1. **TITLE PAGE**

<table>
<thead>
<tr>
<th>Test Drug</th>
<th>Cetirizine dihydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol No.:</td>
<td>MPCE93D0602/5V (Amendment No. 7 – 03 MAR 1999)</td>
</tr>
<tr>
<td>Study Title:</td>
<td>The Early Treatment of the Atopic Child (E.T.A.C.): Evaluation of the efficacy and safety of cetirizine in preventing the onset of asthma in children who suffer from atopic dermatitis. A multi-country, double blind, randomized, placebo-controlled trial.</td>
</tr>
<tr>
<td>Study Subtitle:</td>
<td>Additional 24-month post-treatment follow-up (Study Period V).</td>
</tr>
</tbody>
</table>

**Development Phase:** Phase III (therapeutic confirmatory)

**Indication:** Asthma prevention in atopic children

**GCP statement:** The study described within this report was conducted in accordance with the ICH E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the principles that have their origin from the Declaration of Helsinki and local laws and regulations.

**Dates of inclusion of first subjects:**
- Period I-II (18-month treatment): 17-FEB-1994
- Period III (6-month follow-up): 21-SEP-1995
- Period IV (additional 12-month follow-up): 24-MAY-1996
- Period V (additional 24-month follow-up): 13-JAN-1998

**Dates of completion of last subjects:**
- Period III (6-month follow-up): 10-MAR-1998
- Period IV (additional 12-month follow-up): 11-MAR-1999
- Period V (additional 24-month follow-up): 07-MAR-2001

**Dates of reports:**
- Period I-II (18-month treatment): 24-JUN-1999
- Period III (6-month follow-up): 22-AUG-2000
- Period IV (additional 12-month follow-up): 22-AUG-2000
- Period V (additional 24-month follow-up): 23-JAN-2003

**Present report written by:** Hamdy Adham, MD  
UCB S.A. – Pharma Sector – Clinical Development Europe  
Belgium

**Sponsor’s medical responsible (CRP):** Fabienne Staelens, MD  
UCB S.A. – Pharma Sector – Clinical Development Europe  
Belgium

**Sponsor’s contact person (CTM):** Stefaan Roobaert  
Tel.: +32-2-386 23 30  Fax: +32-2-386 24 20

**Sponsor:** UCB S.A. – Pharma Sector  
Chemin du Foriest  
B-1420 Braine l’Alleud  
Belgium

**Principal Investigators:** See the list of Investigators in Section 6.1.

---

Confidential  
This report is the property of UCB S.A. and may not – in full or in part – be passed on, reproduced, published or otherwise used without the express permission of UCB S.A.
2. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>UCB S.A. – Pharma Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Finished Product:</td>
<td>Zyrtec®</td>
</tr>
<tr>
<td>Name of Active Ingredient:</td>
<td>Cetirizine dihydrochloride</td>
</tr>
<tr>
<td>Subtitle of the Study:</td>
<td>Additional 24-month Post-Treatment Follow-Up (Period V).</td>
</tr>
<tr>
<td>Investigators and Study centers:</td>
<td>The ETAC™ Study group (see Section 6.1).</td>
</tr>
<tr>
<td>No publications related to Study Period V were issued by the time this report was edited.</td>
<td></td>
</tr>
</tbody>
</table>
**Name of Sponsor/Company:**
UCB S.A. – Pharma Sector

**Individual Study Table Referring to Part IV b of the Dossier:**

<table>
<thead>
<tr>
<th>Name of Finished Product:</th>
<th>Volume:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zyrtec®</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of Active Ingredient:</th>
<th>Page:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine dihydrochloride</td>
<td></td>
</tr>
</tbody>
</table>

**Phase of development:**
Phase III (therapeutic confirmatory).

**Objectives:**
The objectives of Period V of the study were the following:
- To assess the maintenance of the therapeutic effect,
- To confirm cetirizine long-term safety (3.5 years after the end of an 18-month treatment),
- To study standard lung functions in this group of high-risk children (not possible before the age of six years),
- Epidemiology: to collect data about the natural course of allergy.

**Methodology:**
This was a double blind, randomized, parallel group, placebo-controlled study. The primary endpoint for efficacy was the time to onset of asthma, defined as 3 separate episodes of nocturnal cough with sleep disturbances, lasting for 3 consecutive nights, or 3 separate episodes of wheezing, in a clinical setting where asthma is likely and other conditions have been excluded. Symptoms were recorded by the parents/legally acceptable representatives on diary cards and validated by the Investigator at the next visit.

