Study A174 – Protocol GHBA-721

A DOUBLE-BLIND, RANDOMISED, PARALLEL GROUP, PLACEBO CONTROLLED MULTICENTRE STUDY TO EVALUATE THE SAFETY AND EFFICACY OF A RANGE OF DOSES OF CETIRIZINE (2.5 MG, 5 MG AND 10 MG ONCE DAILY) IN 6 TO 12-YEAR OLD CHILDREN SUFFERING FROM PERENNIAL ALLERGIC RHINITIS

CLINICAL TRIAL REPORT
FINAL VERSION

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4 December 1992
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SUMMARY

Study A174 (protocol GHBA-721) was designed as a double-blind, randomised, parallel-group placebo-controlled, multicentre trial to evaluate the safety and efficacy of a range of doses of cetirizine in children aged six to 12 years suffering from perennial allergic rhinitis. The trial was conducted in Germany and the Netherlands during two periods: 1990/1991 and 1991/1992. Patients had a documented history of perennial allergic rhinitis, with a skin test or RAST positive to house dust allergen, molds, dog and/or cat hair.

To be enrolled in the trial, patients had to exhibit the following three main symptoms of perennial allergic rhinitis: sneezing, nasal discharge (rhinorrhea), and nasal obstruction. These symptoms were rated according to their intensity: not present at all (0), mild (1), moderate (2), and severe (3). A minimum total score of 5 was required for enrolment. In addition, two accessory symptoms were assessed: pruritus of the nasal mucosa and pruritus of the eyes.

Patients were randomised to one of four treatment groups and received the following doses of study drug: a 2.5 mg, 5 mg, or 10 mg tablet in the cetirizine groups, or one tablet identical in appearance to the cetirizine tablets in the placebo group. All study drugs were taken once a day, in the evening with the evening meal.

A total of 330 patients was enrolled, 130 in the first and 200 in the second enrolment period, respectively. For two of the patients enrolled into the study during the second enrolment period, no CRFs were available since the investigator had mislaid them. Hence, the remaining 328 patients were used for all further assessments, and were randomised as follows: 83 to placebo, 84 to 2.5 mg cetirizine, 85 to 5 mg cetirizine, and 76 to 10 mg cetirizine.

The planned duration of treatment was 12 to 16 days, and for the majority of patients the duration of exposure to study drug was 14 days.

Overall, 311 of the 328 patients completed the three study visits. Of the 328 patients, 16 discontinued prematurely from the study [six (7.2 %), five (6.0%), three (3.5%), and two (2.6%) from the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively] and one patient in the 10 mg group had a partially completed CRF with no information available as to whether the patient completed the study. Three patients (3.6%) in the placebo group and one patient (1.2%) in the 5 mg group discontinued because of lack of efficacy (inadequate therapeutic response). Eight
patients withdrew because of adverse experiences (one, four, two, and one patient in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively). One patient in the placebo group withdrew due to the development of an exclusion criterion and one patient in the 2.5 mg group withdrew due to a protocol violation caused by the use of an unauthorised medication. No dose-related distribution of adverse experiences could be recognised. The remaining two patients discontinued because of reasons unrelated to the study.

The primary efficacy variable was the percentage of patient diary days with a maximum score of less than or equal to one, PDS1. The analysis showed that there were no significant differences in the distribution of PDS1 between treatment groups (p=0.053). However, the positive mean differences between the active treatment groups and placebo suggested that at all doses cetirizine was more effective than placebo, although significance was reached only in the 10 mg group (p=0.016).

The analyses of the variables PDS0 and PDS2 (the percentage of days with a maximum score of 0 and 2 or less, respectively) gave similar results, in that both showed significant differences between the four treatment groups (p=0.030 and p=0.005, respectively). The greatest mean difference between placebo and each of the active treatment groups occurred for the 10 mg group; for both PDS0 and PDS2 they were significant (p=0.008 and p=0.002, respectively), indicating that this group had the most benefit over placebo. The test for linearity was significant only for the variable PDS0, suggesting a dose-related effect on the number of symptom-free days.

These findings were supported to some extent by the investigator assessment of symptoms of perennial allergic rhinitis. At each visit, the scores for the placebo group were higher than those for the active groups indicating that cetirizine, at any dose, was more beneficial than placebo in reducing the symptoms of perennial allergic rhinitis. However, for determination of the most effective dose, the results were not as clear. At Visit 2, the 10 mg group had the least severe score, but it is noteworthy that the 2.5 mg group had a lower score than the 5 mg group; this may be because the 5 mg group had higher scores at baseline. At Visit 3, the mean scores for the three active groups were very similar, although the 2.5 mg group showed slightly higher scores. At endpoint, there was little difference between the three active treatment groups, although all showed a greater improvement in severity scores over placebo.

The investigator global assessment of treatment showed a significant
difference between all treatment groups (p<0.0001). The mean global score suggested that the active treatment groups were more effective than placebo. There was little difference between the 5 mg and 10 mg groups, although both showed a slightly more beneficial effect than the 2.5 mg dose of cetirizine.

The efficacy analysis carried out on evaluable patients showed similar results to those for the intent-to-treat analysis with the exception that the difference in the distribution of PDS1 between the four treatment groups was significant.

In conclusion, the 10 mg dose of cetirizine caused the greatest reduction in symptoms of perennial allergic rhinitis in comparison with placebo, and, thus, could be used to effectively treat children with these symptoms. The lower doses of cetirizine also showed some benefit over placebo, although statistical significance was not reached in all cases. The results suggested a linear dose–response relationship for effect on the mean PDS1 score, which, however, did not prove to be statistically significant. Adverse experiences such as fatigue, suggesting a sedative effect, were rare. The results of this trial confirm the results of previous studies, which have established that 10 mg cetirizine given once daily is a safe and effective dose in children suffering from perennial allergic rhinitis.
1.0 INTRODUCTION

1.1 Background and Rationale

Cetirizine is a potent and selective H_{1}-antagonist with some additional antiallergic pharmacological properties (inhibition of eosinophil infiltration and reduction of histamine concentration), which has been administered to more than 1500 patients in Phase I, II, and III studies.

