A00392, 2004-003858-26

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.

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Sponsor:

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

Official study title:

A pilot, open, monocenter, randomized two parallel groups, clinical efficacy trial: Comparison continuous versus on demand regimen of treatment with levocetirizine 5 mg oral tablets, once a day, in adults suffering from persistent allergic Rhinitis (PER) over six months

2. SYNOPSIS

Name of Sponsor/Company: UCB S.A.–Pharma Sector Belgium	Individual Study Table Referring to Module 5.3.5.2	*(For National Authority Use only)*
Name of Finished Product: Xyzal®	Volume:	
Name of Active Ingredient: Levocetirizine dihydrochloride	Page:	

Title of Study:
A pilot, open, monocenter, randomized two parallel groups, clinical efficacy trial: Comparison continuous *versus* on demand regimen of treatment with levocetirizine 5 mg oral tablets, once a day, in adults suffering from PErsistent allergic Rhinitis (PER) over six months.

Investigator(s):
[redacted]

Study Center:
One

Publication:
None

Studied Period (years):	**Phase of Development:**
First subject enrolled: 11-Mar-2005 Last subject enrolled: 29-Nov-2005	Phase IV–Therapeutic use

Objectives:
Designed as a pilot study, this study aimed to estimate the treatment of the continuous regimen with levocetirizine 5 mg tablets compared to the on demand regimen.

Primary objective:

- To investigate and compare in adults suffering from PER continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg during six months as measured by the evolution of the mean weekly T4SS (T4SS: sum of the individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus, evaluated on a 4-point 0 to 3 scale retrospectively over the past 24 hours).

Secondary objectives:

- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg as measured by the mean monthly T4SS during the six months of treatment.
- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg as measured by the evolution of the mean weekly and monthly individual symptoms scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal congestion (evaluated on a 4-point 0 to 3 scale retrospectively over the past 24 hours) during the six months of treatment.
- Evaluation of the safety profile.

Exploratory objectives:

- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg by the evolution of the inflammatory cells (leucocytes, neutrophils, eosinophils, lymphocytes) concentrations and expression of ICAM-1 in nasal scrapings at the Baseline, after one month, three months and six months of treatment.
- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg as measured by the evolution of the Rhinasthma scores from Visit 4 to Visit 9 during the treatment period of six months in all the subjects.

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- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg as measured by the weekly and monthly number of days with rhinitis symptoms (T4SS > 0) during the six months of treatment.
- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg as measured by the weekly and monthly number of days with acute rhinitis symptoms (T4SS ≥ 6) during the six months of treatment.
- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg in adults suffering from PER as measured by the mean weekly and monthly allergic rhinoconjunctivitis number of intakes of rescue medication (nasal and ocular cromoglicate) during the six months of treatment.
- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg as measured by the mean weekly and monthly number of intakes of concomitant medication (inhaled short acting β_2 agonists, antibiotics) during the six months of the treatment.
- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg as measured by direct costs parameters for PER and specific co-morbidities (asthma, sinusitis, otitis or upper respiratory infections) during the six months of treatment: mean number of days with use of concomitant medication per month, mean number of additional unscheduled physician visits per month, mean number of days hospitalized per month.
- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg as measured by indirect cost parameters for PER and specific co-morbidities (asthma, sinusitis, otitis, upper respiratory infections) during six months of treatment: mean days lost per month in absenteeism, presenteeism (work productivity lost while present at work), full usual daily activities lost and restriction over usual daily activities.
- To compare continuous *vs.* on demand regimen of treatment with levocetirizine 5 mg on quality of sleep evaluated on a VAS over the last month at the Randomization Visit (V2) and after one month (V4), two months (V5), three months (V6), four months (V7), five months (V8), and six months (V9) of treatment.
- To compare incidences of co-morbidities (asthma, sinusitis, otitis or upper respiratory infections) and acute urticaria under the two regimens of treatment over one month, two months, three months, four months, five months and six months of treatment.
- Global Satisfaction with the two regimens of treatment evaluated by both the Investigator and the Subject on a VAS (0 to 10 cm) at the end of the Study.

