Copyright © 2006 UCB, Inc. All rights reserved.

Clinical Study Summary

DEV/CCM/03345.2007

CT Registry ID#: *NCT00152464*
Study No.: A00309

These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.

.

Based on Clinical Study Report document reference code: RRCE06L3017

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Xyzal®Oral Drops	Levocetirizine	Asthma free young atopic children sensitized to grass pollen and/or house dust mite allergens

Name of Sponsor/Company: UCB Pharma SA

Title of Study: The Early Prevention of Asthma in Atopic Children (EPAAC™) study
A multi-country, double blind, placebo-controlled, randomized, parallel group trial: Evaluation of the efficacy and safety of levocetirizine (5 mg/mL oral drops - 0.125 mg/kg b.w. *b.i.d.*) administered for 18 months in preventing the onset of asthma in 12 to 24 months old children who suffer from atopic dermatitis and are sensitized to grass pollen and / or house dust mite allergens.

Investigator(s) (number only):	87
Study Center(s) (number only):	87

Length of Study:		**Phase of Development:**	Phase III (therapeutic confirmatory)
Date first patient enrolled:	20-Mar-2002		
Date last patient completed:	15-Mar-2006		

Abstract:
The primary study objective was to assess the efficacy of levocetirizine (LCTZ) 1.25 mg/kg body weight twice daily given as 0.5 mg/mL oral solution over 18 months of treatment compared with placebo (PBO) to prevent the onset of asthma in 12- to 24-month-old atopic children who suffer from atopic dermatitis (AD) and were sensitized to grass pollen and / or house dust mite allergens and are at risk of developing asthma, with a follow-up 6 months after the end of treatment.
Secondary objectives were to assess the safety of LCTZ in a pediatric population, and to describe the symptoms of asthma and the incidence of urticaria and medications used for asthma or AD.
Exploratory objectives were to describe the primary and secondary objectives 6 months after completion of treatment, to assess the onset of asthma based on wheezing symptoms only, the onset and severity of AD, psychomotor development, and the sensitization to allergens.
Efficacy: the onset of asthma was based on the incidence of symptoms of asthma (wheezing or nocturnal cough); the use and percentage of days of use of asthma and AD medications; incidence and episodes of urticaria; incidence and severity (SCORAD index) of AD; carer's weekly assessment of severity of AD and pruritus. Safety was assessed by physical examination, adverse events (AEs), serious adverse events (SAEs), body mass, hematology and biochemistry laboratory parameters, and the global psychomotor development (GPD) questionnaire. AEs were reported by subjects' parents/legally acceptable representative(s) on the self assessment Daily Record Card (DRC), which was also assessed by the Investigator. Two blood samples were collected for clinical laboratory tests at screening (8 mL at Visit 1) and at the end of the treatment (10 mL at Visit 9).
The primary efficacy variable was analyzed on the ITT population, using a Cox proportional hazard regression model including a term for treatment and a term for each of the factors used in the randomization process. The hazard ratio for the treatment effect between LCTZ and PBO and corresponding 95% confidence interval was estimated by fitting this model.
Descriptive statistics consisted of the number and percentage of subjects with asthma during the treatment period and the cumulative incidence curves of asthma, estimated using the Kaplan-Meier approach. Safety analyses were performed on the ITT population; safety parameters were analyzed descriptively.

Copyright © 2006 UCB, Inc. All rights reserved.

CT Registry ID#: *NCT00152464*
Study No.: A00309

Publication Reference(s) based on the study:
None

Number of Patients:	**Levocetirizine**	**Placebo**
Planned, N:	250	250
Randomized, N:	258	256
Treated, N	255	255
Completed, n (%):	219 (85.9)	215 (84.3)
Number of Patients Withdrawn, n (%):	36 (14.1)	40 (15.7)
Adverse Events, n (%):	6 (2.4)*	3 (1.2)
Other Reasons, n (%):	30 (11.7)	37 (14.5)
Demography:		
Gender (% Females/ % Males):	39/61	36/64
Age (months), mean (SD):	19.28 (3.94)	19.42 (3.86)
Caucasian, n (%):	225 (88.2)	217 (85.1)

* One subject was withdrawn before receiving study medication.

Safety Outcomes:

Summary of treatment emergent adverse events (TEAEs), deaths, other serious adverse events, post-treatment AEs, and other safety:

The mean exposure to LCTZ was 17.33 months (± 3.50) at a dose of 0.125 mg/kg mg/kg body weight twice daily.

Almost all subjects in both groups reported at least one TEAE (96.9% of LCTZ subjects; 95.7% of placebo subjects). Drug related AEs were reported by 13 [5.1%] LCTZ subjects and 16 [6.3%] of placebo subjects). Few AEs lead to discontinuation of study medication (5 [2.0%] LCTZ subjects; 3 [1.2%] placebo subjects).

The most frequent TEAEs that occurred during treatment were related to infections, gastrointestinal disorders, and respiratory disorders (tabulated below). The most common TEAEs were upper respiratory tract infection (52% LCTZ and 49% placebo subjects), pyrexia (33% LCTZ and 28% placebo subjects), nasopharyngitis (31% LCTZ and 29% placebo subjects), rhinitis (29% LCTZ and 28% placebo subjects), cough (23% LCTZ and 27% placebo subjects), pharyngitis (23% LCTZ and 21% placebo subjects), and gastroenteritis (23% LCTZ and 22% placebo subjects). All other TEAEs occurred in <20% of subjects.