Cetirizine (Zyrtec\textsuperscript{®}) is at present marketed in Europe for treatment of allergic rhinitis in adults and is given as a single daily 10 mg dose. Cetirizine has been marketed in Germany for the treatment of seasonal allergic rhinitis in children in tablet form since July 1991 and in drop form since October 1991.
A recently completed pharmacokinetic study of cetirizine in children has shown that a 5 mg dose produces peak blood levels similar to those after a 10 mg dose in adults, a finding consistent with the size-related difference in volume of distribution. The elimination half-life was slightly shorter in the paediatric group and, thus, the area-under-the-curve was also slightly reduced.

From the clinical studies carried out to date with cetirizine in children aged from six to 12 years, it would appear that a daily 10 mg dose given either once or twice daily is an adequate treatment for perennial allergic rhinitis. No severe adverse experiences were noted.

The most frequent side effect reported was sedation following the 10 mg daily dose of cetirizine in 20 of 334 patients, i.e., 6%; this incidence remained the same whether a single or a twice daily dose was administered.

An additional study in children of the same age with seasonal rhinitis has shown that there is no clinically significant difference in effect if cetirizine is given as a single daily dose of 10 mg or as a twice daily dose of 5 mg.

Cetirizine was also studied in children aged six to 12 years suffering from atopic dermatitis and was shown to be well tolerated at doses of 10 mg and 15 mg daily.

These studies in children aged six to 12 years old, have resulted in a proposed daily dose of 10 mg, given either on an o.d. or b.i.d. schedule (5 mg b.i.d.), which is also the recommended dose for adults.

The present study was designed to evaluate the efficacy of three doses of cetirizine given once daily in children with perennial allergic rhinitis in order to assess the dose-effect relationship of cetirizine (see Attachment 1 for protocol).
1.2 Objectives of the Trial

1. To evaluate the dose–response relationship of cetirizine administered once a day in children with perennial allergic rhinitis.

2. To compare the safety and tolerability of multiple doses of cetirizine and placebo in children with perennial allergic rhinitis.

2.0 METHODS

2.1 Trial Design

1. This double-blind, randomised, multicentre parallel group, dose ranging study compared three doses of cetirizine: 2.5 mg, 5 mg, and 10 mg once a day against placebo, for 14 days in children aged six to 12 years suffering from perennial allergic rhinitis (see Flow Chart on following page).

2. Using 39 investigational sites (see Attachment 2 for List of Investigators), 331 patients were screened for entry into this study of which 330 were randomised into one of the four treatment groups. The randomisation list was provided by the statistical department of UCB (see Attachment 3).

3. A group size of 70 evaluable patients was needed to detect a statistically significant difference between placebo and treatment groups based on symptom scores. Each study site was to recruit between eight and 16 patients. Each of the four treatment groups would then have a minimum of 70 evaluable patients at the end of the study.

4. An evaluable patient was defined as a patient who met all entry criteria, had no exclusion criteria, who completed at least one week of treatment or who was withdrawn for lack of efficacy after at least three days of treatment, or for adverse experiences. All patients were to undergo a final visit, even if prematurely withdrawn.
2.1.1 Treatment Definition

2.1.1.1 Pre-study (Visit 0 and Visit 1)

For the purpose of this clinical trial report, the term perennial allergic rhinitis refers to those patients with a positive skin test (prick or intradermal) or a RAST (radioallergosorbent test) for non-seasonal respiratory allergens (e.g., house dust mite, molds, cat and dog dander) (see Section 2.2 for specific inclusion/exclusion criteria).

To be considered as eligible for inclusion into the study, the patients had to have a documented history of perennial allergic rhinitis and had to present with sneezing, nasal discharge (rhinorrhea), and nasal obstruction within the preceding 24 hours, with a total score of at least 5 for rhinitis (see Section 2.2.1).

The parent or guardian gave his/her fully informed written consent to his/her child's participation in the study (see Attachment 3 to the protocol). Children who were able to understand the nature and consequences of the study could also indicate their consent to participation.

Patients treated with the following drugs had to undergo the following washout periods:

- six weeks for astemizole;
- two weeks for systemic corticosteroids or ketotifen;
- seven days for topical corticosteroids (except oral inhalation ≤200 μg/day);
- two days for oral antihistamines (other than astemizole or ketotifen), sodium cromoglycate (nasal or ocular) or decongestants.

Patients not requiring a washout period began the study at Visit 1 instead
of Visit 0 as long as all parameters foreseen at both visits had been measured. Only patients requiring a washout period had to attend both visits.

Patients with seasonal rhinitis at the time of study start or patients undergoing an escalating course of desensitisation therapy were excluded from study participation.

A complete medical history was obtained and a physical examination was performed. A clinical laboratory examination was performed, if possible. Previous treatments for perennial allergic rhinitis were recorded in the Case Report Form (CRF, see Attachment 1 for sample CRF), including the response to those treatments and any side effects which occurred.

A detailed allergy assessment was made.

Patients who satisfied the inclusion and exclusion criteria, on the basis of these previous examinations, were sequentially assigned a unique patient number that corresponded to one of the four treatment groups, as determined by a computer-generated randomisation schedule balanced in blocks of four. Each individual patient’s code was made available to the investigator in a sealed envelope that could be opened only in case of an emergency.

The parent or guardian was given precise instructions concerning the use of medication. The study drug, as tablets in a dosage of 2.5, 5, 10 mg or placebo, was to be taken once a day, with the evening meal, for 14 days. One week of study medication supplies together with a daily record card was given to the parent or guardian at Visit 1.

