A00391, 2004-002971-18

CLINICAL STUDY REPORT SYNOPSIS

Sponsor:

UCB S.A. – Pharma Sector

Chemin du Foriest

1420 Braine-l'Alleud

Belgium

Official study title:

A monocenter, double-blind, randomized trial, with two parallel groups comparing the clinical efficacy of levocetirizine 5 mg capsules and desloratadine 5 mg capsules taken once a day over 3 weeks of treatment in adult subjects suffering from seasonal allergic rhinitis (SAR) due to grass pollen

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)*
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Title of Study:
A monocenter, double-blind, randomized trial, with two parallel groups comparing the clinical efficacy of levocetirizine 5 mg capsules and desloratadine 5 mg capsules taken once a day over 3 weeks of treatment in adult subjects suffering from seasonal allergic rhinitis (SAR) due to grass pollen

Investigator(s):
[redacted]

Study Center:
One center in [redacted]

Publication:
None.

Studied Period (years): First subject enrolled: 11-May-2005 Last subject completed: 11-Jul-2005	**Phase of Development:** Phase IV - Therapeutic exploratory

Objectives:
The **primary objective** of this phase IV trial was to compare the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg as measured by the subjects' satisfaction/dissatisfaction (subject's choice after one week of treatment to continue with the administered treatment or to switch to the alternative treatment) after the first week of treatment.

The **secondary objectives** were:

- To investigate the correlation between the switch and
  - the mean T5SS (T5SS: sum of the 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 of treatment.
  - the mean change from the baseline in T5SS over the first week of treatment.
  - the mean of 5 individual symptom scores over the first week of treatment.
  - the mean change from the baseline in the 5 individual symptom scores over the first week of treatment.
- To compare levocetirizine 5 mg and desloratadine 5 mg after the first week of treatment in the switched population analyzing the reason for dissatisfaction.
- To assess, at the end of the study, subjects' satisfaction/dissatisfaction with their treatment choice after the first week of treatment.
- To investigate subject's evaluation of disease evolution assessed on the standard 7-point Global Evaluation Scale after the first week of treatment.
- To evaluate the safety profile of levocetirizine.

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The **exploratory objectives** were:

- To investigate the clinical efficacy of levocetirizine and desloratadine as measured by
  - the mean change from the baseline in 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 the first week of treatment.
  - the mean change from the baseline in the 4 individual symptoms scores over the first week of treatment.
  - the mean T4SS and mean individual symptom scores over only the days with grass pollen concentration of at least 20, 30 and 40 grains/m³/24 h during Week 1.
  - the mean change in T4SS and 4 individual symptom scores between Week 1 and Week 3 in the two subgroups of subjects.
- To investigate the onset of action of levocetirizine 5 mg and desloratadine 5 mg evaluated as the median time to the first feeling of symptom improvement during the first week of treatment.
- To evaluate the time to the first feeling of sufficient symptom improvement after treatment with levocetirizine 5 mg and desloratadine 5 mg during Week 1.
- To investigate the clinical efficacy of levocetirizine 5 mg and desloratadine 5 mg
  - after 1 week of treatment evaluated on a VAS from 0 to 10 cm,
  - after 1 week of treatment assessed by the impact of the treatment on the quality of sleep and the quality of daily activities evaluated on VAS from 0 to 10 cm.

Methodology:
Double blind, randomized, two parallel groups clinical efficacy evaluation with a switch to the other treatment allowed one week after the randomization. The switch decision was taken by the subject after a discussion with the Investigator during the third visit (V3).

Number of Subjects:
A total of 267 subjects were screened, 200 of whom were randomized and included in ITT population. They were assigned to either the desloratadine group (N = 100) or the levocetirizine group (N = 100). The mean age was 34.5 years and the 200 subjects consisted of 97 females (48.5%) and 103 males (51.5%).

Diagnosis and Main Criteria for Inclusion:

- Adult subjects older than 18 years of either sex.
- Clinical history of SAR known and treated since at least 2 years.
- Positive skin prick test (wheal > 3 mm larger than the diluent control) or RAST (≥3.5 IU/mL) to grass pollen (less than 1 year).
- Minimum mean T5SS of 8 during the baseline 3 to 7 days period.