There were no deaths. SAEs were reported by fewer LCTZ than placebo subjects (12.2% of LCTZ subjects; 14.5% of placebo subjects). Only one SAE was considered related to study medication (a subject treated with placebo; elevated liver enzymes). The most frequently reported SAEs according to primary SOC were respiratory, thoracic and mediastinal disorders (4.7% LCTZ subjects; 7.5% placebo subjects), infections and infestations (5.9% LCTZ subjects; 5.1% placebo subjects), and skin and subcutaneous tissue disorders (1.6% LCTZ subjects; 3.5% placebo subjects). Febrile convulsions were reported as an SAE by 1.4% LCTZ subjects and no placebo subjects and the possibility that LCTZ played a role cannot be conclusively ruled out.

TEAEs leading to withdrawal were as follows: LCTZ – weight increased (1 subject), hypersensitivity (2 subjects), acute lymphocytic leukemia (1 subject), failure to thrive (1 subject), and tonsillitis and dehydration (1 subject); placebo – varicella (1 subject), atopic dermatitis (1 subject), and AST increased (1 subject). LCTZ was not implicated in the development of the SAE acute lymphocytic leukemia.

The incidence of post-treatment AEs (i.e., during the 6-month post-treatment follow-up phase) was lower for subjects who had previously been treated with LCTZ (70.9%) than for those had had received placebo (81.7%). The most frequently reported category of AEs (according to primary SOC) was infections and infestations; the incidence was lower for LCTZ subjects (63.6%) than for placebo subjects (75.7%). Respiratory, thoracic and mediastinal disorders were reported by 15.5% of LCTZ and 14.7% of placebo subjects; general disorders and administration site conditions were reported by 11.8% of LCTZ and 14.7% of placebo subjects. Other AEs according to SOC were

Copyright © 2006 UCB, Inc. All rights reserved.

CT Registry ID#: *NCT00152464*
Study No.: A00309

reported by < 10% of subjects in either group
Most reported AEs were mild and could be attributed to intercurrent respiratory or gastrointestinal infections, exacerbation of allergic disorders, or age-related concerns and the age-related common childhood conditions in the treated target-population, rather than to medication-related AEs.
None of the changes in hematology or biochemistry laboratory parameters were considered clinically significant. No clinically relevant changes in body mass or GPD were noted.
In summary, during the EPAAC™ trial, there were few AEs attributed to study medication or leading to permanent discontinuation. Despite the seemingly high doses of LCTZ administered, the safety profile of LCTZ was similar to that of placebo. Also, height and body mass increased with increasing age, as expected, in both treatment groups. No effects on development of gross motor skills, fine motor skills, or speech and language skills were noted. Changes in hematology and biochemistry tests were similar in the LCTZ and placebo groups and reflected normal development and maturation of organ function. This study, one of the longest prospective, randomized, double-blind, placebo-controlled investigations of the safety of any H_1-antihistamine ever conducted in any age group, confirmed the safety of the H_1-antihistamine LCTZ in young atopic children.

Treatment Emergent Adverse Events (ITT population):	**Levocetirizine (N=255)**	**Placebo (N=255)**
Patients with at least 1 TEAE, n (%):	247 (96.9)	244 (95.7)
Patients with TEAEs (by Primary System Organ Class)	*n (%) [n considered drug-related by the Investigator]*	
Blood and lymphatic system disorders	7 (2.7)	10 (3.9)
Congenital, familial and genetic disorders	3 (1.2)	1 (0.4)
Ear and labyrinth disorders	6 (2.4)	10 (3.9)
Eye disorders	55 (21.6)	51 (20.0)
Gastrointestinal disorders	112 (43.9)	98 (38.4)
General disorders and administration site conditions	90 (35.3)	79 (31.0)
Immune system disorders	11 (4.3)	24 (9.4)
Infections and infestations	244 (95.7)	235 (92.2)
Injury, poisoning and procedural complications	41 (16.1)	24 (9.4)
Investigations	1 (0.4)	3 (1.2)
Metabolism and nutrition disorders	7 (2.7)	7 (2.7)
Musculoskeletal and connective tissue disorders	6 (2.4)	4 (1.6)
Neoplasms benign, malignant and unspecified	2 (0.8)	1 (0.4)
Nervous system disorders	7 (2.7)	7 (2.7)
Psychiatric disorders	7 (2.7)	12 (4.7)
Reproductive system and breast disorders	5 (2.0)	7 (2.7)
Respiratory, thoracic and mediastinal disorders	92 (36.1)	101 (39.6)
Skin and subcutaneous tissue disorders	40 (15.7)	55 (21.6)
Death, SAEs, and Other SAEs:		
Deaths, n (%)	0	0
SAEs, n (%)	31 (12.2)	37 (14.5)
Drug-related SAEs, n (%)	0	1 (0.4)

Copyright © 2006 UCB, Inc. All rights reserved.

CT Registry ID#: *NCT00152464*
Study No.: A00309

Primary Efficacy Outcome:
Over the first 6 months of treatment the incidence of asthma was lower in the LCTZ group than in the placebo group in the ITT population. Thereafter, the Kaplan-Meier curves were increasingly similar and from 8 to 18 months were almost superimposable. The hazard ratio over the 18-month treatment period was 1.002 (p = 0.991; 95% CI: 0.750, 1.338). Statistically significantly fewer LCTZ subjects (27.5%) had episodes of urticaria during the 18-month treatment period than placebo subjects (41.6%), $p < 0.001$.

Date of Report: 03-Aug-2007