Methodology:

Open, monocenter, randomized, two parallel groups clinical efficacy trial comparing continuous *vs.* on demand treatment. Subjects in the "on demand" group were requested to take the drug only when symptoms were present and not as a prevention of symptoms.

The entire treatment period lasted 24 weeks and nine visits were foreseen-V1 (Screening Visit) followed by a one week Screening Period, V2 at the time of the randomization, V3 after one week and V4, V5, V6, V7, V8 and V9 after 1, 2, 3, 4, 5 and six months of treatment.

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Number of Subjects:
Planned: 100 subjects, 50 subjects per group
Screened: 66 subjects
Randomized: 62 subjects
- 31 subjects under the levocetirizine 5 mg continuous regimen
- 31 subjects under the levocetirizine 5 mg on demand regimen,

Due to poor accrual rate, the enrollment of new subjects was stopped. The recruitment period was from 11-Mar-2005 to 29-Nov-2005.

Diagnosis and Main Criteria for Inclusion:
- Male or female out subject, at least 18 years old.
- Clinical history of PER requiring treatment known at least since two years.
- Positive skin prick test (wheal > 3 mm larger than the diluent control) or RAST to HDM and Parietaria (less than one year).
- Minimum mean T4SS of six over the seven days of Baseline Period (minimum 4 days and maximum 10 days).

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

Duration of Treatment:
Exposure to levocetirizine: 24 weeks if continuous regimen, less if on demand regimen.

Reference Therapy:	**Dose and Mode of Administration:**	**Batch Number:**
NA	NA	

Criteria for Evaluation:

Efficacy:

Primary efficacy variable:
- Mean weekly T4SS (T4SS: sum of the individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus, evaluated on a 4-point 0 to 3 scale retrospectively over the past 24 hours).

Secondary efficacy variables:
- Mean monthly T4SS over the six months of treatment.
- Mean weekly and monthly individual symptoms scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal congestion (evaluated on a 4-point 0 to 3 scale retrospectively over the past 24 hours) during the six months of treatment.

Exploratory efficacy variables:
- Concentrations of inflammatory cells (leucocytes, neutrophils, eosinophils, lymphocytes) and ICAM-1 expression in the nasal scrapings at the Baseline and after 1, 3, and six months of treatment.
- Rhinasthma scores for all the subjects from Visit 4 to Visit 9 during six months of treatment.
- Mean weekly and monthly number of days with rhinitis symptoms (T4SS > 0) during the six months of treatment.
- Mean weekly and monthly number of days with acute rhinitis symptoms (T4SS ≥ 6) during the six months of treatment.
- Mean weekly and monthly number of intakes of allergic rhinoconjunctivitis rescue medication (nasal and ocular cromoglicate) during the six months of treatment.

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- Mean weekly and monthly number of intakes of concomitant medication (inhaled short acting β_2 agonists, antibiotics) during the six months of the treatment.
- Mean number of days with use of concomitant medication per month, mean number of additional unscheduled physician visits per month, mean number of days hospitalized per month for PER and co-morbidities during the six months of treatment.
- Mean number of days absenteeism per month, presenteeism, usual daily activities lost and restriction in usual daily activities for PER and its co-morbidities evaluated during the six months of treatment.
- Quality of sleep scores evaluated on a VAS (0 to 10 cm) over the last month at the Randomization Visit and after one month, two months, three months, four months, five months and six months of treatment.
- Incidences of co-morbidities (asthma, sinusitis, otitis, upper respiratory infections) and acute urticaria under the two regimens of treatment over one month, two months, three months, four months, five months and six months of treatment.
- Global Satisfaction evaluated by both the Investigator and the subject on a VAS (0 to 10 cm) at the end of the Study.

