A00394, 2005-000358-65

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

Sponsor:

UCB S.A. – Pharma Sector
Chemin du Foriest
1420 Braine-l'Alleud
Belgium

Official study title:

A multicenter, double-blind, two parallel groups, randomized trial over four weeks of treatment to compare the clinical efficacy and safety of levocetirizine 5 mg oral capsules once daily in the morning vs. desloratadine 5 mg oral capsules once daily in the morning in subjects suffering from Chronic Idiopathic Urticaria (CIU)

2. SYNOPSIS

Name of Sponsor/Company: UCB S.A. Belgium	Individual Study Table Referring to Module 5.3.5.1.	(For National Authority Use only)
Name of Finished Product: Xyzal®	Volume:	
Name of Active Ingredient: Levocetirizine dihydrochloride	Page:	
Title of Study: A multicenter, double-blind, two parallel groups, randomized trial over four weeks of treatment to compare the clinical efficacy and safety of levocetirizine 5 mg oral capsules once daily in the morning *vs.* desloratadine 5 mg oral capsules once daily in the morning in subjects suffering from Chronic Idiopathic Urticaria (CIU)		
Investigator(s): [redacted]		
Study Centers: 135		
Publication: None		
Studied Period: First subject enrolled: 01-Dec-2005 Last subject completed: 03-Jan-2007	**Phase of Development:** Phase IV – Therapeutic use	

Objectives:

Primary Objective:

To compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the mean pruritus severity score over the first week of treatment in subjects suffering from CIU. Pruritus severity was evaluated on 4-point scale retrospectively over the past 24 hours.

Secondary Objectives:

- To compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the mean CIU composite score (sum of the pruritus severity score and the score for the numbers of wheals) over the first and over the four weeks of treatment.
- To compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the mean pruritus severity score over the four weeks of treatment.
- To compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the mean score for pruritus duration, number and size of wheals evaluated on 4-point scales retrospectively over the past 24 hours over the first and over the four weeks of treatment.
- To compare the global satisfaction of the treatment with levocetirizine 5 mg and desloratadine 5 mg assessed by the subjects and the Investigators on a Visual Analog Scale (VAS) from 0 to 10 cm after the first and after the four weeks of treatment.
- Evaluation of the safety profile.

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Exploratory Objectives:

- To compare the onset of action of levocetirizine 5 mg and desloratadine 5 mg as measured by the median time to the first symptom improvement feeling after the drug intake.
- To compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the mean number of comfortable days (pruritus severity score ≤ 1) over the first and over the four weeks of treatment.
- To compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the mean percentage of comfortable days over the four weeks of treatment.
- To compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the proportion of subjects with total control of symptoms over the first and over the four weeks of treatment. Control of symptoms is defined as the occurrence of both a pruritus severity score and a score for number of wheals = 0 on any day during the period considered.
- To compare the global satisfaction of the subjects treated with levocetirizine 5 mg or desloratadine 5 mg at the end of the Study measured as the willingness of the subjects to continue the treatment with the same medication.
- To compare the Health-Related Quality Of Life (HRQOL) after one week and four weeks of treatment with levocetirizine 5 mg and desloratadine 5 mg as assessed by the Dermatology Life Quality Index (DLQI).
- To compare the impact of the disease (CIU) on quality of sleep after one week and four weeks of treatment with levocetirizine 5 mg and desloratadine 5 mg as assessed on a 5-point scale (Very much, A lot, Moderately, Somewhat, Not at all).
- To compare the Global Evaluation of the disease evolution by the subjects and the Investigators after the four weeks of treatment with levocetirizine 5 mg and desloratadine 5 mg on a 7-point Global Evaluation Scale (GES).
- To compare the direct medical cost parameters (medications, additional physician visits, medical procedures and hospitalizations) and indirect cost parameters (workdays and usual daily activity days lost), related to urticaria after treatment with levocetirizine 5 mg and desloratadine 5 mg over the four weeks of treatment.

Methodology:

This was a double-blind, two parallel groups, randomized, multicenter study. The entire Study period lasted five weeks including one week of Baseline and a 4-week treatment period.
Four visits were foreseen: Visit 1: Screening Visit, Visit 2: Randomization, Visit 3: Control Visit and Visit 4: Final Visit at the end of study treatment.