2.1.1.2

Study Treatment Period (Visit 2 to 3)

Patients returned for Visit 2 on Day 8 (Days 6 to 9) for study assessments as for pre-study, to return unused medication and the diary card and to receive further supplies. A new patient diary card was given to each parent or guardian. The entries on the diary card were discussed with the parent/guardian and the results entered in the CRF.

Returned study medication had to be collected by the investigator at each visit and the amount of used drug had to be calculated and noted in the patient’s CRF.

During the intervals between the planned visits, the parent or guardian could contact the investigator if the product did not prove efficacious, or
if any side effects appeared. The investigator could then decide whether or not to continue treatment. If not continuing, the patient had to return, as soon as possible, for the final visit evaluations (Visit 3).

Patients withdrawing from the study for reasons other than treatment-related adverse experiences or lack of efficacy were replaced by additional patients.

2.1.1.3 Final Visit (Visit 3)

All patients had to undergo a final assessment in order to be regarded as completed cases. Patients showing any adverse experiences at the final assessment or having been prematurely withdrawn due to adverse experiences had to be followed up within one week and thereafter as appropriate.

The investigator made a global evaluation of treatment according to a 5-point scale (see Section 2.4.2).

2.1.2 Ethics

The study was conducted in accordance with the Declaration of Helsinki amended by the 29th (Tokyo), the 35th (Venice), and the 41st (Hong-Kong) World Medical Assembly (see Attachment 2 to the protocol). In addition, it was conducted in accordance with applicable European Guidelines on good clinical practice, and German and Dutch regulations regarding conduct of clinical trials.
2.1.3 Data Handling
2.2 Patient Selection

Patients were admitted to the study and screened for eligibility according to the following inclusion and exclusion criteria.

2.2.1 Inclusion Criteria

To be entered into the study, patients had to satisfy the following criteria:

1. The patient selected had to be non-hospitalised and have had an established diagnosis of perennial allergic rhinitis for non-seasonal respiratory allergens (e.g., house dust mite, molds, cat and dog dander) with a positive skin test (prick or intradermal) or a positive RAST.

When these tests had been carried out within the year preceding
entry into the study there was no need for them to be repeated. If this was not the case, then a skin test (prick or intradermal) or a RAST had to be done.

2. The following symptoms had to be present within 24 hours of inclusion into the study:

   - sneezing;
   - nasal discharge (rhinorrhea);
   - nasal obstruction.

3. At the time of study inclusion the total score of rhinitis for these three main symptoms had to be \( \geq 5 \) according to the following 4-point scale that was used to grade each symptom:

   0 = not present at all;
   1 = mild: present, but not inconvenient;
   2 = moderate: inconvenient, but does not interfere with normal daily activities and/or disturb sleep;
   3 = severe: continuously present, and interferes with sleep and/or normal daily activities.

4. Girls or boys who had passed their sixth birthday but not yet their 13th birthday were eligible to participate provided that the parent or legal guardian had been fully informed (and the child where practicable) and had given their written consent for participation.

5. The patient could have been previously treated or untreated for perennial allergic rhinitis. Patients who had been previously treated had to undergo a washout period (see Section 2.1.1.1).

6. All patients had to be free of clinical evidence of any clinically significant concomitant disease as judged by the investigator.

2.2.2 Exclusion Criteria

Patients with the following criteria were to be excluded from the study:

1. Presence of pollen to which the patient was allergic. This exclusion extended to the four weeks immediately preceding the expected appearance of the pollen (see pollen calendar in Attachment 1 of the protocol).

2. Bronchial asthma requiring a change of treatment or requiring
corticosteroids whether systemic or by inhalation at a dose greater than the equivalent of 200 μg betamethasone daily.

3. Atopic dermatitis requiring a change of treatment or the prescription of systemic or topical corticosteroids.

4. 'Vasomotor' or infectious rhinitis.

5. Upper respiratory tract infection (URTI) including acute sinusitis or otitis, within the preceding three weeks.

6. Obstructive nasal polyps and/or significant septal deviation.

7. Hypersensitivity to piperazines, e.g., cetirizine, hydroxyzine.

8. Any clinically relevant renal, hepatic, cardiovascular or other problems precluding the inclusion in a clinical study, according to the investigator's discretion.

9. Any clinically relevant biochemical abnormalities, not linked to the perennial rhinitis.

10. Any generalised infection requiring anti-infectives for URTI.

11. A requirement for therapy with any drug restricted by the protocol.

12. Recourse over the previous six weeks to astemizole, over the previous two weeks to systemic corticosteroids or ketotifen, over the previous seven days to topical corticosteroids (except oral inhalation of ≤200 μg/day), over the previous two days to decongestants, sodium cromoglycate (nasal or ocular) or oral antihistamines (other than astemizole or ketotifen).

13. An escalating course of desensitisation therapy.

14. Participation in another drug trial within the previous three months.

15. Recent or foreseeable changes in life style, e.g., moving house, holidays, etc.

2.3 Treatment

2.3.1 Dose Regimen

One tablet containing 2.5 mg, 5 mg, or 10 mg of cetirizine, or a placebo tablet identical in appearance to the cetirizine-containing tablets had to be administered once a day for 14 days (see Section 2.1 for Flow Chart). Where necessary, a washout period was undertaken prior to administration of study drug (see Section 2.1.1.1).
2.3.3 Concomitant Treatment

The following concomitant medications for perennial allergic rhinitis were not allowed during the entire course of the study:

- antihistamines, decongestants, corticosteroids other than by oral inhalation $\leq 200 \mu\text{g/day}$, sedatives, or topical medication (nasal or ocular).

Patients suffering from concomitant diseases could continue in the study only if the disease course and the treatment prescribed were not expected to influence any study parameters.

The administration of medication required for an acute symptom, e.g.,

- for bronchial asthma: theophylline, $\beta_2$-agonists, inhaled sodium cromoglycate, inhaled corticosteroids $\leq 200 \mu\text{g daily}$, nedocromil or
for atopic dermatitis: topical non-steroidal therapy

was permitted provided that the investigator recorded the drug dosage, frequency and reason for administration on the Other Medication page of the CRF.

