2. SYNOPSIS

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<th>Name of Sponsor /Company:</th>
<th>Individual Study Table Referring to Part IV Of the Dossier Volume:</th>
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<tr>
<td>UCB S.A. Pharma Sector</td>
<td>(For National Authority Use Only)</td>
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<tr>
<th>Name of Finished Product:</th>
<th>Name of Active Ingredient:</th>
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<tr>
<td>Zyrtec&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Cetirizine dihydrochloride</td>
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<table>
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<th>Title of Study:</th>
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<tr>
<td>EARLY TREATMENT OF THE ATOPIC CHILD (E.T.A.C.)</td>
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<tr>
<td>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, RANDOMISED, PLACEBO-CONTROLLED TRIAL</td>
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Subtitle: 18-month Post-Treatment Follow-Up (study periods III & IV)

**Investigators:**
The ETACT<sup>TM</sup> Study Group (see section 6.1.)

**Publications (references)**
Related to the Treatment Period (Periods I and II):

Related to the 18-month Post-Treatment Follow-Up Period (Periods III and IV): None.

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<th>Studied period (years):</th>
<th>Phase of development:</th>
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<tr>
<td>Date of first enrolment:</td>
<td>Phase III</td>
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<td>- Period I-II (treatment):</td>
<td>17 FEB 1994</td>
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<td>- Period III (6-mth Follow-Up):</td>
<td>21 SEP 1995</td>
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<td>- Period IV (additional 12-mth Follow-Up):</td>
<td>24 May 1996</td>
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<td>Date of last completed:</td>
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<td>- Period I-II (treatment):</td>
<td>19 SEP 1997</td>
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<tr>
<td>- Period III (6-mth Follow-Up):</td>
<td>10 MAR 1998</td>
</tr>
<tr>
<td>- Period IV (additional 12-mth Follow-Up):</td>
<td>11 March 1999</td>
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Objectives:
The primary aim of this trial was to evaluate the efficacy of cetirizine after 18-months of treatment in preventing the onset of asthma in children between 12 to 42 months of age, who were at high risk of developing asthma, but were not yet affected. This was also evaluated as exploratory variable for the 36 months of the study (18 months of treatment + 18 months Post-Treatment Follow-Up Period) and is the main object of the present report.

The secondary aims were:
(a) to evaluate the efficacy of cetirizine
   (i) in reducing the severity of asthma,
   (ii) in changing the signs and symptoms of atopic dermatitis,
(b) to assess the long-term safety and tolerability of cetirizine in a large paediatric population.

Several additional analyses were planned either in the protocol or in the Statistical Analysis Plan, amongst others, the onset of asthma in conjunction with elevated total and specific IgE at baseline.

Methodology:
Double-blind, randomised, parallel group, placebo controlled trial.
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 three consecutive nights or 3 separate episodes of wheezing, in a clinical setting where asthma is likely and other conditions have been excluded. All these 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 patients were reviewed and verified by a Data Review Committee consisting of members from UCB and from the Scientific Advisory Board. During the 18-month Follow-Up Period, no study medication was given, patients were followed on a 6-month basis using the same methodology as during the Treatment Period.

Number of patients (planned and analysed):
Planned: 700. Information is available on 830 screened patients. Eight patients never received any treatment number, which leaves 822 who were actually randomised.

Analysed in the Treatment Period:
- For efficacy: Of the 822 randomised patients, 5 never received any treatment, whereas 22 had no follow-up data, leaving 795 patients who constitute the ITT population considered in the efficacy analysis, 397 infants [248 boys, 149 girls] in the placebo group and 398 infants [246 boys and 152 girls] in the cetirizine group.
- For safety, all patients who received study drug and had at least one follow-up safety parameter reported, were analysed, i.e. 795.
**Clinical Study Report for cetirizine ETAC™ 18-mth Post-Treatment Follow-Up**

**Name of Sponsor/Company:** UCB S.A. Pharma Sector  
**Name of Finished Product:** Zyrtec®  
**Name of Active Ingredient:** Cetirizine dihydrochloride

Analysed in the 18-month Post-Treatment Follow-Up Period, for efficacy and safety: 566 (only from centres which enrolled 10 patients or more), 282 infants [167 boys, 115 girls] in the placebo group and 284 infants [175 boys, 109 girls] in the cetirizine group.