Number of Subjects:

Planned: 816, 408 per group
Screened: 976 subjects
Randomized: 886 subjects,

- 438 subjects in the levocetirizine 5 mg group
- 448 subjects in the desloratadine 5 mg group

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Diagnosis and Main Criteria for Inclusion:

At the Screening Visit (Visit 1):

- Male or female subjects, at least 18 years old.
- Clinical history of CIU (*i.e.* episodes of hives of characteristic wheal and flare appearance, occurring regularly, at least three times a week) for a period of at least six weeks during the last three months without an identifiable cause.

During the one-week Baseline Period for at least three days:

- The pruritus severity (over the last 24 hours) had to be minimum two, and
- The number of wheals score (at the moment of evaluation) had to be ≥1.

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
Levocetirizine dihydrochloride 5 mg	Oral capsule 5 mg once daily in the morning.	[redacted]

Duration of Treatment:

Exposure to levocetirizine/desloratadine: four weeks.

Reference Therapy:	**Dose and Mode of Administration:**	**Batch Number:**
Desloratadine 5 mg	Oral capsule 5 mg once daily in the morning.	[redacted]

Criteria for Evaluation:

Efficacy:

Primary Efficacy Variable:

- Pruritus severity score over the first week of treatment.

Secondary Efficacy Variables:

- CIU composite score (pruritus severity score plus number of wheals score) over the first week of treatment and over the entire treatment period.
- Pruritus severity score over the entire treatment period.
- Scores for pruritus duration, number and size of wheals over the first week and over the entire treatment period.
- Global satisfaction score assessed by the subjects and Investigators on a VAS from 0 to 10 cm after the first week and over the entire treatment period.

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Exploratory Efficacy Variables:

- Time to the first feeling of symptoms improvement after drug intake assessed by asking the subjects to note in the diary cards the exact hour of drug intake and the exact hour of first feeling of symptom improvement after the first drug intake.
- Number of comfortable days (pruritus severity score ≤ 1) over the first week of treatment and over the entire treatment period.
- Percentage of comfortable days over the entire treatment period.
- Occurrence of total control of symptoms (pruritus severity and number of wheals = 0) over the first week and over the entire treatment period.
- Willingness of the subject to continue the treatment with the same medication at the end of the Study.
- Mean change from Baseline of the overall DLQI after one week of treatment and after the entire treatment period.
- Frequency distribution by treatment group of the Impact of Urticaria on Sleep scale at each visit from Visit 2 to Visit 4.
- Global Evaluation of the disease evolution by the subjects and the Investigators at the end of treatment.
- Mean number of concomitant medications, additional physician visits, medical procedures, and hospitalizations related to urticaria per subject, over the entire treatment period.
- Mean number of workdays lost (absenteeism, presenteeism and overall workdays lost) and Usual Daily Activities (UDA) lost (full days lost, restriction over UDA and overall UDA lost) related to urticaria per subject per month, over the entire treatment period.

Safety:

Safety Variables:

- Frequency, severity, nature and duration of adverse events reported by the subjects during the whole duration of the Study.
- Evaluation of physical examination abnormalities.

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Statistical Methods:

Primary Efficacy Analysis:

The primary hypothesis to be tested in this Study was that the clinical efficacy of levocetirizine 5 mg is superior to that of desloratadine 5 mg. This hypothesis was tested two-tailed at the 5% level of significance. The mean pruritus severity scores during the first week of treatment were analyzed using an analysis of covariance (ANCOVA) model including treatment as factor with two levels (one for each treatment group), Baseline score, and center. The treatment group difference was estimated by the difference in least square (LS) means together with 95% CI. The test and p-value were based on these estimated LS Means through a contrast between the treatment groups. If the normality assumption underlying ANCOVA appeared to be violated, a non-parametric approach was used.

Secondary Efficacy Analyses:

The daily recorded variables related to the duration and intensity of the disease (mean pruritus severity score over the Entire Treatment Period; mean pruritus duration, mean number and size of wheals scores, mean CIU composite score over one week of treatment and over entire treatment period) were analyzed similarly to the primary efficacy variable.