2.4 Methods of Assessing Efficacy

2.4.1 Symptoms of Perennial Allergic Rhinitis

At each visit the investigator assessed the patient for the presence of the following symptoms using a 4-point scale (for scores see Section 2.2.1):

Main Symptoms
- sneezing;
- nasal discharge (rhinorrhea);
- nasal obstruction;

Accessory Symptoms
- pruritus of the nasal mucosa;
- pruritus of the eyes.

At entry the patient had to present with the three main symptoms and had to score a total of ≥ 5 for the three main symptoms.

Parents or guardians also had to score all five symptoms on a daily basis on the patient diary card.

2.4.2 Global Assessment of Treatment

A global assessment of treatment was made by the investigator at the final visit, according to the following 5-point scale:

0 = worsening;
1 = no change;
2 = slight improvement;
3 = good improvement;
4 = excellent improvement, i.e., all the symptoms have disappeared.
2.5 Methods of Assessing Safety

2.5.1 Safety Evaluations

2.5.1.1 Medical History

A full medical history (including allergy and specific perennial allergic rhinitis problems) and drug history were obtained and a complete physical examination was conducted at baseline.

The physical examination was repeated at each visit or at any time when a patient was withdrawn from the study. This examination consisted of a review of major organ systems and measurement of weight and vital signs (sitting systolic and diastolic blood pressure and sitting pulse). In addition, height was measured at baseline.

2.5.1.2 Laboratory Evaluations

If possible, at pre-study and at final visit, haematology and clinical biochemistry tests were done including:

- haemoglobin, haematocrit, RBC (red blood cells), WBC (white blood cells) and differential, creatinine, SGOT, SGPT, and total bilirubin.

These evaluations were not mandatory. If they were not done at Visit 1 they did not have to be done at the final visit.

2.5.1.3 Adverse Experiences

At each evaluation the investigator determined whether any adverse clinical experiences had occurred. An adverse clinical experience was defined as any unintended change in structure (signs) or function (symptoms) of the body, whether or not considered drug-related. The patients were questioned in a general way and no specific adverse symptoms were suggested.
2.7 Summary of Statistical Methods

2.7.1 Comparability of Treatment Groups at Baseline

Differences between treatment groups with respect to demographic and baseline variables were to be tested by the chi-square test\(^2\) for the categorical variables (e.g., sex, baseline severity scores of individual symptoms) or one-way analysis of variance test\(^3\) for the continuous variables (e.g., age). However, due to the non-normality of the data, a non-parametric alternative, the Kruskall-Wallis test\(^4\), was used for the comparison of continuous variables between treatment groups. These tests were considered to be informative regarding the size of the random differences between the four treatment groups.

2.7.2 Efficacy Analysis

Analysis of efficacy was to be performed on data from all "evaluable" patients in the study. An intent-to-treat analysis was also to be performed for all randomised patients. Initially, however, an intent-to-treat analysis was performed on all patients who took at least one dose of study drug. This was followed by an efficacy analysis of all evaluable patients.

2.7.2.1 Evaluation by the Patient

The highest score of the five rhinitis symptoms (sneezing, nasal discharge, nasal obstruction, pruritus of the nasal mucosa, and pruritus of the eyes) was evaluated each day for each patient. The following variables were derived for each patient based on the daily maximum score for the period
between Day 2 and the last day of evaluation:

1. PDS0 = the percentage of days with a maximum score of 0;
2. PDS1 = the percentage of days with a maximum score of 1 or less;
3. PDS2 = the percentage of days with a maximum score of 2 or less.

Analysis of variance, with treatment and baseline severity as main effects, was to be used to compare treatment groups for each of the above three variables. Baseline was defined as the highest of the five symptom scores for the day of first dose of study drug (Day 1) and the previous day. However, due to the non-normality of the data, the Cochran-Mantel-Haenszel (CMH) mean score test\(^5\) using modified ridits, controlling for baseline severity score, was used for the comparison of the treatment groups, at the 0.05 level of significance.

Further unplanned analyses carried out included pairwise comparisons of each of the three cetirizine groups with the placebo group, using the CMH mean score test as described above. Due to there being multiple comparisons, a pairwise comparison was regarded as significant at \(\alpha=0.05\) if \(p \leq \alpha/3\) (0.0167). A test for linearity between the three cetirizine groups was also undertaken using the CMH correlation test with modified ridits, controlling for baseline severity score, at the 0.05 level of significance.

The variable PDS1 constituted the principal criterion for the judgment of efficacy.

### 2.7.2.2

**Evaluation by the Investigator**

The CMH mean score test using the actual scores as assigned by the investigator, stratified by baseline severity score, was used to compare the treatment groups at Visits 2 and 3, and at endpoint with respect to the five rhinitis symptoms. Baseline was defined as the evaluation before starting treatment (Visit 1). Endpoint was defined as the evaluation at Visit 3 or at the time of termination from the study.

The CMH mean score test using the actual scores as assigned by the investigator, stratified by baseline severity score, was also used to compare the treatment groups at each visit and at endpoint with respect to the highest score of the five rhinitis symptoms. The level of significance was set at 0.05.

Global evaluation was analysed using the row-mean score version of the CMH test, with the actual scores as assigned by the investigator, at a 0.05
level of significance.

2.7.3 Safety Analysis

The proportion of adverse experiences observed in the four treatment groups, after assignment to COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms)\(^6\) categories, was to be compared using the chi-square test. However, due to the very small numbers the proportions of adverse experiences in the three cetirizine groups combined were compared with the proportion in the placebo group using Fisher's Exact test\(^4\), after assignment to COSTART categories.

2.7.4 Sample Size Calculation

A total sample of 280 evaluable patients or 70 per group was required to detect the difference of 20 units (%) between the cetirizine group and the placebo group for the variable PDS1 (residual standard deviation of 40), with two-sided significance level of 0.05 and power of 0.85.

