PROTOCOL A143-101O: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY OF THE SAFETY OF ZYRTEC (CETIRIZINE HYDROCHLORIDE) SYRUP IN PEDIATRIC SUBJECTS 6 MONTHS TO 11 MONTHS OF AGE.

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Study Publication: None

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Phase of Development: Phase 3

Study Objectives: The purpose of this study was to evaluate the safety of Zyrtec (cetirizine) syrup in pediatric subjects 6 months to 11 months of age with an allergic condition such as rhinitis, urticaria or any other condition for which the use of an antihistamine is appropriate.

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study. Subjects received Zyrtec syrup or matching placebo syrup orally at a dosage of 0.25 mg/kg twice daily for 7 days.

Subjects who satisfied the inclusion and exclusion criteria underwent a physical examination, including vital signs, baseline symptom evaluation for sleep, irritability and tremor, and an electrocardiogram (ECG). They were given cetirizine syrup or matching placebo syrup orally at a dosage of 0.25 mg/kg twice daily for 7 days. The subject’s parent or legal guardian was given a daily diary and was asked to record significant observations pertaining to the subject’s sleep pattern, irritability, and presence of tremor. No efficacy assessments were recorded in this study.

At the completion of the 7 day treatment period, the parent or legal guardian administered the morning dose of study medication to the subject and returned to the clinic with the subject. At the clinic, the subject underwent a complete physical examination including vital signs. A 12-lead ECG recording was performed approximately two hours (± 1 hr) after administration of the study medication. At this final visit, an assessment of the daily diary entries and adverse events were made. The study staff called the subject’s parent or legal guardian 7 days after the last visit to inquire about any concomitant medications or adverse events since the last visit.
Evaluation Groups:

<table>
<thead>
<tr>
<th></th>
<th>Cetirizine</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>42</td>
<td>44</td>
<td>86</td>
</tr>
<tr>
<td>Completed Study</td>
<td>37</td>
<td>39</td>
<td>76</td>
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<tr>
<td>Evaluated for Efficacy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Assessed for Safety</td>
<td>42</td>
<td>43</td>
<td>85</td>
</tr>
</tbody>
</table>

Diagnoses and Criteria for Inclusion of Subjects: This study included male and female pediatric subjects 6 months to 11 months of age with a diagnosis of allergic rhinitis, urticaria, atopic dermatitis or other conditions that were, in the opinion of the investigator, appropriately treated with an antihistamine. Subjects with a history of previous antihistamine use but no current diagnosis were also eligible for inclusion.

Drug Administration:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cetirizine Syrup</th>
<th>Placebo Syrup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>1 mg/mL cetirizine hydrochloride syrup</td>
<td>Matching placebo syrup</td>
</tr>
<tr>
<td>Dosage</td>
<td>0.25 mg/kg twice daily for 7 days</td>
<td>0.25 mL/kg twice daily for 7 days</td>
</tr>
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<td>Route</td>
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</table>

Source: Section 11, Item 6

Efficacy and Safety Evaluations: No efficacy data was collected in this study.

Data for 85 subjects were evaluated for safety. Vital signs, physical examination findings, adverse events and appropriately timed ECGs in relationship to drug administration were recorded. Physical examinations were conducted and vital signs and ECGs evaluated at Baseline and at the completion of the study. ECG evaluations had to include a QTc interval determination. The subject's normal pattern of baseline symptoms (restlessness during sleep, irritability/fussiness, and tremor) were evaluated on Day 1 and recorded in the case report form (CRF) by the study site personnel. On each day after Day 1, the subject's parent or legal guardian recorded the responses to the questions on sleep, irritability, and tremor over the past 24 hour interval, in the daily diary. Descriptive statistics of clinical, ECG, and diary adverse event data were used to describe the safety profile of the test drug. No laboratory tests were required by the protocol.
Statistical Methods: Approximately 80 subjects were to be randomized into the study at approximately 20 centers with the expectation that a minimum of 30 subjects per treatment group (Zyrtec syrup or placebo) would complete the study.

All demographic and safety data are summarized using the current version of Pfizer Worldwide Safety Standards (WSS), using COSTART terminology. Descriptive statistics of clinical, ECG, and diary adverse event data were used to describe the safety profile of the test drug. ECG evaluations at Baseline included QTc interval determination.

The mean changes in QTc (linear corrected QT interval value) from Baseline to Visit 2 were compared between treatment groups using a two-sample t-test. The test was two-sided with a 5% significance level. The 95% confidence interval for the mean difference between treatment groups was also calculated.

Efficacy Results: Not applicable.

