplemental analysis the baseline by treatment interaction was not significant (p=0.67).

In another supplemental analysis the baseline by country interaction was not significant (p=0.82).

The above analyses show significance of all doses and dose response ordering. The judgment of the appropriate dose is not obvious from efficacy considerations only.

3.1.2.3 Study a222

There were 803 patients randomized, of whom 797 were in the intent-to-treat population. The per-protocol population had 696 patients.

Table 19 below provides the results of the equivalence analysis on the per-protocol population for the four-symptom total system score.

Table 19 Equivalence analysis for the four-symptom score (per protocol population)

Period	Treatment	N	Mean (SD)	Adjusted mean (SE)	Diff in Adjusted means (90% CL)
Baseline	Lctz 5 mg	281	7.91 (2.11)		
	Cetirizine 10-mg	278	7.81 (2.03)		
Total Trt. Period	Lctz 5mg	280	4.03 (2.24)	4.00 (0.124)	
	Cetirizine 10mg	278	3.87 (2.26)	3.89 (0.0124)	-0.12 (-0.41, 0.17)

The 90% CI is contained within the 20% interval (-0.78, 0.78) calculated from the cetirizine mean score. The sponsor stated that, by the pre-specified rule, the two treatments were considered clinically equivalent.

Table 20 provides the results of the comparison of levocetirizine and cetirizine with placebo for the ITT population.

Table 20 Global and pairwise comparisons for the total four-symptom score (ITT population)

Period	Treatment	N	Mean (SD)	Adjusted mean (SE)	Difference (97.5% CI)	P-value
Baseline	Placebo	160	7.83 (2.05)			
	Lctz 5mg	319	7.94 (2.11)			
	Cetirizine 10mg	318	7.79 (2.10)			
Total Trt. Period	Placebo	158	5.81 (2.26)	5.81 (0.169)		
	Lctz 5mg	317	4.11 (2.32)	4.09 (0.119)	1.73 (1.26, 2.19)	<0.001
	Cetirizine 10mg	315	3.90 (2.29)	3.93 (0.119)	1.88 (1.42, 2.35)	<0.001

Both Levocetirizine and cetirizine were significantly different from placebo in the total four-symptom total assessment.

Table 21 provides the results of the equivalence analysis for the four-symptom score as assessed by the investigator using the per protocol population.

Table 21 Equivalence analysis for the four-symptom score assessed by the investigator (per protocol population)

Visit	Treatment	N	Adjusted mean (SE)	Difference in adjusted means (90% CI)
Total Trt. Period	Lctz 5 mg	281	3.70 (0.17)	
	Cetirizine 10mg	276	3.24 (0.18)	-0.46 (-0.87, -0.05)

Using the sponsor's rule levocetirizine and cetirizine were not equivalent. The 90% CI was not contained within the 20% interval (-0.65, 0.65) calculated from the cetirizine mean score. It should be further noted that the 90% CI does not contain 0.

In seasonal allergic rhinitis trials typically more weight is given to the patient's assessments than to the investigator's assessments.

3.1.3 Perennial Allergic Rhinitis Studies

3.1.3.1 Study a00266

A total number of 368 adult and adolescent subjects were screened for the study, of which 74 subjects were screening failures. Consequently, 294 subjects at 26 centers in South Africa were randomized to treatment: 144 subjects in the placebo group and 150 subjects in the levocetirizine 5 mg group.

Two hundred and seventy-six (276) subjects completed the study (94 %). The 18 subjects who stopped the trial have been classified in five categories (see Table 22 below).