This sample size was actually based on the distribution of the four mean responses being uniformly distributed over the clinically relevant difference given, therefore the power as stated in the protocol is incorrect. The actual power on which the sample size was based is 0.75\(^7\).

It was assumed that 18% of the enrolled patients would not be evaluable and, thus, approximately 340 patients would need to be enrolled in the study.

3.0 RESULTS

3.1 General Study Conduct
A total of 330 patients was enrolled, 130 in the first and 200 in the second enrolment period, respectively, patient numbers being allocated at the entry visit (Visit 0/1). For two of the patients (Lawrenz/528347 and Lawrenz/528348), which were the only data during the second
3.2 Demography
Of the 328 patients, 311 completed the study while 16 patients discontinued prematurely [six in the placebo group (7.2%), five in the 2.5 mg group (6.0%), three in the 5 mg group (3.5%), and two in the 10 mg group (2.6%)] and one patient in the 10 mg group (Lawrenz/528021) had a partially completed CRF with no information available as to whether the patient completed the study. Reasons for premature
The patient population for the intent-to-treat analysis consisted of 328 patients aged five to 12 years (mean±STD: 8.9±1.85, 8.6±1.76, 9.2±1.93, and 9.3±1.85 years, for the placebo, 2.5 mg, 5 mg and 10 mg groups, respectively). There was no significant difference between the age distributions of the four groups (p=0.095, Table 7). The respective percentage ratios of male:female patients were 54.2%:45.8%, 54.8%:45.2%, 70.6%:29.4%, and 57.9%:42.1% in the four treatment groups. Although the sex ratio was uneven in the 5 mg and 10 mg groups, no significant difference was found in the sex ratios between the four groups (p=0.104, Table 7). The uneven sex ratio was not expected to affect the analyses, since sex is not considered to influence the efficacy of cetirizine. Most patients were Caucasian in origin (97.6%, 95.2%, 94.1%, and 100.0% in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively); there was no difference in the distribution of race across the four groups. Thus, the treatment groups were well matched at baseline with respect to age and race.

Vital signs for the patients included in the intent-to-treat analysis are given in Listing 5 and summarised in Tables 8.1 to 8.4. At baseline, weight ranged from 17.00 to 70.00 kg with means±STD of 31.31±7.878 kg, 31.47±8.414 kg, 34.29±8.101 kg, and 34.65±9.678 kg in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively. Sitting systolic blood pressure ranged from 80 to 140 mmHg. Sitting diastolic blood pressure ranged from 40 to 90 mmHg. Sitting pulse ranged from 55 to 132 bpm.

All patients were symptomatic outpatients who had a diagnosis of perennial allergic rhinitis established for a period of up to 12 years (mean±STD: 3.0±1.91, 3.1±1.82, 3.2±2.22, and 3.0±1.74 in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively). No significant difference in the duration was found across treatments (p=0.902, Table 7). Further, eligibility of patients was checked against all medication taken within the six weeks prior to enrolment in the study. Of the 328 patients, 49 (59.0%), 42 (50.0%), 45 (52.9%), and 36 (47.4%) of patients in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively, took one or more prior medications (Table 9). Based on this previous treatment, patients entered a washout period where necessary.

The diagnosis was confirmed in all patients by a positive skin test/RAST
to either house dust, house dust mite, moulds or cat/dog hair.

Most patients had previously received treatment for the perennial allergic rhinitis: 63 (75.9%), 60 (71.4%), 63 (74.1%) and 54 (71.1%) in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively (Listing 7).

Patient medical history was unremarkable in all patients included in the analyses and did not relate to or interfere with the current primary diagnosis.

Almost all patients had a diagnosis of allergic asthma, allergic bronchitis, atopic dermatitis and/or seasonal rhinitis (Listing 2).

Concomitant medications were given to treat either secondary diseases or adverse experiences in 25 (30.1%), 26 (31.0%), 22 (25.9%), and 20 (26.3%) patients in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively (Table 10).

The physical examination at Visit 0/1 showed signs of perennial allergic rhinitis affecting the nose and occasionally the eyes.

### 3.3

#### Efficacy

### 3.3.1

**Patient Assessment of Symptoms of Perennial Allergic Rhinitis**

Table 11 shows the baseline severity score for the patient assessment of symptoms of perennial allergic rhinitis as well as the values of PDS0, PDS1, and PDS2. Table 12 summarises the distribution of the baseline score by treatment group. Tables 13.1 to 13.3 show the distribution of the PDS variables in each baseline severity group and Table 13.4 gives summary statistics for these variables.

For the patient assessment of symptoms of perennial allergic rhinitis, the treatment groups were well matched at baseline (p=0.567, Table 12). Regardless of this, however, all analyses were stratified by the baseline scores to allow for differences that may have existed between the patient populations with regard to the severity of symptoms prior to treatment.

#### 3.3.1.1

**PDS0**

On average, patients assigned to the placebo group had 7.07% of their treatment days with a maximum score of 0 (i.e., free of symptoms of perennial allergic rhinitis) compared with 6.39%, 8.24%, and 14.41% in the 2.5 mg, 5 mg, and 10 mg groups, respectively (Table 13.4). There
was a significant difference (p=0.030) in the distribution of PDS0 between the four groups. Table 13.5 shows that although the 2.5 mg dose of cetirizine appeared to be less effective than placebo in the relief of symptoms (mean percentage difference = -0.68%), the difference in the distributions between these two groups was not significant (p=0.572). Due to there being multiple testing, pairwise comparisons were regarded as significant at $\alpha=0.05$ if $p \leq \alpha/3$ (0.0167). The PDS0 value was higher for patients in the 5 mg group compared with placebo (mean percentage difference = 1.17%), but the difference between the distributions was not statistically significant (p=0.216). The 10 mg dose was found to be significantly more effective than placebo at relieving the symptoms of perennial allergic rhinitis with a difference in means of 7.34% (p=0.008). Figure 2.1 shows the mean PDS0 with one standard error for each treatment group. The increase in PDS0 with higher doses of cetirizine was confirmed by the significant test of linearity for the three doses of cetirizine. This suggested that efficacy of cetirizine, as assessed by the percentage of symptom-free days, increased with higher doses.