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
Levocetirizine dihydrochloride	5 mg capsule once a day (morning)	[redacted]

Duration of Treatment:
4 weeks including a 3 weeks treatment period

Reference Therapy:	**Dose and Mode of Administration:**	**Batch Number:**
Desloratadine	5 mg capsule once a day (morning)	[redacted]

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Criteria for Evaluation:

Efficacy:

Primary efficacy variable:

Percentage of subjects who decided to switch to the alternative treatment at the end of Week 1.

Secondary efficacy variables:

- T5SS over Week 1 – mean absolute score and mean change in score from baseline.
- Individual symptom scores over Week 1 – mean absolute score and mean change in score from baseline.
- Global Evaluation Scale at the end of Week 1.
- Reasons for switching to the alternative treatment at the end of Week 1.
- Number of subjects, at the end of Week 3, satisfied by their choice to switch to the alternative treatment.

Exploratory efficacy variables:

- T4SS over Week 1 - mean absolute score and mean change in score from baseline.
- T4SS over Week 3 - mean change in score from Week 1.
- Individual symptom score over Week 3 - mean change in score from Week 1.
- Time to first feeling of symptom improvement during Week 1.
- Time to first feeling of sufficient symptom improvement during Week 1.
- VAS score rating the speed of overall symptom relief at the end of Week 1.
- VAS score rating the severity of blocked nose at randomization and at the end of Week 1 – mean absolute score and mean change in score from randomization to the end of Week 1.
- VAS score rating the speed of blocked nose relief at the end of Week 1.
- VAS score rating the impact on quality of sleep and daily activities at the end of Week 1.

Safety:

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

Statistical Methods:

The primary efficacy variable was analyzed using the Fisher's exact test.
Logistic regressions were used to investigate the correlation between the switch and the symptom scores or Global Evaluation Scale.
The Global Evaluation Scale was compared between treatment groups using a Cochran Mantel-Haenszel test.
All exploratory analyses were carried out with descriptive statistics, no statistical inference was performed.
The number, nature and duration of adverse events were analyzed descriptively.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

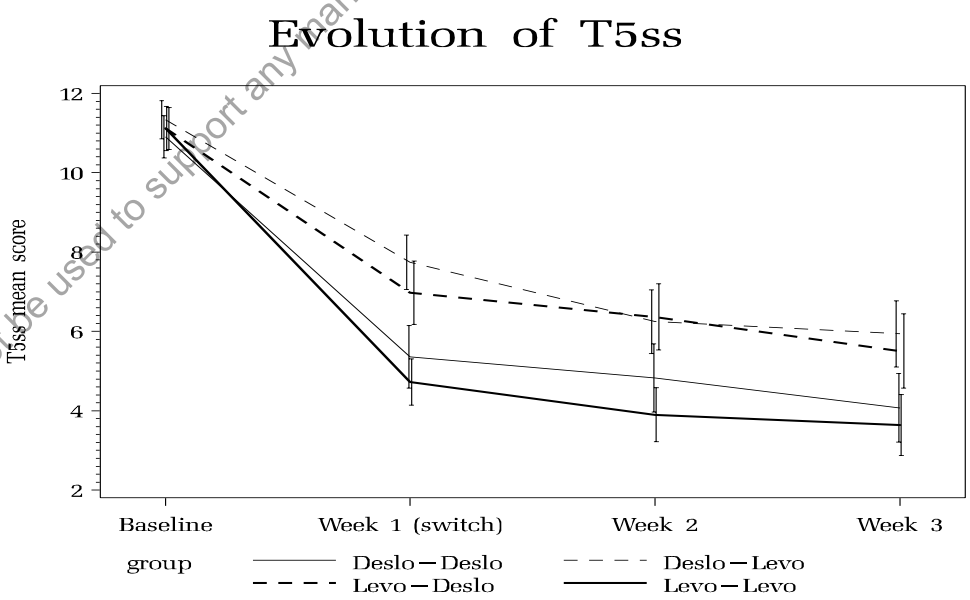
- **Primary endpoint**

Fifty-five subjects (55%) in the desloratadine group and fifty-seven (57%) in the levocetirizine group decided to switch to the alternative treatment at the end of Week 1.
The decision to switch to the alternative treatment did not differ significantly between treatment groups (p = 0.887). The statistical analysis performed on the PP population confirmed this result (p = 1.000).