Global satisfaction was analyzed by means of the Cochran-Mantel-Haenzel test on the ranks.

Exploratory variables and outcome research variables were analyzed descriptively. The time to the first feeling of symptom improvement was estimated by the median, obtained from Kaplan-Meier curves for the levocetirizine 5 mg and the desloratadine 5 mg treatment groups.

Analyses of Safety Data:

The number, nature, and duration of adverse events, and physical examination abnormalities were analyzed descriptively.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

A total of 976 subjects were screened. Ninety (90) subjects were ineligible for randomization: 886 were randomized of whom 832 subjects (93.9%) completed the Study. The 886 randomized subjects were included in the ITT Population and 733 subjects were included in the PP population.

The mean (SD) age was 43.1 (15.1) years and there were more females (66.6%) than males (33.4%). Besides idiopathic urticaria, which was the medical condition of the Study, the other most common medical conditions reported in medical history were 'Menopause' (13.7%), followed by 'Hypertension' (12.6%) and 'Asthma' (4.6%).

At Baseline, the subjects were clearly symptomatic with a mean pruritus severity score (±SD) of 2.19 (0.53) in the levocetirizine 5 mg group and 2.22 (0.54) in the desloratadine 5 mg. The treatment groups were well balanced with respect to Baseline characteristics.

A good compliance was observed for both treatment groups: 95.6% of subjects in the levocetirizine 5 mg group having compliance between 80% and 120%, and 96.1% in the desloratadine 5 mg group.

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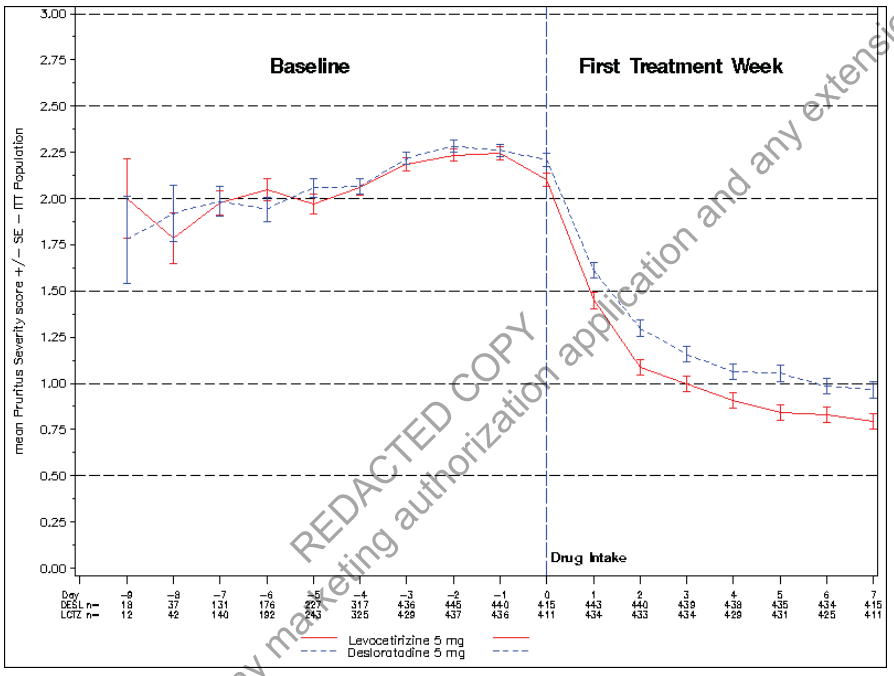
Primary Efficacy Variable: Mean pruritus severity score

The mean weekly pruritus severity score are displayed in Figure 2:1.

Figure 2:1 Mean Daily Pruritus Severity Score (± SE) - ITT Population



The profiles of the mean pruritus severity score during the First Treatment Week indicated a relief of symptoms in both treatment groups.