3.3.1.2 PDS1

The percentage of days with a maximum score of 1 or less was expected to be greater for patients on active treatment (i.e., those assigned to the cetirizine groups). In patients allocated to the placebo group, on average 37.36% of their treatment days had a maximum score of 0 or 1. This increased to 46.44%, 46.90%, and 50.31% for patients receiving 2.5 mg, 5 mg, and 10 mg cetirizine, respectively. The difference in the distributions of PDS1 over the four groups was found to be non-significant (p=0.053). On comparing each dose of cetirizine with placebo, although the mean PDS1 was higher in all the cetirizine groups, only the 10 mg dose showed a significant increase in the percentage of days with a score of 1 or less (p=0.016). A post hoc estimate of power for the global comparison of PDS1 was 47%. This estimate was based on a parametric test using observed means and an overall standard deviation of 36.06. Figure 2.2 suggests a slight dose-related increase in PDS1, but the CMH correlation test was found to be non-significant (p=0.446).

3.3.1.3 PDS2

On average, patients in the placebo group had 70.02% of their treatment days with a maximum score of 2 or less. The mean PDS2 was 80.73%, 79.28%, and 84.47% for the 2.5 mg, 5 mg, and 10 mg groups, respectively. There was a significant difference (p=0.005) in the distribution of PDS2 between the four groups and pairwise comparisons with placebo showed a significant shift in the distribution of PDS2.
associated with all doses of cetirizine. Figure 2.3 shows the mean PDS2 with one standard error for each treatment group. The non-significant test for linearity (p=0.537) suggested that although the cetirizine doses were more effective than placebo, the efficacy of the higher doses did not increase linearly with respect to PDS2.

3.3.1.4 Summary of Patient Diary Data

In summary, the 10 mg dose of cetirizine showed a clear advantage over placebo in terms of the number of symptom-free days. The mean PDS0 showed a significant linear relationship with increasing doses of cetirizine (p=0.026). The main efficacy variable PDS1 showed a similar marked effect with the 10 mg dose over placebo, but the test of linearity proved to be non-significant. PDS2 showed all doses of cetirizine to be better than placebo.

Figure 3.1 shows the mean maximum severity score as assessed by the patient, over baseline and treatment days. All treatment groups showed a marked reduction in the mean severity score after the first dose of study drug. The placebo group and the 2.5 mg group had similar mean severity scores on the second day after treatment, the 5 mg group showed a further decrease, and the 10 mg group showed the greatest decrease in severity score.

Initially, there was a decrease in all symptom scores in the four treatment groups. However, after the first day of treatment, there was a less severe reduction in severity score in all four groups. Over time, there was a marked difference in severity score on each day with the most severe scores occurring in the placebo group and severity decreasing with increasing cetirizine dose. The most pronounced difference was that observed between the 10 mg and placebo groups. There was a less distinct difference between the 2.5 mg and 5 mg groups compared with placebo. This pattern suggested a possible dose-related effect of cetirizine on the mean maximum severity score. The important decline in the placebo group was due to the placebo effect.

Figure 3.2 shows the mean sneezing score for each treatment group on each day. A similar pattern to the mean severity score was observed, although there was less distinction between the 5 mg dose and the 10 mg dose groups.

Figure 3.3 shows the mean nasal discharge score. There appeared to be little difference between the placebo group and the 2.5 mg dose in the first week of treatment, with the placebo group, in fact, showing lower
scores for the first four days. After Day 7, the effect of the different doses of cetirizine became more distinct, with the highest dose showing the lowest scores and the placebo group the highest.

Figure 3.4 shows the mean nasal obstruction score. Initially there was little difference between the 2.5 mg and 5 mg groups; after Day 7 there was a distinct difference between the 5 mg and 10 mg doses compared with the two other groups, and by Day 13 this difference became apparent between the three active treatment groups and placebo.

Figure 3.5 shows the mean pruritus of the nasal mucosa score, while Figure 3.6 shows the mean pruritus of the eyes score. Both exhibit similar patterns to those observed in Figures 3.1 to 3.4, except that the baseline scores were not as close as those seen with the other three symptoms.

3.3.2 Investigator Assessment of Symptoms

The severity of symptoms as assessed by the investigator was not significantly different between treatment groups at baseline across all groups with respect to the main symptom score (p=0.876), the accessory symptom score (p=0.686), and the five symptom scores individually (see Table 7).
at endpoint, by baseline severity score. At baseline, the mean severity scores were very similar in each of the four treatment groups, ranging from 2.61 to 2.72 (Table 15.4). At Visit 2 there was a significant difference (p=0.022) between the four groups with the placebo group having the highest mean severity score and the 10 mg group having the lowest mean severity score. Surprisingly, the mean severity score was lower for the 2.5 mg group than for the 5 mg group. At Visit 3, the mean severity score for the placebo group was highest, there was little difference between the three active treatment groups, and the CMH test had a non-significant result. The evaluation at endpoint showed significant differences between treatments (p=0.019); the placebo group had the highest severity score, with the means for the cetirizine groups
being very similar. These results are presented in Figure 4.1. In summary, cetirizine had a marked effect upon symptoms of perennial allergic rhinitis, this effect being greatest for the 10 mg dose group at Visit 2. At Visit 3, there was a clear effect of cetirizine over placebo but there was little difference between the three doses. This suggested that for the immediate (i.e., over one week) relief of symptoms, a higher dose of cetirizine was more effective, but with regard to the long-term improvement of symptoms there was little difference between doses.

