STUDY A152 CLINICAL REPORT

Multi-centre double-blind Study of the Safety and Efficacy of a Once Daily Dose of 10 mg Cetirizine (1 mg/ml Oral Solution) or 5 mg Astemizole (1 mg/ml Oral Suspension) given one hour before the evening meal over 4 weeks to children aged 6 to 12 years old suffering from Perennial Allergic Rhinitis.

Protocol Number: PCE89F071

Investigators:

Great Britain

Dr S A Ahmed
Dr T Baker
Dr M Chandra
Dr S Chatterjee
Dr S K Chouksey
Dr N J Cook
Dr A Cuthill
Dr M Golten
Dr P L Hurst
Dr J Miller
Dr J R Nankani
Dr J Parr
Dr A Pawlowicz
Dr M Pimm
Dr C N N Roberts
Dr H Sabbubba
Dr P Saul
Dr J Taylor
Dr D Williamson

Wednesbury
Congleton
Bolton
Bolton
Manchester
Avon
Cardiff
Cardiff
Widnes
Cheadle Hulme
Wrexham
Barry
Penarth
Weston-Super-Mare
Hereford
Caerphilly
Chester
Bristol
Cardiff

Monitor:

European Pharmaceutical Investigation Consultants Limited
15/16 King Charles House
Cavalier Court
Bumpers Farm
Chippenham
Wiltshire
SN14 6LH
England

Author of Clinical Report:

Dr H C Cash
Medical Director

Signature

Date 26/July/92
# Table of Contents

Summary | 4–5
---|---
I Introduction | 6
II Methods | 6
A. STUDY SCHEME | 6–7
B. PATIENT POPULATION | 7–10
C. THE TREATMENTS | 10
   1. Study medications | 10
   2. Contra-indicated medications | 10
   3. Concomitant medications | 11
D. CONDUCT OF THE STUDY | 11
   1. Clinic assessments | 11
   2. Diary cards | 11
   3. During visit 1 | 12–13
   4. During visit 2 | 13
   5. During visit 3 | 13
   6. Unscheduled visits | 14
E. EVALUATION OF EFFICACY | 14
   1. Investigator assessments | 14
   2. Patient assessments | 15
F. EVALUATION OF TOLERANCE | 15
   1. Laboratory tests | 15
   2. Adverse events | 15–16
G. COMPLIANCE WITH TREATMENT | 16
H. STATISTICAL METHODS | 16
   1. General | 16–17
   2. Estimation of missing data | 17
   3. Daily diary cards | 17–18
   4. Rhinitis symptoms recorded at clinic visits | 19
   5. Global evaluations | 19
   6. Data other than rhinitis symptoms recorded at clinic visits | 19–20
   7. Safety evaluation | 20–21
III Results

A. TIME-FRAME/ENROLMENT

B. DEMOGRAPHY

C. MEDICAL HISTORY AND PHYSICAL EXAMINATION

D. ANALYSIS OF EFFICACY

1. Evaluation of symptoms of rhinitis - daily diary cards
2. Evaluation of symptoms of rhinitis - by the investigator at each visit
3. Global evaluation of treatment by the investigator

E. ANALYSIS OF TOLERANCE

1. Adverse events
2. Laboratory tests

F. NON-COMPLIANCE/PROTOCOL DEVIATIONS

1. Non-compliance with treatment regimens
2. Patients failing to complete study
3. Non-compliance with inclusion/exclusion criteria
4. Violations of visit schedules
5. Change in patient's condition which made him/her a protocol violator
6. Incorrectly completed diary cards

IV Discussion

V Conclusion

References

Tables : from 1 to 16

Figures : from 1 to 17

* * * * * * * *

Appendix 1 List of patients by investigator and by group:treatment number/CRF number (=second part of trt number) initials

Page

RRCE91G1503 3

Page

Final Version/HCC/HJD/220692
Summary

One hundred and four patients, aged between 6 and 12 years, suffering from perennial allergic rhinitis were enrolled at 19 centres into this double-blind study, comparing the efficacy and toleration of cetirizine (solution) with that of astemizole (suspension).

Patients took the treatment once daily, one hour prior to the evening meal, for four consecutive weeks; patients were randomly allocated to receive either 10 mg cetirizine 10 ml solution plus 5 ml placebo astemizole suspension, or 5 mg astemizole 5 ml suspension plus 10 ml placebo cetirizine solution.

Each evening during the four weeks study period, the children were required, with parental assistance, to complete a diary card in which the severity of the symptoms of perennial allergic rhinitis were recorded for that day. The symptoms evaluated were sneezing, runny nose, blocked nose, itchy nose and itchy eyes.

Events occurring during the study period and medications, other than study medication, taken by the patient were also recorded in the diary card.

The same investigator made an assessment of the symptoms of perennial allergic rhinitis at three clinic visits during the course of the study. These clinical assessments were at inclusion, following two weeks, and following four weeks of treatment. The symptoms assessed were sneezing, rhinorrhoea, blocked nose, itchy nose and itchy eyes.

At the final clinic visit the investigator made a global assessment of the response to treatment.

The toleration of the test medications was based upon the adverse events recorded in the diary cards or elicited at the clinic visits, and laboratory safety tests conducted at the beginning and end of the treatment period.