During the First Treatment Week, the adjusted mean pruritus severity score was 1.02 in the levocetirizine 5 mg group and 1.18 in the desloratadine 5 mg group.
The difference between the two treatment groups was 0.16 [0.07; 0.26] (adjusted mean difference [95% CI]).
Levocetirizine 5 mg showed a statistically significant superiority to desloratadine 5 mg during the First Treatment Week ($p < 0.001$).

Secondary Efficacy Variables:

Results from comparisons between levocetirizine 5 mg and desloratadine 5 mg indicate:

- The superiority of levocetirizine 5 mg was observed for the pruritus severity score, the CIU composite score and the duration of pruritus score over the First Treatment Week and over the Entire Treatment Period.
- The superiority of levocetirizine 5 mg was observed for size of wheals score during the First Treatment Week.

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- The threshold of significance was not reached for the number of wheals score, however the levocetirizine 5 mg was slightly better than the desloratadine 5 mg during the First Treatment Week and over the Entire Treatment Period.
- After one week of treatment, the subject's global satisfaction, assessed by a VAS, was statistically significantly ($p = 0.012$) better in the levocetirizine 5 mg group (mean VAS ± SD: 7.04 ± 2.48 cm) than in the desloratadine 5 mg group (mean VAS ± SD: 6.57 ± 2.70 cm). Also, at the end of the treatment period, the subject's global satisfaction was statistically significantly ($p = 0.021$) better in the levocetirizine 5 mg group (mean VAS ± SD: 7.62 ± 2.68 cm) than in the desloratadine 5 mg group (mean VAS ± SD: 7.33 ± 2.64 cm).
- After one week of treatment, the Investigator's global satisfaction was statistically significantly ($p = 0.030$) better in the levocetirizine 5 mg group (mean VAS ± SD: 7.20 ± 2.36 cm) than in the desloratadine 5 mg group (mean VAS ± SD: 6.78 ± 2.65 cm). At the end of the treatment period, the Investigator's global satisfaction for the both treatments was not statistically significantly different. Nevertheless, the Investigator's global satisfaction was slightly higher in the levocetirizine 5 mg group (mean VAS ± SD: 7.65 ± 2.60 cm) than in the desloratadine 5 mg group (mean VAS ± SD: 7.46 ± 2.61 cm).

Exploratory efficacy variables

The better performance of levocetirizine 5 mg compared to desloratadine 5 mg was further supported by the evaluation of several exploratory variables:

- More subjects reported a feeling of symptom improvement in the levocetirizine 5 mg group (95.9%) than in the desloratadine 5 mg group (93.9%). The median time [95% CI] to first feeling of improvement was 24h55 [22h30; 27h30] in the levocetirizine 5 mg group and 28h55 [25h00; 35h10] in the desloratadine 5 mg group.
- The subjects in the levocetirizine 5 mg group had more comfortable days than the subjects in the desloratadine 5 mg group (median = 91.7% in the levocetirizine 5 mg group and 86.2% in the desloratadine 5 mg group over the Entire Treatment Period).
- The occurrence of a total control of symptoms (pruritus severity score and a score for number of wheals equal to 0) was higher in the levocetirizine 5 mg group (7.6% of subjects) than in the desloratadine 5 mg group (6.1% of subjects) during the First Treatment Week and over the Entire Treatment Period (4.6% and 2.9%, respectively).
- At the Final Visit, 338 subjects (79.2%) in the levocetirizine 5 mg group were willing to continue the same medication compared to 327 subjects (76.8%) in the desloratadine 5 mg group.
- There was no difference between the two groups concerning health related quality of life assessed by DLQI.
- At the end of the treatment period the quality of sleep was improved compared with the start of the Study in the two treatment groups. At the end of the Study, 66.8% of the subjects in the levocetirizine 5 mg group considered their sleep to be unaffected by urticaria compared to 63.2% of subjects in the desloratadine 5 mg group.
- Both subjects and Investigators reported similar Global Evaluations of disease evolutions. The incidence of marked improvement of disease at the end of the treatment period was slightly higher in the levocetirizine 5 mg group (58.4% for subjects and 57.3% for Investigators) than in the desloratadine 5 mg group (53.1% for subjects and 53.8% for Investigators).