- **Secondary endpoints**

1. T5SS and individual symptoms scores over baseline and Week 1

The reduction in **T5SS**, as reflected by the mean change from baseline of T5SS over Week 1, was greater in the levocetirizine group than in the desloratadine group.
The mean (SD) reduction in T5SS reached –6.39 (2.23) in subjects who remained treated with levocetirizine and –5.59 (2.86) in subjects who remained treated with desloratadine. The mean (SD) reduction in T5SS reached –4.09 (2.71) in subjects who switched from levocetirizine to desloratadine and –3.59 (2.70) in subjects who switched from desloratadine to levocetirizine.



The same trends were observed for the **individual symptom scores**.

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2. Global Evaluation Scale

Results from a global assessment of disease evolution performed by the subjects at the end of Week 1 did not differ significantly between treatment groups (p = 0.080). An improvement ("marked", "moderate" and "slight" – three categories combined) was reported by 91% of the subjects treated with levocetirizine and 83% of the subjects treated with desloratadine.

3. Decision to switch to the alternative treatment and reasons

The most common reason to switch to the alternative treatment, at the end of Week 1, was the lack of efficacy: 47.4% of the subjects under levocetirizine and 51.4% of the subjects under desloratadine. Correlation results between the decision to switch to the alternative treatment at the end of Week 1 and the mean individual symptom scores (ISS) over Week 1 indicate an overall significant increase in the probability of switching to the alternative treatment when individual symptom scores are increasing. Whether the subjects were assigned to desloratadine 5 mg or to levocetirizine 5 mg did not seem to affect this probability of switching to the alternative treatment.

4. Satisfaction / dissatisfaction with the choice made

At the end of Week 3, only a few subjects who decided to keep the same treatment during the whole Study were dissatisfied with their choice (6.8% in the desloratadine Group and 4.7% in the levocetirizine Group). Among those who decided to switch, the proportion (20%) of subjects dissatisfied with the switch from levocetirizine to desloratadine was nearly twice higher than the proportion (11.1%) of subjects dissatisfied with the switch from desloratadine to levocetirizine.

- **Exploratory endpoints**

1. Symptom scores over time

Over Week 1, the mean (SD) T4SS decrease reached - 4.39 (2.25) in the levocetirizine group and - 3.85 (2.47) in the desloratadine group.
Over Week 2, the lowest mean T4SS was obtained for the treatment sequence LCTZ/LCTZ followed by DESL/DESL. Mean scores were very close for DESL/LCTZ and LCTZ/DESL. The trends are thus similar to those observed for the mean T5SS.
Between Week 1 and Week 3, the best improvement in the mean T4SS was obtained for the treatment sequence DESL/LCTZ followed by LCTZ/DESL.
In Subjects who switched to the alternative treatment at Week 1, the trends in T4SS and T5SS observed during the second period of the Study *i.e.* during Weeks 2 and 3 are of major interest.
The improvement gained by desloratadine was slightly lower than the one gained by levocetirizine during Week 1. However, after the switch to levocetirizine *i.e.* between Week 1 and Week 3, the T4SS and T5SS profiles of these Subjects crossed the profiles of Subjects who switched from levocetirizine to desloratadine. At Week 3 (Study End), the mean T4SS and T5SS scores were higher in Subjects who switched from desloratadine to levocetirizine than in Subjects who switched from levocetirizine to desloratadine.

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2. Time to first feeling of improvement and sufficient improvement

A feeling of **improvement** was recorded in 92% of the subjects treated with levocetirizine and in 85% of the subjects treated with desloratadine. In these subjects, the median ($Q_1 – Q_3$) time to this feeling was 4.25 (2.50 – 9.08) hours under levocetirizine and 3.04 (1.00 – 6.83) hours under desloratadine.

A feeling of **sufficient improvement** was recorded in 72% of the subjects treated with levocetirizine and in 65% of the subjects treated with desloratadine. In these subjects, the median ($Q_1 – Q_3$) time to this feeling was 19.00 (6.17 – 33.75) hours under levocetirizine and 27.25 (4.92 – 73.42) hours under desloratadine.

