A00401, 2004-002823-42

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 multicentre, double-blind, parallel, randomized, placebocontrolled study: Evaluation of the efficacy and safety of levocetirizine 5 mg and desloratadine 5 mg administered orally as capsules once daily, in the morning, over two weeks in patients suffering from Allergic Rhinitis (AR)

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 multicentre, double-blind, parallel, randomized, placebo-controlled study: Evaluation of the efficacy and safety of levocetirizine 5 mg and desloratadine 5 mg administered orally as capsules once daily, in the morning, over two weeks in patients suffering from Allergic Rhinitis (AR).

Coordinating Investigators:
For [redacted]
For [redacted]
For [redacted], Ospedale San Martino, Largo Rosana Benzi, 10, I-16132 Genova

Study Centers:
70 centers approximately planned. Among them, 56 have recruited subjects.

Publication:
None

Studied Period (years):	**Phase of Development:**
First subject enrolled: 21-Apr-2005 Last subject completed: 12-Sep-2005	Phase IV – Therapeutic Use

Objectives:
The **primary objective** was to compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the mean change from the baseline of Total 4 Symptom Score (T4SS) over two weeks of treatment. T4SS: sum of the individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus, evaluated on a 4-point scale retrospectively over the past 24 hours.

The **secondary objectives** were:

- To compare clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by
  - the mean change from the baseline of T4SS over the first week of treatment,
  - the mean change from the baseline of the 5 individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus and nasal congestion evaluated on a 4-point scale retrospectively over the past 24 hours, over the first week and over two weeks of treatment.
- To compare clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg vs. placebo as measured by the mean change from the baseline of
  - T4SS and
  - the 5 individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus and nasal congestion

  evaluated on a 4-point scale retrospectively over the past 24 hours, over the first week and over two weeks of treatment.

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:	

- To compare the onset of action of levocetirizine 5 mg and desloratadine 5 mg as measured by the first time point, after the first drug intake when the difference between the active treatment and placebo on T4SS becomes statistically significant.
- To compare the subject's global evaluation of disease evolution with levocetirizine 5 mg and desloratadine 5 mg assessed by the Investigators and subjects at the end of the treatment on a 7-point Global Evaluation Scale (GES).
- Evaluation of the safety profile.

The **exploratory objectives** were:

- To compare the onset of action of levocetirizine 5 mg and desloratadine 5 mg as measured by the median time to the first feeling of symptom improvement after the drug intake.
- To compare levocetirizine 5 mg and desloratadine 5 mg at the end of the study on the basis of the subjects' willingness to use the same medication during the next allergic rhinitis episode.
- To compare the subjects' global satisfaction with levocetirizine 5 mg and desloratadine 5 mg measured on a VAS from 0 to 10 cm. This evaluation was done at the end of the treatment.
- To compare direct medical costs parameters (use of concomitant medications, additional physician visits, medical procedures required and number and length of hospitalizations) and indirect cost parameters (workdays and usual daily activity (UDA) days lost), related to allergic rhinitis and its co-morbidities, of levocetirizine 5 mg, desloratadine 5 mg and placebo over the two weeks of treatment.

Methodology:
Double-blind, randomized, placebo-controlled three parallel groups multicentre study.
The entire study period lasted three weeks including the 2-week treatment period. Three visits were foreseen: V1 at the screening, V2 at the time of the randomization, and V3 after two weeks of treatment.

Number of Subjects:
The number of subjects planned was 81 in the placebo group and 324 in each treatment group (levocetirizine 5 mg and desloratadine 5 mg). A total of 765 subjects were randomized and included in ITT population: 88 subjects in the placebo group, 335 subjects in the desloratadine 5 mg group and 342 subjects in the levocetirizine 5 mg group. The mean age was 34.4 years and the 765 subjects consisted of 431 females (56.3%) and 334 males (43.7%).