The data related to the primary endpoint for all subjects were reviewed and verified by a Data Review Committee consisting of members from UCB and from the Scientific Advisory Board (SAB). No study medication was given during this 24-month Follow-Up Period (Period V). Subjects were followed on a 6-month basis (Visit 12 to Visit 15), using the same methodology as during the Treatment Period.

**Number of subjects:**
**Planned:** 700 subjects.
Information is available on 830 screened subjects. Eight subjects did not receive a treatment number, consequently, 822 subjects were actually randomized to a treatment group (Period II).

**Analyzed in the Treatment Period:**
- For efficacy: of the 822 randomized subjects, 5 subjects did not receive any treatment and follow-up data were not available for 22 subjects. Therefore, 795 subjects constituted the ITT population and were considered in the efficacy analysis: 397 subjects in the placebo group and 398 subjects in the cetirizine group.
- For safety: all the 795 subjects who received at least one dose of the study medication and had at least one follow-up safety parameter reported were considered for the safety analysis.

**Analyzed in Period V (24-month Follow-Up Period) for efficacy and safety:** 335 subjects: 169 subjects in the placebo group and 166 subjects in the cetirizine group.
### Name of Sponsor/Company:
UCB S.A. – Pharma Sector

### Individual Study Table
Referring to Part IV b of the Dossier:

### Name of Finished Product:
Zyrtec®

### Volume:

### Name of Active Ingredient:
Cetirizine dihydrochloride

### Page:

### Diagnosis and main criteria for inclusion:
For the treatment period:
Subjects aged 1-2 years with symptoms of atopic dermatitis for at least one month before enrolment according to the modified criteria for diagnosis of atopic dermatitis in infants. Subjects had to have at least one parent or sibling with a history of atopic disease (atopic dermatitis, allergic rhinitis or asthma).

For Period V (24-month Post-Treatment Follow-Up Period):
All the subjects who were included at qualifying centers and participated in the previous Follow-Up Periods (Periods III and IV).

### Test product, dose and mode of administration:
For the treatment period:
Cetirizine 0.25 mg/kg b.i.d., orally.

**Batch numbers:** 66 and 68.

For Period V (24-month Post-Treatment Follow-Up Period):
Not applicable.

### Duration of treatment:
For the treatment period:
18 months.

For Period V (24-month Post-Treatment Follow-Up Period):
Not applicable.

### Reference therapy, dose and mode of administration:
For the treatment period:
Placebo in a dosage equivalent to that of the active substance, orally.

**Batch numbers:** 65P and 67P.

For Period V (24-month Post-Treatment Follow-Up Period):
Not applicable.

### Criteria for evaluation:
**Efficacy:**
For the treatment period:
The primary endpoint was the time to onset of asthma. The definition of asthma was based on a predefined number of episodes of wheezing and nocturnal cough. To be considered as clinically significant, a risk reduction of at least 30% had to be observed at the end of the Treatment Period.

Secondary endpoints:
1. Asthma: the frequency and severity of asthmatic episodes, based on the classes of treatments used for prevention or treatment, as well as the number of days of use of such treatments.
2. Atopic dermatitis: the standard score for signs and symptoms of AD (SCORAD system), the classes of treatments used and the number of days of their use.

For Period V:
The evaluation of efficacy was primarily based on the time to onset of asthma over the whole 60-month period of the study. As exploratory variables, standardized lung function tests were performed for this high-risk group of children (flow volume slope before and after β2 mimetic intake) that were not possible to perform before the age of six years.
<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>Individual Study Table Referring to Part IV b of the Dossier:</th>
<th>(For National Authority Use only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCB S.A. – Pharma Sector</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of Finished Product:</th>
<th>Volume:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zyrtec®</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of Active Ingredient:</th>
<th>Page:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine dihydrochloride</td>
<td></td>
</tr>
</tbody>
</table>

**Safety:**

For the treatment period:
The safety parameters were vital signs, physical examination, adverse events, intercurrent diseases, ECG parameters, blood chemistry, hematology and urinalyses. Development assessments were performed, using the Behavioral Screening Questionnaire (BSQ), the McCarthy test and the General Medical Questionnaire (GMQ).

For Period V:
The safety parameters consisted of physical examination (weight and height), concomitant medication and adverse events.