**Diagnosis and main criteria for inclusion:**  
**Treatment Period:** Infants 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. Patients had to have at least one parent or sibling with a history of atopic disease (atopic dermatitis, allergic rhinitis or asthma).  
**18-mth Post-Treatment Follow-Up:** All patients included at qualifying centres and who completed at least the first 6 months of post-treatment follow-up and up to the 18 months post-treatment follow-up.

**Test product, dose and mode of administration, batch number:**  
**Treatment Period:** Cetirizine at the dosage of 0.25 mg cetirizine/kg b.i.d., via oral route.  
Cetirizine batch numbers: 66 and 68.  
**18-mth Post-Treatment Follow-Up:** Not applicable. No study medication administered.

**Duration of treatment**: 18 months during Treatment Period (Period II) only.

**Reference therapy, dose and mode of administration, batch number:**  
**Treatment Period:** Placebo, dosage equivalent to 0.25 mg/kg b.i.d. via oral route.  
Batch numbers: 65P and 67P.  
**18-mth Post-Treatment Follow-Up Period:** Not applicable. No study medication administered.
### Clinical Study Report for cetirizine ETACTM 18-mth Post-Treatment Follow-Up

**Name of Sponsor /Company:** UCB S.A. Pharma Sector  
**Name of Finished Product:** Zyrtec®  
**Name of Active Ingredient:** Cetirizine dihydrochloride

### Criteria for evaluation:

**Efficacy:**
- Primary endpoint: time to diagnosis of the onset of asthma (definition of asthma based on a predefined number of episodes of wheezing and nocturnal coughing). To be considered clinically significant, a risk reduction of at least 30% had to be observed at the end of the Treatment Period.
- Secondary endpoints:
  - Asthma: frequency of asthmatic episodes and severity based on classes of treatments used for preventing/treating asthma episodes, as well as the number of days of use of such treatments;
  - Atopic dermatitis: standard score for signs and symptoms of atopic dermatitis (SCORAD system), and classes of treatments used for atopic dermatitis and number of days of use.

**Safety:**
- Vital signs, physical examinations, adverse events and intercurrent diseases collected from interviews and diary cards, ECGs read centrally by a cardiologist who did not have access to the study code, blood chemistry, haematology and urinalyses performed by a central laboratory, compliance checks (during the Treatment Period only). Developmental assessments (BSQ, McCarthy and GMQ) were performed and will be reported separately as described in the protocol.

### Statistical methods:
- Occurrences of asthma in the treatment groups were examined by use of Kaplan-Meier survival curves. The differences between the curves were analysed using the logrank test, and estimated by means of relative risk with its associated 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 analysed by means of a t-test or Mann-Whitney test, when appropriate.
- Fisher's exact test was used to evaluate the adverse event data.

### Summary – Conclusions:

**A. Treatment Period (reported in full in report MRCE98L1301):**

**A.1 Efficacy results**

In the ITT population, the incidence of asthma was 38.0% in the placebo group, as expected in the protocol, vs. 37.7% in the cetirizine group. There was no statistically significant difference between infants treated with cetirizine or placebo in terms of the number of infants developing asthma or the time to onset of asthma over the 18-month Treatment Period, using either the ITT population or the Per Protocol population.
In the placebo group, the risk for developing asthma was significantly higher in patients with raised levels of total IgE (≥30 kU/l) (RR of 1.30), or specific IgE (≥0.35 kUA/l) for Grass Pollen, House Dust Mites (HDM) or Cat Dander (RR between 1.42 and 1.68) compared to patients with normal levels of IgE at baseline. The findings with Grass Pollen had never been demonstrated before.

Compared to placebo, cetirizine significantly prevented the occurrence of asthma in patients sensitised 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 patients with elevated IgE to Grass Pollen and HDM, which are therefore considered 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<0.050), and the same magnitude of the between-groups difference (at least a 30% risk reduction) as for the primary objective of the study.

In patients becoming asthmatic, the frequency of episodes of asthma and the severity of asthma did not differ between the groups. Interestingly, the mean consumption of anti-asthmatic medications was lower in the cetirizine group for each of the three main classes of anti-asthmatic medications.

Regarding the primary disease, 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 and subscores. The number of patients taking oral anti-histamines as rescue medication was significantly less in the cetirizine group (p=0.030). In patients 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 placebo.