Safety variables:
Physical examination and frequency, severity, nature and duration of adverse events reported by the subjects during the whole duration of the Study.

Statistical Methods:
The primary analysis was the evaluation of the primary efficacy variable on the basis of the ITT Population. The ITT Population consisted of all randomized subjects.
All tests were performed two-sided at the 5% level of significance.
The primary efficacy variable was analyzed by means of repeated measures analysis of variance controlled for the factors treatment, week, and treatment by week interaction, and with the Baseline values as covariate. This analysis was performed using SAS PROC MIXED. The treatment effect on each treatment week was estimated by means of a 95% confidence interval obtained from the repeated measures model.
Safety assessments were based upon physical examinations and the recording of adverse events.

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SUMMARY CONCLUSIONS

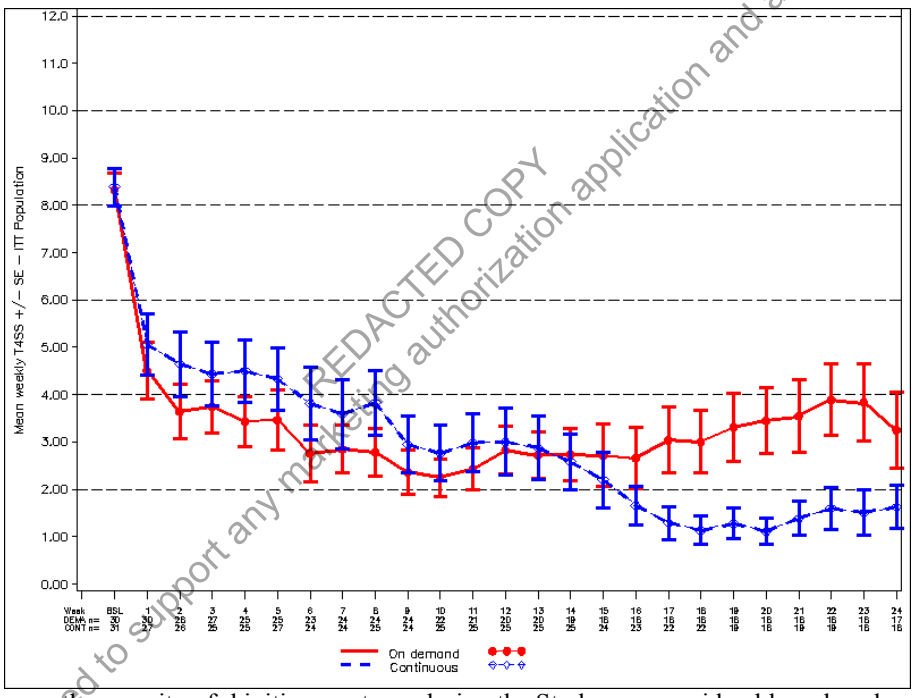
EFFICACY RESULTS:

Sixty-two (62) randomized subjects were included in the ITT Population and fifty-two (52) subjects were included in the PP population. The proportion of drop-outs was important, especially under the on demand regimen (29.0% under the continuous regimen and 41.9% under the on demand regimen).

During Baseline Period, the mean (SD) T4SS were similar in both treatment regimens: 8.39 (2.22) under the continuous regimen and 8.33 (1.95) under the on demand regimen.

Primary efficacy variable

Mean Weekly T4SS (± SE) - ITT Population



For both regimens, the severity of rhinitis symptoms during the Study was considerably reduced compared to the Baseline symptoms.

The mean T4SS over the Total Treatment Period was lower under the continuous regimen (adjusted mean ± SE = 2.89 ± 0.43) than under the on demand regimen (adjusted mean ± SE = 3.15 ± 0.44). The difference between the two regimens was 0.27 [-0.96; 1.50] (adjusted mean difference [95% CI]) and was not statistically significant (p = 0.667).

From Week 1 to Week 13, inclusive, the rhinitis symptoms were slightly more severe under the continuous regimen. None of the differences between the two regimens was statistically significant.