**Statistical methods:**
The occurrences of asthma were examined by means of Kaplan-Meier survival curves. The differences between the curves were analyzed using the logrank test and estimated by means of relative risk with its 95% confidence interval. Homogeneity of treatment effect across IgE levels at baseline was performed using the asymptotic Chi-square inference based on the Breslow-Day test. An exploratory analysis using the Cox proportional hazard model was performed as well to investigate the effects of different subgroup variables (based on IgE levels at baseline). The secondary variables were analyzed by means of a t-test or Mann-Whitney test, when appropriate. Fisher’s exact test was used to evaluate adverse event data. In addition, descriptive statistics (number of observations, mean, median, standard deviation, minimum and maximum values) were used for the presentation of lung function data in Period V.

**SUMMARY – CONCLUSIONS:**

**EFFICACY RESULTS:**

**Study Period II (Treatment period - reported in full in report MRCE98L1301):**

**Efficacy results:**

In the ITT population, the incidence of asthma was 38.0% in the placebo group, as expected in the protocol, versus 37.7% in the cetirizine group. There was no statistically significant difference between the two treatment groups in terms of the number of subjects developing asthma or the time to onset of asthma over the 18-month Treatment Period, using either the ITT population or the PP population.

In the placebo group, the risk of developing asthma was significantly higher in subjects with raised levels of total IgE (≥ 30 kIU/L) (RR of 1.30), or specific IgE (≥ 0.35 kIU/L) for grass pollen, house dust mites (HDM) or cat dander (RR between 1.42 and 1.68) compared to subjects with normal levels of IgE at baseline. The findings with grass pollen have never been demonstrated before.

Compared to placebo, cetirizine significantly prevented the occurrence of asthma in subjects sensitized to grass pollen [RR = 0.47, 95% CI (0.26; 0.86)] or to HDM [RR = 0.56, 95% CI (0.35; 0.89)]. There was only a limited overlap between subjects with elevated IgE to grass pollen and HDM, therefore, they were considered as independent. The analysis in the high-risk groups used the same endpoint (Kaplan-Meier for the onset of asthma), the same statistical test (logrank), the same cut-off for type I error (p < 0.05) and the same magnitude of the difference between groups (at least a 30% risk reduction) as for the primary objective of the study.

In subjects who became asthmatic, the severity and the frequency of episodes of asthma did not differ.
between the treatment groups. However, the mean consumption of anti-asthmatic medication was lower in the cetirizine group for each of the three main classes of medicaments.

Regarding atopic dermatitis, the study showed a continuous decline in the intensity of signs and symptoms over time in both groups. There was no treatment effect on the SCORAD (score for atopic dermatitis) and sub-scores. The number of subjects who took oral anti-histamines as rescue medication was significantly less in the cetirizine group (p = 0.030). In subjects with a high SCORAD index at baseline, a corticosteroid-sparing effect (significant reduction of the percentage of days of use of moderate to potent topical corticosteroids, p = 0.014) was observed in the cetirizine group compared to the placebo group.

Safety results:
The adverse events profile was similar in the two treatment groups. There was no significant difference between the groups for neurological or cardiovascular signs or symptoms. Many infants received macrolide co-medication, without any untoward cardiovascular effect. Some laboratory results differed between the groups, but none were considered as clinically significant. Significantly fewer subjects reported urticaria as an adverse event in the cetirizine group (p < 0.001) during the treatment period. This effect disappeared after stopping the study medication.

Study Period V (additional 24-month Follow-Up Period):
Efficacy results:
Prevention of asthma:
In the cetirizine group, asthma developed in 223 (56.0%) subjects compared to 209 (52.6%) subjects in the placebo group over the 60-month period of the study. The relative risk for developing asthma was [cetirizine to placebo = 1.064 (95% CI: 0.937; 1.209)]. The median time to onset of asthma was 806 days in the cetirizine group and 834 days in the placebo group. No statistically significant difference was observed between the two treatment groups (log-rank test: p = 0.360).