A.2 Safety Results

The adverse events profile was similar in the two treatment groups. There was no significant difference between the groups for neurologic or cardiovascular signs or symptoms. The QTc interval (Bazett’s correction) was not influenced by treatment. Many infants received macrolide co-medications, without any untoward cardiovascular effect. Some laboratory results differed between the groups, but none were considered clinically significant. Significantly fewer patients reported urticaria as an adverse event in the cetirizine group (p<0.001). Children in the cetirizine group had a slightly increased weight gain during the Treatment Period compared to placebo. The mean difference in weight gain between the cetirizine and placebo groups was 0.25 kg, which was considered as not clinically relevant.
B. 18-month Post-Treatment Follow-Up Period (Study Periods III & IV)

At qualifying centres, 566 patients who have completed the 6-month Post-Treatment Follow-Up Period (Period III) entered the additional 12-month follow-up period (Period IV) without study medication (282 in the placebo group and 284 in the cetirizine group) and constitute the V11 Follow-up ITT population. Of these, 548 have completed 18-month post-treatment follow-up.

B.1 Efficacy results

Regarding asthma, the following findings observed during the Treatment Period were confirmed:
- the continuous increase of the occurrence of asthma as a function of time;
- the absence of an overall difference in the occurrence of asthma, when IgE risk factors are ignored (52.0% and 50.4% in the placebo group and the cetirizine group respectively);
- the importance of elevated IgE levels to Grass Pollen, HDM and Cat in early childhood as risk factors for the development of asthma;
- the persistence throughout the 18-month Post-Treatment Follow-Up Period of a relevant effect of cetirizine, reducing the occurrence of asthma in patients with elevated IgE at baseline to Grass Pollen (RR=0.67; 95% CI = [0.47-0.95]) or HDM (RR=0.81; 95% CI = [0.62-1.07]).

This specific treatment effect is balanced, in the ITT population, by a slight non clinically relevant raise in the occurrence of asthma in the patients who were non sensitized to Grass Pollen or HDM at baseline and were treated by cetirizine.

The analysis, within the V11 Follow-up ITT Population, of "active asthma" (A+) patients – defined as patients who became asthmatic during the study and wheezed at least one day in the last 12 months (i.e. Period IV, the complete interval between V9 and V11) – confirmed the results observed for asthma.

Regarding atopic dermatitis, the SCORAD Index continued to decrease in both treatment arms. The corticosteroid-sparing effect observed in the cetirizine treated group during the Treatment Period, disappeared during the 18-month Post-Treatment Follow-Up Period. The consumption of antihistamines as rescue medication which was reduced during the Treatment Period in the cetirizine group was not different in the two treatment groups in the 18-month Post-Treatment Follow-Up Period. This reinforces the assumption that these effects observed during the Treatment Period, are due to cetirizine treatment.

B.2 Safety results

There was no clinically relevant difference between the groups with respect to any of the safety parameters measured.
C. 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 36-month study period (18-month treatment and 18-month Post-Treatment Follow-Up).

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 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 of asthma.

Cetirizine prevented the onset of asthma in these high risk groups during the period of treatment, reducing the risk of developing asthma by 53% in the case of atopy towards Grass Pollen and 44% in the case of atopy towards HDM, these reductions being clearly greater than the 30% reduction considered as clinically relevant. A longer follow up was conducted at centres having entered 10 patients or more and the relevant effect of cetirizine persisted through the end of the 18-month follow-up period without treatment, in a more pronounced way for atopy towards Grass Pollen than towards HDM.

The analysis, within the V11 Follow-up ITT Population, of "active asthma" (A+) patients – defined as patients who became asthmatic during the study and wheezed at least one day in the last 12 months (i.e. Period IV, the complete interval between V9 and V11) – confirmed the results observed for asthma.

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 antihistamines as rescue medication which was reduced during the Treatment Period in the cetirizine group was not different in the two treatment groups in the 18-month Post-Treatment Follow-Up Period. This reinforces the assumption that these effects observed during the Treatment Period, are due to cetirizine treatment.

Cetirizine was very 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
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Name of Finished Product:  
Zyrtec®

Name of Active Ingredient:  
Cetirizine dihydrochloride

2-5 years. There were no effects on QTc, even when combined with macrolide antibiotics. Urticaria was significantly less frequently reported in the cetirizine group during treatment, 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 18-month Post-Treatment Follow-Up Period, there were no observable adverse effects attributed to the prior 18-month treatment with cetirizine.

Date of report: 22 August 2000