Safety Results: Safety data in this study is consistent with data collected in other cetirizine studies in children and do not reveal any unexpected safety concerns. No serious adverse events were reported during this study. A total of 9 subjects who received study drug discontinued from the study. Three subjects in the cetirizine treatment group and 3 subjects in the placebo group discontinued from the study due to treatment-emergent adverse events. Of these discontinuations, 3 (cetirizine: 1, placebo: 2) were attributed to study drug treatment.

No unexpected treatment-emergent adverse events were reported during the study. There was no apparent difference in the incidence and severity of the treatment emergent adverse events by age group (6-8 months and 9-11 months) between the two treatment groups. In general, subjects in the 6-8 month age group in both treatment groups experienced a higher proportion of adverse events compared to the 9-11 month old subjects. Overall, there were fewer all causality or treatment-related adverse events in the cetirizine treatment group than in the placebo treatment group. Sixty-nine subjects (cetirizine: 31/42, 73.8%, placebo: 38/43, 88.4%) reported 148 (cetirizine: 63, placebo: 85) adverse events. Treatment-related adverse events were reported for a total of 46 subjects (cetirizine: 19/42, 45.2%; placebo: 27/43, 62.8%). The most common treatment emergent adverse events in both treatment groups were nervousness, insomnia, and somnolence. The majority of the treatment-related adverse events were more frequent in the placebo treatment group than in the cetirizine group. The diary data show that the CNS symptomatology was similar in the cetirizine and placebo treatment groups, and there was no evidence of any adverse effects on sleep pattern, irritability, and tremor after cetirizine treatment.

There was no clinically meaningful median change in respiration rate during the study. There were no clinically meaningful changes in vital signs or physical examination findings in any subject during the study. Although 20 subjects (cetirizine: 10, placebo: 10) had clinically significant changes in vital signs from Baseline to last observation, none were considered meaningful in the context of behaviour/activity of an infant during a medical examination.

No clinically significant QTc intervals were observed in any subject at Baseline. The group mean changes in the ECG parameters (heart rate, PR interval, QRS interval, QT interval) from Baseline to Endpoint during cetirizine and placebo treatment were not clinically meaningful and did not indicate a difference between cetirizine and placebo treatment in either age group. There were no subjects with clinically significant changes in any ECG parameter during the study. Administration
of cetirizine did not increase or prolong the QTc interval when compared to placebo treatment and was not associated with any safety concerns.

**Summary and Conclusions:** Study A143-1010 was designed to assess the safety of Zyrtec (cetirizine) syrup in pediatric subjects 6 months to 11 months of age with any condition for which the use of an antihistamine is appropriate. No efficacy evaluations were conducted.

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in which subjects were to receive cetirizine syrup or matching placebo syrup orally at a dosage of 0.25 mg/kg twice daily for 7 days. The following clinical endpoints were studied: adverse events, changes in vital signs, physical examinations and ECGs. Descriptive statistics were used to describe the safety data including adverse events, ECGs, changes in physical examinations, and vital signs. The mean changes in QTc from Baseline to Visit 2 were compared between treatment groups using a two-sample t-test. The test was two-sided with a 5% significance level. The 95% confidence interval for the mean difference between treatment groups was also calculated.

Eighty-six subjects were randomized to one of two treatment groups: cetirizine – 42 subjects; placebo – 44 subjects. One subject was randomized to receive placebo but was discontinued from the study prior to receiving medication leaving 43 subjects in the placebo group. For the majority of subjects, the medical condition for inclusion in the study was a primary diagnosis of allergic rhinitis. The duration of therapy was ≤5 days for 9 subjects, 5½ to 6½ days for 6 subjects, and ≥7 days for 70 subjects.

No serious adverse events were reported during this study. A total of 76 subjects completed the study. Nine subjects discontinued from the study after receiving study drug. Of these 9 subjects, 3 cetirizine-treated subjects and 3 placebo-treated subjects discontinued due to treatment-emergent adverse events. There was no apparent difference in the incidence and severity of the treatment emergent adverse events by age group (6-8 months and 9-11 months) between the two treatment groups. In general, subjects in the 6-8 month age group in both treatment groups experienced a higher proportion of adverse events compared to the 9-11 month old subjects. The CNS symptoms recorded as adverse events were similar in the cetirizine and placebo treatment groups, with no evidence of any adverse effects on sleep pattern, irritability, and tremor after cetirizine treatment. No effect on QTc interval was observed after treatment with cetirizine.

In summary, the safety data in this study is consistent with data collected in other Zyrtec studies and do not reveal any unexpected safety concerns in the treatment of infants aged 6-11 months with 0.25 mg/kg Zyrtec syrup for up to 7 days.