At Week 14 and until the end of the Study (Week 24), these symptoms were less severe under the continuous regimen compared to the on demand regimen.

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The differences between the two regimens were statistically significant from Week 17 to Week 23, in favor of the continuous regimen.
The highest mean difference between the two regimens was obtained at Week 20 and estimated at 2.06 (95% CI [0.66; 3.47]; p = 0.004), in favor of the continuous regimen.
Furthermore, under the on demand regimen, the symptoms increased after Week 16 and until Week 23. Nevertheless, these profiles should be considered with caution since the number of subjects decreased substantially over time: at Week 24, only 57.4% of the subjects remained in the Study[a].
The primary endpoint results on the PP Population were similar to the results obtained on the ITT Population. During the Total Treatment Period, the difference between the two regimens was not statistically significant (p = 0.863). The differences between the two regimens were statistically significant from Week 18 to Week 21. The highest difference for the mean T4SS between the two regimens, reached at Week 20, was 2.09 (95% CI [0.37; 3.81]; p = 0.017), in favor of the continuous regimen.

Secondary efficacy variables

- From Month 1 to Month 3, inclusive, the rhinitis symptoms (measured by mean monthly T4SS) were slightly more severe under the continuous regimen. None of the differences between the two regimens was statistically significant. From Month 4 to Month 6, the rhinitis symptoms were more severe under the on demand regimen compared to the continuous regimen. The highest difference for the mean T4SS between the two regimens, equal to 1.57 (95% CI [0.28; 2.87]), was reached at Month 5 and was statistically significant (p = 0.018).
- For sneezing score and rhinorrhea score, the two regimens were significantly different at Month 5 and 6, in favor of the continuous regimen. For nasal pruritus score, the highest difference between the two regimens was reached at Month 5, but was not significant. For ocular pruritus score and nasal congestion score, the highest differences between the two regimens were reached at Month 5 and were statistically significant, in favor of the continuous regimen. At that time, the adjusted mean [95% CI] difference was 0.36 [0.06; 0.65] (p = 0.019) for the ocular pruritus score and 0.44 [0.01; 0.88] (p = 0.046) for the nasal congestion score.
- The severity of rhinitis symptoms (measured by the change from Baseline in mean T4SS) was reduced more effectively under the continuous regimen (adjusted mean ± SE at Month 6 = -6.12 ± 0.63) compared to the on demand regimen (adjusted mean ± SE at Month 6 = -4.02 ± 0.63), taking into account the level of symptoms at the Baseline. The difference of the change from Baseline in mean T4SS between the two regimens was statistically significant during Months 5 and 6, in favor of the continuous regimen.
- For the individual symptom scores, the mean change from Baseline in sneezing score, as well as in rhinorrhea score, of the two regimens was statistically significantly different at the end of the Study (Month 5 and Month 6), in favor of the continuous regimen. For nasal pruritus and ocular pruritus, the same significant differences were observed but only during Month 5; nasal congestion did not reach statistical significance at Month 5 (p = 0.059). Two other significant results were observed, but in favor of the on demand regimen: rhinorrhea during Month 1 and nasal pruritus during Month 3.

[a] Percentage calculated on the sixty one subjects for whom a Baseline score was available

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Exploratory efficacy variables