Tables 16.1 to 20.4 and Figures 4.2 to 4.6 summarise the individual symptom scores. At Visit 2, the mean sneezing score was significantly different between treatments (p=0.003). Figure 4.2 shows that this significant result was because of the difference between the placebo group and all three cetirizine groups. At Visit 3, the severity score decreased as the dose increased. This relation held at endpoint, suggesting that for the symptom sneezing the severity score was dose-related.

At Visit 2, the severity of nasal discharge was greatest for the placebo group; it was also higher for the 5 mg group than for the 2.5 mg group, but the overall difference in means was not significant. The mean scores were significantly different at Visit 3 (p=0.010), with a dose-related decrease in severity. The same pattern was observed at endpoint.

The mean severity scores for nasal obstruction at Visit 2 for each treatment group were not significantly different. At Visit 3 and at endpoint the severity was greater in the placebo group than in any other group, the means were only significantly different at endpoint (p=0.049).

The mean score for pruritus of the nasal mucosa was significantly different between treatments at Visit 2 (p=0.001), again with the placebo group having the most severe score. There was little difference in severity scores between the 5 mg and 2.5 mg groups, with the 10 mg group showing the lowest mean severity score. The difference between treatments was not significant at Visit 3 and at endpoint, but there was a decrease in severity with increased dose.

The mean score for pruritus of the eyes showed significant differences between treatments at Visit 2 only (p=0.008); the scores for the 5 mg and 10 mg groups were equal and both were lower than that for the 2.5 mg group. Significant differences were not found at Visit 3 and at endpoint, although for both periods the placebo group showed higher symptom scores than the cetirizine groups.
3.3.3 Investigator Global Assessment

The investigators assessed the global effect of treatment at the final visit on a five-point scale. The results are shown in Table 21.1 and summarised in Table 21.2. Only 320 of the 328 patients randomised had an assessment.

The investigators assessed 37.5% of patients in the placebo group to have shown excellent or good improvement (11.3% excellent) with 62.5% assessed as having worsened, having had no change or slight improvement. In the 2.5 mg group, 51.8% of patients had excellent or good improvement (10.8% excellent) and 48.2% worsened, had no change or slight improvement. The figures in the 5 mg group were: 66.3% excellent or good improvement (15.7% excellent), 33.7% worsened, no change or slight improvement; in the 10 mg group the figures were: 66.2% excellent or good improvement (21.6% excellent), 33.8% worsened, no change or slight improvement. The distribution of global assessment scores was significantly different between the four groups (p<0.0001). Table 21.2 shows that the largest differences were between the placebo group, the 2.5 mg group, and the 5 mg group. There was very little difference between the 5 mg and 10 mg groups in the mean global score, although a higher percentage of patients was shown to have excellent improvement in the 10 mg group.

3.3.4 Efficacy Analysis of Evaluable Patients

An efficacy analysis was also carried out using evaluable patients, with 73, 78, 77, and 70 patients in each of the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively. Reasons for non-evaluability are given in Table 3.2. The patient assessment of symptoms of perennial allergic rhinitis are summarised in Tables 13.6 to 13.10. The main difference from the intent-to-treat analysis was the significant difference in the distribution of PDS1, the main efficacy variable, over the four treatment groups (p=0.028). A post hoc estimate of power for the global comparison of PDS1 was 58%. There was also a significant pairwise comparison between the 5 mg and placebo groups for PDS1 (p=0.017). Tables 15.5 to 15.8 give the distribution of scores and summarise the results of the investigator assessment of symptoms of perennial allergic rhinitis. Tables 16.5 to 16.8, 17.5 to 17.8, 18.5 to 18.8, 19.5 to 19.8, and 20.5 to 20.8 give the same information for the individual symptoms as assessed by the investigator. Tables 21.3 and 21.4 summarise the results for the investigator global assessment.

The results from this analysis of evaluable patients substantiate those
from the intent-to-treat analysis.

3.4 Safety

3.4.1 Data Set Analysed

Of the 330 patients enrolled into the study, 328 received at least one dose of study drug and had safety follow-up information. Two patients were excluded from the safety analysis since their CRFs were mislaid by the investigator: Lawrenz/528347 and Lawrenz/528348 from the 10 mg and 5 mg groups, respectively.

Overall, 83, 84, 85, and 76 patients in the placebo, 2.5 mg, 5 mg, and 10 mg cetirizine groups, respectively, were evaluable for the safety analysis. Table 6 provides, by treatment group, the duration of treatment for the patients in the safety analysis except for two who had missing last dose dates: one patient in the placebo group (Braun/528184) and one patient in the 10 mg group (Lawrenz/528021). The duration of treatment ranged from one to 48 days (see Section 3.1.1, Point 2), with the majority of patients receiving 14 days of treatment, as required by the protocol (Listing 12). The mean duration of treatment±STD was similar among the different treatment groups: 14.7±4.25, 14.2±2.19, 14.5±2.36, and 14.2±2.54 days in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively. Overall demographic data for patients evaluable for safety did not reveal any important between-treatment differences.

3.4.2 Safety Tests

Safety tests were conducted to monitor patient safety as described in Section 2.5.1.
3.4.3 Adverse Experiences

Methods of recording, classifying and reporting adverse experiences are detailed in Section 2.5.1.3. Listing 13 reports clinical adverse experiences by patient, using the preferred terms from the COSTART terminology.
system together with any investigator comment. There were no laboratory adverse experiences reported. Listing 9, Concomitant Medications, includes details of the medication administered as a result of an adverse experience.
A total of 65 patients reported one or more adverse experiences during the course of the study: 15 of 83 patients (18.1%) in the placebo group,
21 of 84 patients (25.0%) in the 2.5 mg group, 12 of 85 patients (14.1%) in the 5 mg group, and 17 of 76 patients (22.4%) in the 10 mg group (Table 23).