Table 22 Number (%) of subjects who discontinued the treatment, by reason and treatment. ITT population

Reasons of study discontinuation	**Placebo (N = 144)**	**Lctz 5 mg (N = 150)**	**Total (N =294)**
Lack of efficacy	8 (5.6%)	2 (1.3%)	10 (3.4%)

Withdrawal of consent	3 (2.1%)	0 (0.0%)	3 (1.0%)
Adverse event	2 (1.4%)	0 (0.0%)	2 (0.7%)
Other	0 (0.0%)	2 (1.3%)	2 (0.7%)
Lost to follow-up	0 (0.0%)	1 (0.7%)	1 (0.3%)

Both treatment groups were comparable in demographic and baseline symptom assessments. Fifty-seven percent of the subjects were female and 68 % were Caucasian, 17% were Mixed/other, 13% were Asian/Pacific Islander, and 2% were Black. Mean age was 29 years. (Age Range was 12-71 years.)

Centers 2 and 25 were pooled into pooled center 98. Center 18 and 22 were pooled into pooled center 99.

Tables 23 and 24 present the mean T4SS/24 and T3SS/24, respectively, evaluated in the evening during Week 1 and during the total two week treatment period-for the ITT population. Both T4SS/24 and T3SS/24 showed significance at Week 1 and over the total 2 week treatment period.

Table 23 Mean T4SS/24 evaluated in the evening during Week 1 and during the total two week treatment period- ITT Population

Period	Treatment	N	Mean	(SD)	Adjusted mean [(a)]	(SE)	Diff. vs. placebo [95 % CI]	P-value
Baseline	Placebo	142	7.44	(1.80)				
	Lctz 5 mg	150	7.69	(1.82)				
Week 1	Placebo	142	6.10	(2.28)	6.16	(0.193)		
	Lctz 5 mg	150	5.00	(2.38)	4.94	(0.185)	1.22 [0.73, 1.71]	<0.001
First 2 week period	Placebo	142	5.34	(2.26)	5.39	(0.183)		
	Lctz 5 mg	150	4.21	(2.20)	4.17	(0.176)	1.22 [0.76, 1.69]	<0.001

[(a)] From an ANCOVA model with baseline score as covariate and pooled center and treatments as factors.

Table 24 Mean T3SS/24 evaluated in the evening during Week 1 and during the total two week treatment period- ITT Population

Period	Treatment	N	Mean	(SD)	Adjusted mean [(a)]	(SE)	Diff. vs. placebo [95 % CI]	P-value
Baseline	Placebo	142	5.79	(1.41)				
	Lctz 5 mg	150	5.98	(1.38)				
Week 1	Placebo	142	4,82	(1.75)	4.87	(0.148)		
	Lctz 5 mg	150	3.91	(1.82)	3.86	(0.142)	1.00 [0.63, 1.38]	<0.001
First 2 Week period	Placebo	142	4.24	(1.69)	4.28	(0.137)		
	Lctz 5 mg	150	3.33	(1.65)	3.29	(0.132)	0.99 [0.64, 1.34]	<0.001

(a) From an ANCOVA model with baseline score as covariate and pooled center and treatments as factors.

Levocetirizine 5 mg was also significantly more effective than placebo for T3SS/24 averaged over the total 6 week treatment period.

3.1.3.2 Study a00304

A total number of 371 children were screened for the study, of which 65 subjects were screening failures. Consequently, 306 children at 25 centers in South Africa were randomized to treatment: 152 subjects in the placebo group and 154 subjects in the levocetirizine 5 mg group.

Two hundred and ninety-seven (297) children completed the study (97.1%). The 9 children who stopped the trial have been classified in four categories (see Table 25 below).

Table 25 Number (%) of children who discontinued the treatment, by reason and treatment. ITT population

Reasons of study discontinuation	**Placebo (N = 152)**	**Lctz 5 mg (N = 154)**	**Total (N =306)**
Adverse event	2 (1.3%)	2 (1.3%)	4 (1.3%)
Lack of efficacy	2 (1.3%)	1 (0.6%)	3 (1.0%)
Other	0 (0.0%)	1 (0.6%)	1 (0.3%)
Withdrawal of consent	1 (0.7%)	0 (0.0%)	1 (0.3%)

Both treatment groups were comparable in demographic and baseline symptom assessments. Thirty-nine percent of the subjects were female and 28.8% were Caucasian, 5.6% were Black, 21.6% were Asian/Pacific Islander, and 44.1% were Mixed/Other. Mean age was 9.9 years. (Age Range was 6-13 years.)