Prevention of asthma – Exploratory analyses:
Treatment-atopic characteristic and treatment-subgroup interaction:
Sensitizations to egg, cat dander, grass pollen, house dust mites and peanuts are important risk factors for developing asthma. In addition, sensitization to grass pollen and peanuts interacts significantly with treatment.
Multivariate analysis and the probability of developing asthma:
The final model shows that treatment, sensitization to grass pollen and to house dust mites at baseline are related to the time to onset of asthma. Sensitizations to grass pollen and house dust mites are significant as main factors. Interactions between sensitization to grass pollen and treatment and between sensitization to grass pollen and sensitization to house dust mites were also found to be significant.
Analysis regarding treatment and allergens – Subgroup analysis:
Subjects who began the study with raised baseline levels of IgE to house dust mites and grass pollen and received cetirizine still had a reduced risk of developing asthma (around 3.5 years after stopping the study medication) compared to those who received placebo. This reduction was higher for grass pollen. In sensitized subjects at baseline, cetirizine prevented the development of asthma compared to placebo over the 60-month study period (Grass pollen: cetirizine 58.3% asthmatic subjects versus 79.4% in the placebo group – House dust mites: cetirizine 66.1% asthmatic subjects versus 70.6% in the placebo group). However, in subjects not sensitized at baseline to these allergens, there is a small non-clinically relevant increase in the likelihood of developing asthma under cetirizine versus placebo.
Evolution of asthma:
According to the pre-defined classification of active asthma, the frequency distribution is balanced. No statistically significant difference was detected between the two treatment groups.

Lung function:
Lung function data:
No significant changes were observed between the 2 groups for key variables (FEV₁, MMEF, percent change in FEV₁ or MMEF₂₅-₇₅ after a β₂ pharmacodynamic test).

Lung function data by sensitization status at baseline:
Although the number of sensitized subjects at baseline was relatively small, a relevant difference was observed for the percent change in MMEF₂₅-₇₅ after a pharmacodynamic test with a β₂ agonist in subjects with elevated IgE for grass pollen (25.55% in the placebo group and 11.70% in the cetirizine group) and for HDM (35.27% in the placebo group and 16.13% in the cetirizine group). This difference was not observed for subjects not sensitized to grass pollen or HDM.

Lung function data by type of evolution of asthma:
According to the time of diagnosis of asthma and the presence or absence of wheezing during the last year of follow-up, subjects were classified in 1 of 4 groups: no asthma, early onset asthma, late onset asthma and continuous asthma. No significant differences were observed in the mean and median values between asthmatic and non-asthmatic children. For both FEV₁ and MMEF₂₅-₇₅, no reference data are available for this age group. Moreover, the relatively small number of subjects does not allow for a definitive conclusion. However, the potential benefit of cetirizine in these subgroups of subjects could be examined more closely, since a clinically relevant level could not be determined from the literature and the results are based on a small number of subjects.

Relationship between lung function data:
The same trend was observed between the cetirizine and placebo groups.

Sensitization status:
For the population of Period V, the sensitization status over the study period was as follows:
- Increased for cat dander, grass pollen, house dust mites, birch and the total IgE,
- Decreased for egg,
- Stable for cow’s milk and peanuts.

Safety results:
For Period V, adverse events were reported and documented during each visit of this long-term Follow-Up Period, including those events which might have corresponded to the study disease (e.g. nocturnal cough). As no study medication was administered, the reported AEs are not considered as treatment-emergent. The most commonly reported adverse events involved the respiratory system, the resistance mechanism, the body as a whole and the skin and appendages. No difference was observed in the mean and median number of subjects with adverse events in the two treatment groups.

No deaths were reported during Period V (24-month Follow-Up Period). A total of 25 other serious adverse events were reported: 8 events in the placebo group and 17 events in the cetirizine group. All the reported SAEs involved hospitalization except one, which was life threatening (subject S 07/0966 in the placebo group: anaphylactic reaction to a known allergy to milk).

At Visit 15, the mean weight and height were comparable and age-appropriate between the two treatment
groups. The classes of concomitant medication were comparable between the two treatment groups. However, in the cetirizine group, more medication was used for the respiratory system, e.g. nasal and throat preparations, anti-asthmatics and cough/cold preparations and in the placebo group, more medication was used for the sensory organs, e.g. ophthalmological and otological preparations.

OVERALL CONCLUSION:

In this population of infants suffering from atopic dermatitis with a family history of atopy, the incidence of asthma was not influenced by treatment over the whole 60-month period of the study. However, in the placebo group, subgroups were identified with a significantly increased risk of developing asthma. Raised total IgE level and/or raised specific IgE levels to grass pollen, house dust mites and/or cat dander were predictive of subsequent development of asthma. The importance of these factors as predictors of asthma in early childhood was poorly known when this study was planned. This is the first study to reveal that elevated IgE to grass pollen is also a potent risk factor for the development of asthma.