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- Comparing the direct medical cost parameters of both treatment groups shows that:
  1. The consumption of concomitant medications for CIU was low in both treatment groups.
  2. Five subjects in the levocetirizine 5 mg group and six subjects in the desloratadine 5 mg group required at least one additional physician visit for urticaria.
  3. Two subjects in the desloratadine 5 mg group reported a concomitant medical procedure for urticaria, while there was no concomitant medical procedure in the levocetirizine 5 mg group.
  4. One subject in the levocetirizine 5 mg group ('Surgical procedure on carpal tunnel syndrome') and three subjects in the desloratadine 5 mg group were hospitalized. In the desloratadine 5 mg group, one hospitalization for 'Anxiety' was related to CIU and lasted one day, the hospitalization for '*Diabetes mellitus*' lasted 14 days whilst the other, for 'Gastroenteritis', lasted one day.
- Comparing the indirect cost parameters of both treatment groups shows that:
  1. The percentage of subjects restricted at work was similar in both treatment groups (57.5% in the levocetirizine 5 mg group and 57.4% in the desloratadine 5 mg group).
  2. Over the Entire Treatment Period, the median number of working days lost per month, the median of the productivity lost at work and the median of the overall work productivity lost were null in both treatment groups.
  3. The median number of full days per month with inability to perform UDA, the median of the restriction in UDA and the median of the overall loss of UDA were null for the two treatment groups.

Therefore, no clear difference between the treatment groups could be established for the direct and the indirect cost parameters.

SAFETY RESULTS:

Overall, 279/886 subjects (31.5%) reported treatment-emergent Adverse Events (AEs). This incidence of AEs was similar in both treatment groups: 33.8% in the levocetirizine 5 mg group and 29.2% in the desloratadine 5 mg group. Four subjects (0.9%) had at least one AE that led to permanent study drug discontinuation in the levocetirizine 5 mg group and three subjects (0.7%) in the desloratadine 5 mg group. In the desloratadine 5 mg group, two subjects had a serious treatment-emergent adverse event (SAE): '*Diabetes mellitus*' for one subject and 'Myocardial infarction' for the other, the latter leading to the death of the subject. These SAEs were considered by the Investigator as unrelated to the study drug.

Overall, the incidence of drug-related treatment-emergent AEs was slightly higher in the levocetirizine 5 mg group (60 subjects, 13.7%) than in the desloratadine 5 mg group (50 subjects, 11.2%). The most common drug-related treatment-emergent AE was 'Somnolence' reported by 26 subjects (5.9%) in the levocetirizine 5 mg group and by 13 subjects (2.9%) in the desloratadine 5 mg group.

The most frequent treatment-emergent AEs with an incidence of at least 2% in one treatment group were 'Headache', 'Somnolence', 'Fatigue', 'Abdominal pain upper' and 'Nausea'. The incidence of 'Headache' was lower in the levocetirizine 5 mg group (8.0%) than in the desloratadine 5 mg group (10.7%). However, the incidence of 'Somnolence' was higher in the levocetirizine 5 mg group (7.1%) than in the desloratadine 5 mg group (3.1%).

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CONCLUSIONS:

CIU causes both physical and psychological distress in patients. The CIU patients, estimated at least at 0.5% of the population, need a treatment not only relieving the physical symptoms but also increasing the quality of life. Therefore, this Study was designed to evaluate both aspects by comparing levocetirizine 5 mg and desloratadine 5 mg in similar conditions of current medical practice.

In conclusion, this Study showed that levocetirizine 5 mg offers a better improvement than desloratadine 5 mg to subjects suffering from CIU during four weeks of treatment. The symptom reduction achieved with levocetirizine 5 mg was higher than with desloratadine 5 mg, with high statistical significance during the First Treatment Week and over the Entire Treatment Period for the severity of pruritus. The superiority of levocetirizine 5 mg was confirmed in almost all other symptom scores and additional parameters such as subject's global satisfaction.

Safety data fully support the safety profile of both levocetirizine and desloratadine. There was no unexpected finding during the course of the study. Adverse events, which might be expected during treatment with an H_1 receptor antagonist, have been observed in both treatment groups.

Report Date: 01-Oct-2007