Diagnosis and Main Criteria for Inclusion:

- Male or female subjects older than 18 years.
- Clinical history of AR known since at least two years.
- Positive skin prick test (wheal ≥ 3 mm larger than the diluent control) or RAST to grass pollen (less than one year).
- Minimum mean T4SS of 6 over the 3 to 7 days baseline period.

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

Duration of Treatment:
Exposure to levocetirizine/desloratadine: two weeks

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

Criteria for Evaluation:

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:	

Efficacy:

Primary efficacy variable:

Change from the baseline of T4SS (T4SS: sum of the individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus, evaluated on a 4-point scale retrospectively over the past 24 hours) over two weeks of treatment with levocetirizine 5 mg, desloratadine 5 mg or placebo.

Secondary efficacy variables:

- Change from the baseline of T4SS over the first week of treatment with levocetirizine 5 mg, desloratadine 5 mg or placebo.
- Change from the baseline of the individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus and nasal congestion over the first week and over two weeks of treatment with levocetirizine 5 mg, desloratadine 5 mg or placebo.
- T4SS during the first 6 hours after the first drug intake.
- Subject's global evaluation of disease evolution with levocetirizine 5 mg and desloratadine 5 mg assessed by the Investigators and subjects on a GES at the end of the treatment.

Exploratory efficacy variables:

- Time to the first feeling of symptom improvement after levocetirizine 5 mg and desloratadine 5 mg treatment defined as the time difference between the hour of very first drug intake and the hour of first feeling of symptom improvement.
- Willingness to use the same medication during the next allergic rhinitis episode after treatment with levocetirizine 5 mg or desloratadine 5 mg.
- The subjects' Global satisfaction with levocetirizine 5 mg and desloratadine 5 mg measured on a VAS from 0 to 10 cm. This evaluation was done at the end of the treatment.
- Mean number of concomitant medications used, additional physician visits, medical procedures required, number and length of hospitalizations, workdays lost (absenteeism, presenteeims and overall workdays lost) and usual daily activities lost (full days lost, restriction over UDA and overall UDA lost), related to allergic rhinitis or its co-morbidities, over the two weeks of treatment with levocetirizine 5 mg, desloratadine 5 mg and placebo.

Safety variables:

Frequency, severity, nature and duration of adverse events reported by the subjects during the whole duration of the study, physical examination and vital signs.

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:	

Statistical Methods:

Primary efficacy variable 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 change from the baseline in mean T4SS and in individual symptom scores was analyzed using an analysis of covariance (ANCOVA) model including treatment as factor with three 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 the 95% CI for this difference. The test and p-value were based on these estimated LS Means through a contrast between the appropriate treatment groups. If the normality assumption underlying ANCOVA appeared to be violated, a non-parametric approach was used.

Secondary and exploratory efficacy variables analyses:

The time to the onset of action after the first drug intake was analyzed using a repeated measures analysis of covariance model. The model included treatment, time (hourly during the first 6 hours on Day 1, daily thereafter), and center as factors, as well as the treatment by time interaction and the baseline score as covariate. An unstructured variance covariance matrix was applied.

Global evaluation of disease evolution using a GES was analyzed by means of the Cochran-Mantel-Haenszel test on the ranks.

Exploratory variables (willingness to re-use medication, VAS and direct/indirect cost parameters) 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 desloratadine 5 mg treatment groups.

Safety analysis:

The number, nature, and duration of adverse events, and the vital signs were analyzed descriptively.