Cetirizine prevented the onset of asthma in these high-risk groups during the treatment period, reducing the risk of developing asthma by 53% in case of atopy towards grass pollen and by 44% in case of atopy towards house dust mites. These reductions are considered as clinically relevant. The effect of cetirizine persisted during the 18-month post-treatment Follow-Up Period (Period IV), being more pronounced for atopy towards grass pollen than house dust mites. The analysis of the active asthma subjects (A+) – defined as subjects who became asthmatic during the study and wheezed at least one day in the last 12 months – during Period IV confirmed the results observed for asthma.

The evaluation of efficacy for Period V was primarily based on the time to onset of asthma after starting the study medication, over the entire 60-month period of the study. The results obtained did not show any differences between the two treatment groups. Asthma developed in 56.0% of subjects in the cetirizine group and in 52.6% of subjects in the placebo group. Regarding the median time to onset of asthma, the difference between the two groups was not statistically significant.

Univariate analysis (Cochran-Mantel-Haenszel and Breslow-Day test) confirmed that sensitizations to egg, cat dander, grass pollen, house dust mites and peanuts were important risk factors for developing asthma. Moreover, sensitization to grass pollen and peanuts interacted significantly with treatment. Multivariate analysis (Cox Proportional Hazards Model) revealed that treatment, sensitization to grass pollen and to house dust mites at baseline are related to the time to onset of asthma. Interactions between sensitization to grass pollen and treatment and between sensitization to grass pollen and sensitization to house dust mites were also found to be significant. The risk of developing asthma was lower in the cetirizine group than in the placebo group for subjects with elevated IgE to grass pollen.

The SCORAD index of atopic dermatitis continuously decreased in both treatment arms. Although cetirizine did not show an effect on this endpoint, it had a significant corticosteroid-sparing effect in children with a high SCORAD index at baseline. This effect of cetirizine disappeared after discontinuation of treatment. The consumption of anti-histamines as rescue medication, which was reduced during the Treatment Period in the cetirizine group, was not different in the two treatment groups during Periods IV and V. This reinforces the assumption that the observed effects during the Treatment Period were due to cetirizine treatment.

Since sensitization to grass pollen and house dust mites at baseline were predictive for the development of
**Name of Sponsor/Company:**  
UCB S.A. – Pharma Sector

**Name of Finished Product:**  
Zyrtec®

**Name of Active Ingredient:**  
Cetirizine dihydrochloride

---

a further analysis was performed in subgroups of subjects determined on the basis of their sensitization status at baseline to each of these two IgEs. Subjects with raised baseline levels of IgE antibodies to house dust mites and grass pollen and received cetirizine had a reduced risk of developing asthma compared to those who received placebo. This reduction was higher for grass pollen. However, it should be emphasized that in subjects not sensitized at baseline to these allergens, there is a small non-clinically relevant increase in the likelihood of developing asthma under cetirizine versus placebo. Subjects with elevated IgE to grass pollen at baseline and received cetirizine had also a longer median time to onset of asthma than those who received placebo.

Nevertheless, the evolution of asthma was similar in the two treatment groups. Regarding lung function variables, no significant differences were observed between cetirizine and placebo groups. Although a statistically relevant difference between cetirizine and placebo groups was observed for the percent change in MMEF25-75 after a pharmacodynamic test with a β2 agonist in subjects with elevated IgE for grass pollen and house dust mites at baseline, the small number of subjects does not allow for a reliable conclusion.

During the Treatment Period, cetirizine was well tolerated at the dose of 0.25 mg/kg b.i.d. for up to 18 months, even in cases of overdose. The dosage used in the study is 1 to 2 times higher than the dosage recommended for the treatment of allergic rhinitis and chronic idiopathic urticaria in children aged 2 – 5 years. There were no effects on QTc, even when combined with macrolide antibiotics. Urticaria was significantly less reported in the cetirizine group during the Treatment Period, but was comparable to placebo after treatment discontinuation. This was interpreted as indirect evidence of the previously established therapeutic effect of cetirizine on urticaria. During the whole 42-month Post-Treatment Follow-Up Period (Periods IV and V), there were no observable adverse effects attributed to the prior 18-month treatment with cetirizine.

During Period V, the percentage of subjects with adverse events and the mean number of adverse events per subject were similar in the two treatment groups. No clinically relevant differences were observed between the two groups. Physical examinations did not reveal any issue of a particular interest. No deaths were reported and the other serious adverse events were either related to the study disease or expected in this age group of subjects.

**Date of the report:**  
23-JAN-2003