No centers were pooled for the ITT analyses of symptom scores.

Tables 26 and 27 present the mean T4SS/24 and T3SS/24, respectively, evaluated in the evening during week 1 and during the total two week treatment period for the ITT population. Both T4SS/24 and T3SS/24 showed significance at Week 1 and over the total 2 week treatment period.

Table 26 Mean T4SS/24 evaluated in the evening during Week 1 and during the first two week treatment period- ITT Population

Period	Treatment	N	Mean	(SD)	Adjusted mean [(a)]	(SE)	Diff. vs. placebo [95 % CI]	P-value
Baseline	Placebo	152	7.51	(1.85)				
	Lctz 5 mg	154	7.53	(1.85)				
Week 1	Placebo	152	7.11	(2.20)	7.11	(0.148)		
	Lctz 5 mg	153	6.45	(2.36)	6.44	(0.148)	0.67 [0.26, 1.08]	0.001
First 2 week period	Placebo	152	6.75	(2.21)	6.76	(0.152)		
	Lctz 5 mg	154	6.07	(2.34)	6.06	(0.151)	0.69 [0.27, 1.12]	0.001

[(a)] From an ANCOVA model with baseline score as covariate and pooled center and treatments as factors.

Table 27 Mean T3SS/24 evaluated in the evening during Week 1 and during the total two week treatment period- ITT Population

Period	Treatment	N	Mean	(SD)	Adjusted mean [a]	(SE)	Diff. vs. placebo [95 % CI]	P-value
Baseline	Placebo	152	5.94	(1.44)				
	Lctz 5 mg	154	5.87	(1.49)				
Week 1	Placebo	152	5.66	(1.70)	5.64	(0.116)		
	Lctz 5 mg	153	5.08	(1.80)	5.11	(0.116)	0.53 [0.20, 0.85]	0.002
First 2 Week period	Placebo	152	5.39	(1.70)	5.36	(0.120)		
	Lctz 5 mg	154	4.77	(1.79)	4.79	(0.120)	0.57 [0.23, 0.90]	<0.001

[a] From an ANCOVA model with baseline score as covariate and pooled center and treatments as factors.

Levocetirizine 5 mg was also significantly more effective than placebo for T3SS/24 averaged over the total 4 week treatment period.

3.2 Evaluation of Safety

For the full evaluation of safety see the Medical officer review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

The sponsor did not provide a discussion of efficacy results in subgroups.

Study a00304 showed efficacy of levocetirizine in children. All the other studies discussed in this review were in adults and all of which demonstrated efficacy of levocetirizine.

The efficacy of levocetirizine in gender and race subgroups can be inferred from efficacy of cetirizine in these subgroups. In the studies discussed in this review most of the subjects were Caucasian with very few blacks. Therefore this reviewer did not attempt any subgroup analysis by race.

4.2 Other Special/Subgroup Populations

The sponsor did not provide a discussion of efficacy results in any special subgroup population. In all studies discussed in this review, baseline was highly significant. As is typical, the more severe in symptoms a patient is at baseline, the more improvement there is in symptoms on treatment.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

There were no statistical issues with this submission. The reviewer was able to duplicate the sponsor's results from derived data files provided by the sponsor except for minor rounding differences.

5.2 Conclusions and Recommendations

A dose-ranging study a217 showed 2.5 mg levocetirizine, 5 mg levocetirizine, and 10 mg levocetirizine to be more effective than placebo in patient assessed T4SS/24 (total of sneezing, runny nose, nasal pruritus, and ocular pruritus assessed over the last 24 hours) averaged over the two-week treatment period in adults and adolescents. Study a00268 demonstrated efficacy of 5 mg levocetirizine over placebo in patient assessed Total Nasal Symptom Score (T3SS/24) averaged over the first week and over the total six week treatment period in adults and adolescents with seasonal allergic rhinitis.