- Under the continuous regimen, the amount of neutrophils increased after one month (median = 3.50, Q1 = 1.00, Q3 = 7.00) and afterwards returned to Baseline value (median = 1.00, Q1 = 0.00, Q3 = 4.00). In contrast, under the on demand regimen, the amount of neutrophils increased up to three months (median = 4.00, Q1 = 2.00 , Q3 = 10.00) and remained constant thereafter. A slight decrease was observed in eosinophils under the continuous regimen and not under the on demand regimen. The median (Q1, Q3) percentages of lymphocytes were equal to zero for all the time points and for both treatment regimens. Concerning the macrophages, a slight increase was observed in both regimens. The epithelial cells decreased slightly under the on demand regimen (median at baseline = 93.0% and at 6 months = 90.0%, [Q1, Q3] = [89.00, 95.50] and [86.00, 96.00], respectively), while no change was observed under the continuous regimen (median at baseline = 94.5% and at 6 months = 94.0%, [Q1, Q3] = [89.00, 96.00] and [87.00, 96.00], respectively). The ICAM-1 parameter increased slightly after three and six months of treatment under the continuous regimen and after six months of treatment under the on demand regimen.
- The comfortable days (T4SS = 0: days without symptoms) were absent until Month 2 for both treatment regimens; thereafter, the subjects under the continuous regimen had more comfortable days than the subjects under the on demand regimen.
- Until Month 3, the median percentage of days with acute rhinitis symptoms (T4SS ≥ 6) was higher for the subjects under the continuous regimen compared to those under the on demand regimen. From Month 4 to the end of the Study, the median percentage of days with acute rhinitis symptoms was 0% under the continuous regimen and was between 1.8 to 3.7% under the on demand regimen.
- After six months of treatment, the quality of sleep was improved compared with the start of the Study under both levocetirizine 5 mg regimens.
- For both regimens, the consumption of rescue medication was globally low, especially for ocular cromoglicate. Consumption of nasal cromoglicate decreased during the last three months under the continuous regimen but remained almost constant under the on demand regimen.
- Only three subjects had a co-morbidity: 'Upper respiratory infection' for two subjects and 'Otitis episode' for one subject. These three subjects were all under the on demand regimen.
- The mean VAS of the treatment satisfaction assessed by the subject was similar under both regimens. The Investigator's evaluation was slightly better under the continuous regimen compared to the on demand regimen.
- The decrease in factor and total scores of the Rhinasthma questionnaire was substantial for all subjects but did not show any clear difference between the two treatment regimens.
- The consumption of concomitant medications for allergic rhinitis or its co-morbidities was low in both regimens. No subjects required additional physician visits under the continuous regimen, whereas, four subjects needed additional physician visits under the on demand regimen. There was only one concomitant medical procedure (under the on demand regimen) and no hospitalization.
- No clear difference between the treatment regimens could be established for the direct and the indirect costs.

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SAFETY RESULTS:

The safety of both treatment regimens was excellent, as expected from the knowledge of levocetirizine 5 mg. Only four subjects (13.3%) under the continuous regimen and 10 subjects (31.3%) under the on demand regimen experienced at least one treatment-emergent AE. The most common treatment-emergent AE was 'Somnolence' and concerned one subject under the continuous regimen and three subjects under the on demand regimen. All the AEs termed 'Somnolence' were considered as drug-related. In addition, one subject, under the on demand regimen, withdrew due to an AE ('Somnolence'). All AEs were consistent with the administration of an H_1 receptor antagonist. Neither SAE, nor death occurred during the trial.

CONCLUSIONS:

In conclusion, this Pilot Study provided an estimation of the difference in symptom severity between the continuous regimen and the on demand regimen of treatment with levocetirizine 5 mg. Over a treatment period of six months, both treatment regimens were highly effective in reducing the symptoms but the difference between the two regimens was not significant.

Nevertheless, it is noticeable from the curve profiles that the treatment period is divided into two phases: an early phase (up to three or four months) with no significant difference between the two regimens, followed by a later phase (after three or four months) when the efficiency of a long-term therapy under a continuous regimen becomes evident. This difference in efficacy was not due to a difference in compliance between the two regimens since the compliance remained constant throughout the Study in both groups.

The results show the beneficial effect of a continuous long-term therapy with levocetirizine 5 mg compared to an on demand therapy in subjects suffering from PER. Moreover, this long-term administration did not lead to any particular safety concerns, confirming the good safety profile of levocetirizine 5 mg.

Report Date: 12-Jun-2007