Adverse experiences not related to the intake of study drug occurred in 13 (15.7%), 16 (19.0%), 10 (11.8%), and 12 (15.8%) patients in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively (Table 24.1). These adverse experiences included fever, flu, headache, and abdominal pain. In addition, three patients complained of dizziness: one each (1.2-1.3%) in the placebo, 2.5 mg, and 10 mg groups.
Eight patients discontinued from the study because of adverse experiences: one patient (1.2%) in the placebo group had two non-serious adverse experiences requiring hospitalisation; by definition, an adverse experience resulting in hospitalisation is termed a "serious adverse experience". Four patients (4.8%), two patients (2.4%), and one patient (1.3%) in the 2.5 mg, 5 mg, and 10 mg groups, respectively, had a total of 12 non-serious adverse experiences. All patients discontinued due to adverse experiences are summarised in the following table:

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Patient Number</th>
<th>Adverse Experience</th>
<th>Maximum Intensity</th>
<th>Relationship to Study Drug</th>
<th>Serious (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Steiner/528038</td>
<td>Obstructad Stomach pain</td>
<td>Moderate Severe</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>Balike/528269</td>
<td>Nausea</td>
<td>Moderate</td>
<td>Unlikely</td>
<td>No</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>Bauer/528391</td>
<td>Bronchitis</td>
<td>Moderate</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>Leupold/528028</td>
<td>Fever</td>
<td>Severe</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>Overbeck/528216</td>
<td>Dizziness</td>
<td>Moderate</td>
<td>Highly probable</td>
<td>No</td>
</tr>
<tr>
<td>5 mg</td>
<td>Bauer/528231</td>
<td>Virus infection</td>
<td>Moderate</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>5 mg</td>
<td>Tacke/528078</td>
<td>Pharyngitis</td>
<td>Moderate</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>10 mg</td>
<td>Lameer-Engel/527014</td>
<td>Itching exanthema Pharyngitis</td>
<td>Mild Moderate</td>
<td>Possible</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pinpoint exanthema over trunk</td>
<td>Mild</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tonsillitis</td>
<td>Moderate</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>

It is noteworthy that for two patients (Enzel/528041 in the placebo group and Overbeck/528279 in the 5 mg group), who prematurely withdrew from the study because of an inadequate therapeutic response, the investigator recorded the worsening of symptoms as an adverse experience (allergic rhinopathy for Enzel/528041 and worsened rhinitis for Overbeck/528279). Subsequently, the investigator indicated that the patients were discontinued from taking study drug due to the adverse experience. Additionally, one further patient had an adverse experience resulting in discontinuation of the study drug (Bulle/528335 in the 2.5 mg group). However, the reason for premature discontinuation from the study was because of a protocol violation. This protocol violation was
4.0 DISCUSSION

Overall, 311 of the 328 patients randomised to receive one of the four study drugs completed the three study visits. Of the 328 patients, 16 discontinued prematurely from the study [six (7.2%), five (6.0%), three (3.5%), and two (2.6%) from the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively] and one patient in the 10 mg group had a partially completed CRF with no information available as to whether the patient completed the study. Three patients (3.6%) in the placebo group and one patient (1.2%) in the 5 mg group discontinued because of lack of efficacy (inadequate therapeutic response). Eight patients withdrew because of adverse experiences (one, four, two, and one patient in the placebo, 2.5 mg, 5 mg, and 10 mg groups, respectively). One patient in the placebo group withdrew due to the development of an exclusion criterion and one patient in the 2.5 mg group withdrew due to a protocol violation caused by the use of an unauthorised medication. No dose-related distribution of adverse experiences could be recognised. The remaining two patients discontinued because of reasons unrelated to the study.

The primary efficacy variable was the percentage of patient diary days with a maximum score of less than or equal to one, PDS1. The analysis showed that there were no significant differences in the distribution of PDS1 between treatment groups. However, the positive mean differences between the active treatment groups and placebo suggested that at all doses cetirizine was more effective than placebo, although significance was reached only in the 10 mg group.

The analyses of the variables PDS0 and PDS2 (the percentage of days with a maximum score of 0 and 2 or less, respectively) gave similar results, in that both showed significant differences between the four treatment groups. The greatest mean difference between placebo and each of the active treatment groups occurred for the 10 mg group; for both PDS0 and PDS2 they were significant, indicating that this group had the most benefit over placebo. The test for linearity was significant only for the variable PDS0, suggesting a dose-related effect on the number of symptom-free days.
These findings were supported to some extent by the investigator assessment of symptoms of perennial allergic rhinitis. At each visit, the scores for the placebo group were higher than those for the active groups indicating that cetirizine, at any dose, was more beneficial than placebo in reducing the symptoms of perennial allergic rhinitis. However, for determination of the most effective dose, the results were not as clear.

The investigator global assessment of treatment showed a significant difference between all treatment groups. The mean global score suggested that the active treatment groups were more effective than placebo. There was little difference between the 5 mg and 10 mg groups, although both showed a slightly more beneficial effect than the 2.5 mg dose of cetirizine.

The efficacy analysis carried out on evaluable patients showed similar results to those for the intent-to-treat analysis with the exception that the difference in the distribution of PDS1 between the four treatment groups was significant.

Thus, comparison of the four treatment groups indicated a clinical improvement of the symptoms of perennial allergic rhinitis on treatment with 10 mg cetirizine compared with placebo.

5.0 CONCLUSION

In conclusion, the 10 mg dose of cetirizine caused the greatest reduction in symptoms of perennial allergic rhinitis in comparison with placebo, and, thus, could be used to effectively treat children with these symptoms. The lower doses of cetirizine also showed some benefit over placebo, although statistical significance was not reached in all cases. The results suggested a linear dose–response relationship for effect on the mean PDS1 score, which, however, did not prove to be statistically significant for the intent-to-treat population. Adverse experiences such as fatigue, suggesting a sedative effect, were rare. The results of this trial confirm the results of previous studies, which have established that 10 mg cetirizine given once daily is a safe and effective dose in children suffering from perennial allergic rhinitis.

6.0 REFERENCES


6. Department of Health and Human Services (DHHS). COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms). Rockville, Maryland: DHHS, FDA.