SUMMARY – CONCLUSIONS

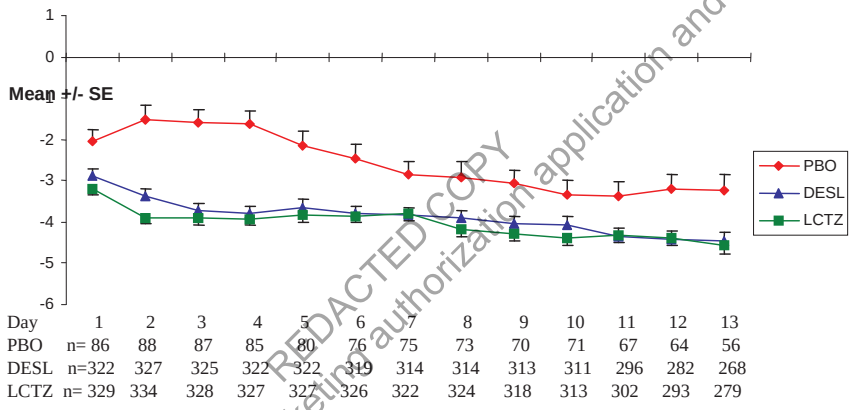
Name of Sponsor/Company: UCB S.A. Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product: Xyzal ®	Volume:	
Name of Active Ingredient: Levocetirizine dihydrochloride	Page:	

EFFICACY RESULTS:

- Primary endpoint

For the ITT population, change in mean T4SS from the baseline, over the total treatment period, was slightly higher in the levocetirizine 5 mg group (adjusted mean = -4.06) than in the desloratadine 5 mg group (adjusted mean = -3.76).

Mean Changes from the Baseline of the Daily T4SS as a Function of Time - ITT Population



Day	1	2	3	4	5	6	7	8	9	10	11	12	13
PBO n=	86	88	87	85	80	76	75	73	70	71	67	64	56
DESL n=	322	327	325	322	322	319	314	314	313	311	296	282	268
LCTZ n=	329	334	328	327	327	326	322	324	318	313	302	293	279

The difference between these treatment groups (desloratadine *versus* levocetirizine) was 0.30 with a 95% confidence interval of [-0.06; 0.66], overlapping the value 0. The difference between desloratadine and levocetirizine did not differ significantly (p = 0.102) for the ITT population.
Statistical analysis of the PP population provided similar conclusions (p = 0.150 and the mean difference between the two active groups was 0.29 with a 95% confidence interval of [-0.10; 0.67]).

- Secondary endpoints

Over the first treatment week, the reduction in T4SS in subjects treated with desloratadine and in those treated with levocetirizine did not differ significantly (p = 0.110) even if change in mean T4SS from the baseline was slightly higher in the levocetirizine 5 mg group (adjusted mean = -3.81) than in the desloratadine 5 mg group (adjusted mean = -3.52).

The difference in adjusted means between desloratadine and levocetirizine for sneezing score was statistically significant (p = 0.021 over the first treatment week and p = 0.025 over the total treatment period). This difference was 0.12 in favor of levocetirizine 5 mg group with a 95% confidence interval of [0.02; 0.23] over the first treatment week and of [0.01; 0.22] over the total treatment period.
For rhinorrhea, nasal pruritus and ocular pruritus scores, the differences in adjusted means between desloratadine and levocetirizine were not statistically significant even if they were always in favor of the levocetirizine 5 mg group. For nasal congestion score, there was no difference in adjusted means between desloratadine and levocetirizine.

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:	

The difference in change from the baseline of T4SS, sneezing, rhinorrhea, nasal pruritus and ocular pruritus scores between placebo and levocetirizine 5 mg and between placebo and desloratadine 5 mg groups were highly statistically significant ($p < 0.001$) over the first treatment week and over the total treatment period. Only nasal congestion score did not differ between placebo and levocetirizine 5 mg or between placebo and desloratadine 5 mg groups.

Concerning the onset of action, statistical significance, in a comparison with placebo, was reached at 4 hours after the first intake of levocetirizine and remained at 5 and 6 hours. In a comparison with placebo, such a statistical significant difference was not obtained within the first 6 hours following the first intake of desloratadine.

Results from a global assessment of disease evolution performed by the Investigators and subjects at the end of the treatment visit did not differ significantly between desloratadine 5 mg and levocetirizine 5 mg groups. An improvement ("marked", "moderate" and "slight" – three categories combined) was reported by 80.1% of Investigators and 80.0% of subjects in the levocetirizine 5 mg group and 78.3% of Investigators and 76.8% of subjects in the desloratadine 5 mg group.