Study a00266 demonstrated efficacy of 5 mg levocetirizine over placebo in patient assessed Total Nasal Symptom Score (T3SS/24) averaged over the first week and over the first four weeks of the treatment period in adults and adolescents with perennial allergic rhinitis due to dust mites. Study a00304 demonstrated efficacy of 5 mg levocetirizine over placebo in patient assessed Total Nasal Symptom Score (T3SS/24) averaged over the first week and over the first two weeks of the treatment period in children with perennial allergic rhinitis due to dust mites.

Study a00269 demonstrated efficacy of 5 mg levocetirizine over placebo in patient assessed pruritus, number and size of wheals averaged over the first week and averaged over the whole treatment period in adults with Chronic Idiopathic Urticaria (CIU). Study a00270 demonstrated efficacy of 2.5 mg levocetirizine, 5 mg levocetirizine, and 10 mg levocetirizine over placebo in patient assessed pruritus, number and size of wheals averaged over the first week and averaged over the whole treatment period in adults with CIU.

The doses of levocetirizine (2.5 mg, 5 mg, and 10 mg) all showed efficacy and usually with dose response ordering. The appropriate dose is not obvious from efficacy considerations only. The 10 mg dose causes more somulance than the other two doses. If a subject cuts the scored 5 mg tablet in half, they should have an effective dose at 2.5 mg q.d.

That levocetirizine 5mg, similarly to cetirizine 10mg, can be dosed once a day is supported by pruritus, size and number of wheals, evaluated at the moment in CIU Study a00270, mean size and number of wheals evaluated at the moment in CIU Study 00269, and T3SS/1 (evaluated over the last hour) in SAR Study a00268

The doses of levocetirizine (2.5 mg, 5 mg, and 10 mg) all showed efficacy and usually with dose response ordering. The appropriate dose is not obvious from efficacy considerations only. The 10 mg dose causes more somulance than the other two doses. If a subject cuts the scored 5 mg tablet in half, they should have an effective dose at 2.5 mg q.d.

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

Statistical Filing Review

NDA:	22064
Drug Name :	Xyzal (levoceterizine dihydrochloride) 5 mg Tablets
Indication:	Symptomatic treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria
Applicant:	UBC, Inc
Dates:	Electronic Submission dated July 24, 2006
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical reviewers:	James Gebert, Ph.D.
Concurring Reviewer:	Ruthanna Davi, M.S., Team Leader Statistics
Medical Division:	Division of Allergy and Pulmonary Drug Products (HFD-570)
Clinical reviewer:	R. Boucher, M.D.
Project manager:	L. Garcia
Keywords:	Clinical studies

FILING CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Safety and efficacy for gender, racial, and geriatric subgroups investigated	Yes*
Data sets in EDR conform to applicable guidances.	Yes**

*Although an analysis of efficacy and safety by gender, race, and age was provided by the sponsor in the context of each study report, an integrated summary of efficacy (including investigation of efficacy by gender, race, and age) was not provided.

**This comment pertains to the datafiles in this submission. Although not a refuse-to-file issue, it should be noted that the sponsor has not supplied analysis data sets (derived datasets) for the pivotal studies. The raw data may be useful for archival purposes but will not be conducive to statistical analyses. For example, the sponsor's primary efficacy variable for the seasonal and perennial allergic rhinitis studies was change from baseline in the mean Total Symptom Complex. The sponsor has included raw symptom assessments in a dataset but whether they were baseline or on-treatment assessments could not be determined from that dataset. The medical division has suggested that the ocular pruritis symptom should not have been included in the Total Symptom Complex. The more appropriate symptom complex, excluding the ocular pruritis symptom, was not analyzed by the sponsor and would be very difficult (if not impossible) to conduct using the archival data sets provided in the submission.

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/s/

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