2. SYNOPSIS

Name of Sponsor /Company: UCB S.A. Pharma Sector
Individual Study Table Referring to Part IV Of the Dossier (For National Authority Use Only)

Name of Finished Product: Zyrtec®
Volume:

Name of Active Ingredient: Cetirizine dihydrochloride
Page:

Title of Study:
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, RANDOMISED, PLACEBO-CONTROLLED TRIAL.

Investigators:
The E.T.A.C.® Study Group
Composition of the Scientific Advisory Board:
- J.O. Warner (Southampton, GB), Chairman
- L. Businco (Roma, I)
- K. Knol (Groningen, NL)
- G. Casimir (Bruxelles, B)
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- T.L. Diepgen (Erlangen, D)
- C. Naspitz (São Paulo, BR)
- M. Kjellman (Linköping, S)
- U. Wahn (Berlin, D)

Publication (reference)1
- Scoring of atopic dermatitis by SCORAD using training atlas by investigators from different disciplines. Pediatr Allergy Immunol 1997; 8:28-34.

1 Copies of these publications are available under Appendix 16.1.11 Publications based on the Study
**Objectives:**
The primary aim of this trial was to evaluate the efficacy of cetirizine 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.

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 preplanned 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, 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 an independent Data Review Committee.

**Number of patients (planned and analysed):**
Planned: 700. Information is available on 830 screened patients. Eight patients have never received any treatment number and/or treatment, which leaves 822 who were actually randomised. Of these, 5 never received any treatment, whereas 22 had no follow-up data, leaving 795 patients who constitute the ITT population considered in the analysis.

Analysed:
- For efficacy: 795 (Intent-To-Treat population), 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.

**Diagnosis and main criteria for inclusion:**
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).
Test product, dose and mode of administration, batch number:
Cetirizine in 20 ml bottles of oral solution at a concentration of 10 mg cetirizine/ml.
The recommended dosage was 0.25 mg cetirizine/kg b.i.d., via oral route.
Cetirizine batch numbers: 66 and 68

Duration of treatment: 18 months

Reference therapy, dose and mode of administration, batch number:
Placebo, in 20 ml bottles of oral solution, batch numbers: 65P and 67P.

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 relative risk reduction of at least 30% had to be observed.
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. Developmental assessments were performed towards the end of the study 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 and 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:

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-months treatment period, using either the ITT population or the Per Protocol populations.

In the placebo group, the relative risk (RR) for developing asthma was significantly higher in patients with raised levels of total IgE (≥230 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% relative risk reduction) as for the primary objective of the study. However in patients with normal levels for all IgE, the probability of developing asthma was significantly increased in the cetirizine group (RR=1.48; 95%CI = [1.00 - 2.18]).

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.
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.

Conclusion

The incidence of asthma in the ITT population was not influenced by treatment. However, in the control group, subgroups were identified with a significantly increased risk of developing asthma. In this population of infants suffering from atopic dermatitis with a family history of atopy, 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 understood when this study was planned. This study in fact revealed that elevated IgE to Grass Pollen is also a potent risk factor. Cetirizine prevented the onset of asthma in these high risk groups, reducing the relative risk 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 expected decrease of 30%.

The SCORAD index of atopic dermatitis improved continuously 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. Less rescue antihistamines were needed in the cetirizine group.

There was no significant differences in adverse event profiles between the two groups except for urticaria which was significantly less reported in the cetirizine group. There were no effects on QTc, event when combined with macrolide antibiotics. 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 2-5 years.

Date of report: 21 April 1999