- Exploratory endpoints

The incidence of no reported feeling of improvement was similar in the two active groups (around 21%). From Kaplan-Meier curves, median time to the first feeling of symptom improvement was equal to 4 hours under desloratadine and to 3.5 hours under levocetirizine.

In the levocetirizine 5 mg group, 62.8% of subjects were willing to use the same medication during the next allergic rhinitis episode compared to 60.6% in the desloratadine 5 mg group.

At the end of the treatment, the subjects' global satisfaction, assessed using a VAS, was similar (mean around 6 cm) in the desloratadine and the levocetirizine 5 mg groups.

The consumption of concomitant medications for allergic rhinitis or its co-morbidities was low in all treatment groups. In addition, there were few additional physician visits (4 subjects: 2 in the levocetirizine group; 2 in the desloratadine group), only one concomitant medical procedure (in the desloratadine group) and no hospitalizations.

The loss of productivity was lower in the levocetirizine 5 mg group (overall work productivity lost was 1.46 days per month and overall loss of UDA was 2.17 days per month) than in the two other groups. In the desloratadine group, there were 1.89 days per month of overall work productivity lost and 3.21 days per month of overall loss of UDA.

SAFETY RESULTS:

The safety results obtained in this study were consistent with previous knowledge concerning levocetirizine. The most common TEAEs reported were headache, somnolence, fatigue and asthenia.
Headache was considered as related to study drug for 1.1% of subjects in the placebo group, 1.8% in the desloratadine 5 mg group and 1.2% in the levocetirizine 5 mg group.

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:	

Somnolence was related to study drug for 2.4% subjects in the desloratadine 5 mg group and 2.9% in the levocetirizine 5 mg group; there was no somnolence in the placebo group.
There were 3 severe TEAEs in the desloratadine 5 mg group (asthma, ear infection and somnolence) and one in the levocetirizine 5 mg group (rhinitis).
No death occurred during this study.
One subject under levocetirizine had a serious TEAE, "tachycardia, high blood pressure", not related to the study drug, leading to hospitalization and to permanent study drug discontinuation.
Six subjects discontinued the trial due to rhinitis and dyspnoea in the desloratadine 5 mg group and pruritus, rhinitis, somnolence and tachycardia in the levocetirizine 5 mg group.

No relevant change in vital signs and no relevant abnormality in physical examination were observed.

CONCLUSIONS:
1. Compared to subjects treated with desloratadine 5 mg, subjects treated with levocetirizine 5 mg experienced

- A higher reduction in the Total 4 Symptom Score over the first week of treatment and the entire treatment period. However, the difference between the two treatment groups did not reach the statistical threshold of significance.
- A significantly higher reduction in the sneezing score over the first week of treatment and over the entire treatment period. A trend in favour of levocetirizine was observed when considering the rhinorrhea, nasal and ocular pruritus scores. No difference between desloratadine and levocetirizine was observed concerning nasal congestion score.

2. Both levocetirizine and desloratadine induced, when compared to Placebo, a significant decrease in T4SS, sneezing score, rhinorrhea score, nasal and ocular pruritus scores over the first week of treatment and the entire treatment period. Neither desloratadine 5 mg nor levocetirizine 5 mg reduced nasal congestion *versus* placebo.

3. The T4SS data collected every hour during the 6 hours following the first drug intake showed that

- The action of levocetirizine 5 mg was detectable at 4 hours, 5 hours and 6 hours (sustained statically significant reduction *versus* placebo).
- The action of desloratadine 5 mg was not detectable within the 6 hours following the first drug intake (no difference *versus* placebo).

4. Safety data fully support the safety profile of levocetirizine and desloratadine. The SAE (tachycardia) for which a subject,pertaining to the levocetirizine group, has been hospitalized was, as assessed by the Investigator, a moderate event not related to the study drug.
There was no unexpected finding during the course of the Study. Adverse events, which might be expected during a treatment with an H1 receptor antagonist, have been observed in both treatment groups.

Report Date:
27-Mar-2006