3. VAS Scores

Symptom relief was observed in 90% of the subjects treated with levocetirizine and in 83% of the subjects treated with desloratadine. Higher VAS scores indicate either a quicker onset of overall symptom/ blocked nose relief or a higher quality of sleep/daily activities. For both treatment groups, the VAS scores are summarized below. These results consistently show a trend according to which a quicker onset of both the overall symptom relief and the blocked nose relief and a higher quality of sleep and daily activities would have been obtained in subjects treated with levocetirizine than in subjects treated with desloratadine.

		Desloratadine 5 mg	**Levocetirizine 5 mg**
Speed of Overall Symptom Relief	Mean (SD)	5.75 (2.42)	6.27 (2.62)
	Median	6.30	7.10
	Q1 – Q3	4.00 - 7.60	4.60 - 8.00
Speed of Blocked Nose Relief	Mean (SD)	5.15 (2.56)	5.88 (2.62)
	Median	5.20	6.30
	Q1 – Q3	3.00 - 7.40	3.95 - 8.10
Impact on Quality of Sleep	Mean (SD)	6.10 (2.98)	6.34 (3.00)
	Median	6.50	6.60
	Q1 – Q3	4.50 - 8.55	4.70 - 9.20
Impact on Quality of Daily Activities	Mean (SD)	5.69 (2.98)	6.28 (2.91)
	Median	6.25	6.60
	Q1 – Q3	3.15 - 8.30	4.00 - 8.90

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SAFETY RESULTS:

The safety results obtained in this study were consistent with previous knowledge concerning levocetirizine.
The most common adverse events were headache (16.8% of subjects in the desloratadine group and 20.8% in the levocetirizine group), fatigue (7.7% of subjects in the desloratadine group and 10.4% in the levocetirizine group), diarrhoea (2.6% in the desloratadine group and 0.6% in the levocetirizine group) and epistaxis (2.6 % in the levocetirizine group).
Fatigue was reported by 30 subjects and recorded at study entry in two subjects assigned to levocetirizine.
Fatigue was considered to be related to the study drug in 6.5% of the subjects treated with desloratadine and in 9.7% of the subjects treated with levocetirizine.
Headache was considered to be related to the study drug in 2.6% of the subjects treated with desloratadine and 1.3% of the subjects treated with levocetirizine.
There was no AE leading to a permanent study drug discontinuation, no serious AE, no death recorded during the study.
No relevant change in vital signs and no relevant abnormality in physical examination was observed.

CONCLUSIONS:

Between Subjects treated either with levocetirizine 5 mg or with desloratadine 5 mg, there was no difference in the percentage of switch to the alternative treatment.

For other variables than the primary endpoint variable, the study was not powered to detect statistically significant differences between groups. However, the examination of trends indicate

1. a more pronounced improvement of T4SS and T5SS in subjects treated with levocetirizine 5 mg than in subjects treated with desloratadine 5 mg during one week. This improvement in symptom scores was not reflected in the switching behaviour in spite of a significant correlation to symptom scores. Thus, the primary endpoint does not appear to be sufficiently discriminative to be useful in clinical trials. The main reason may be confounding of the switching decision by unreported curiosity.
   Furthermore, the subjects involved in this Study did not have the opportunity to compare the two treatments before taking the decision to switch to the alternative treatment or to pursue the same treatment. This led to switch decisions based on individual expectations, rather than on a sound experience with the two drugs. This is re-inforced by the fact that, at the time of the decision, the subjects who decided to switch to the alternative treatment (levocetirizine or desloratadine) were significantly less relieved by their first treatment that the-ones who decided to stick with their first treatment.

2. a higher satisfaction with levocetirizine than with desloratadine. In particular, the percentage of subjects dissatisfied with the switch from levocetirizine to desloratadine was nearly twice higher than the percentage of subjects dissatisfied with the switch from desloratadine to levocetirizine.

3. a trend for a faster overall symptom relief, a faster blocked nose relief, a higher satisfaction with quality of sleep and daily activities, and a better blocked nose relief.

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4. the incidence of feeling of no improvement in the desloratadine group was about twice of that in the levocetirizine group.

5. the first feeling of sufficient improvement would have occurred earlier in subjects treated with levocetirizine than in subjects treated with desloratadine.

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

Report Date: 09-Mar-2006