All of the patients who received study medications were included in the analysis of efficacy and safety; 51 patients received cetirizine and 53 patients were treated with astemizole.

Based upon an appraisal of clinical symptom severity recorded by the investigator and the severity of symptoms recorded by the patients in the diary cards, both cetirizine and astemizole were effective in the treatment of perennial allergic rhinitis in these children.
The primary measure of efficacy was the percentage of asymptomatic days recorded in the diary cards, a median difference of 15% being considered as clinically significant. The median percentage of asymptomatic days was zero in both groups. Both products can be claimed to have similar efficacy since the 95% confidence limits of the difference between cetirizine and astemizole are -3 and 0%.

There were also no differences between the groups for any of the secondary measures of efficacy, with the exception of results in favour of astemizole for the global response to treatment (p= 0.023) and the maximal symptom score (p= 0.035), both recorded by the investigator at the last visit.

Cetirizine and astemizole were well tolerated and there were no statistically significant differences in frequency of reported adverse events. There were no clinically significant laboratory abnormalities recorded during the course of this study with either treatment.
I  Introduction

Cetirizine is a potent anti-histamine of the piperazine group which has an established role in the treatment of seasonal rhinitis and perennial rhinitis in adults.\textsuperscript{1, 2, 3, 4, 5} The recommended daily dose of cetirizine for rhinitis in adults is 10 mg.

The plasma half life of cetirizine in children (6.5 Hours) is shorter than in adults (9.5 Hours)\textsuperscript{6}. Therefore, initial studies in children were based upon a twice daily regimen.

A dose selection study in children aged between 6 and 12 years, with seasonal allergic rhinitis, established the efficacy and safety of cetirizine 5 mg twice daily\textsuperscript{7}.

Another study showed that, in children aged between 6 and 12 years suffering from seasonal allergic rhinitis, there were no clinically significant differences between cetirizine administered as a single 10 mg dose, or as 2 separate 5 mg doses. In a further study in children, aged between 3 and 6 years old suffering from atopic dermatitis, cetirizine at a dose of 10 mg daily was shown to be well tolerated\textsuperscript{8}.

Astemizole, a potent, long acting histamine H\textsubscript{1} receptor antagonist, has been approved for use in children with allergic rhinitis; the recommended dose is 5 mg daily. Astemizole has been formulated as a suspension for ease of use in children\textsuperscript{9, 10, 11, 12}.

The objective of the present study was to compare the efficacy and safety of 10 mg cetirizine (solution) and 5 mg astemizole (suspension), when administered once daily to children aged 6 to 12 years with perennial allergic rhinitis.

II  Methods

A. Study Scheme

This Phase III, randomized, double-blind, parallel group study was planned to enrol a total of 200 children, aged between 6 and 12 years, with a diagnosis of perennial allergic rhinitis. Twenty investigators were required to enrol a minimum of 6 and up to a maximum of 20 patients each.
The enrolment of patients was suspended from the 1st of May to the end of August 1990. This was to avoid the pollen allergy season.

Prior to embarking upon this study, approval for the protocol from an appropriate Ethics Committee was sought.

The following Ethics Committees reviewed and approved protocol number PCE89 FO71:-
B. Patient Population

Prior to inclusion in this study, the parent or legal guardian of the child was required to give written informed consent, having previously read a patient information sheet and discussed the implications of the study with the investigator.
Boys and girls aged between 6 and 12 years of age, attending out-patient clinics, with a diagnosis and one year history of perennial allergic rhinitis to pollen allergens were eligible for enrolment into this study.

The diagnosis of sensitivity to perennial allergens such as house dust mite and/or animal danders was confirmed by a skin prick test (Pfazet). In addition, from January 1st to the end of April (1990 and 1991) an aliquot of the patient’s plasma, obtained at enrolment, was subjected to an ELISA test for seasonal pollen allergens. Those patients who had a positive pollen ELISA test were withdrawn from the study.

At the time of enrolment into the study, the patient was required to be experiencing an active phase of perennial allergic rhinitis, characterised by the following three "prime" symptoms: - sneezing, rhinorrhoea and blocked nose.

To be eligible for inclusion, the total score for these 3 symptoms at the time of screening had to be equal to or greater than 5. (Based upon a 4 point scale where 0 = absence of symptom and 3 = severity of symptom leading to disturbance of sleep and/or impairment of the patient’s normal daily activity).

Those patients with any of the following symptoms or conditions were not eligible for enrolment in this study:-

- a known allergy to a pollen which was present in the period preceding the study and/or was likely to be "raised" during the study period.

- asthma likely to require a change of therapy during the course of the study, or needing corticosteroids either systemically or by inhalation in a dose greater than 400 mg daily.

- atopic dermatitis needing a change of established treatments, or requiring systemic or topical corticosteroids either just prior to or during the study period.

- vasomotor or infectious rhinitis.
- an upper respiratory tract infection, in the three weeks prior to screening for this study.
- obstructive nasal polyps.
- a history of hypersensitivity to piperazines or astemizole.
- a clinically relevant, renal, hepatic or cardiovascular disease or a condition which would make participation in this study advisable.
- clinically significant laboratory haematological or biochemical abnormalities not related to perennial allergic rhinitis.
- the presence of any infection likely to necessitate a course of antibiotic treatment during the study period.
- treatment with the following drugs during the pre-study periods specified:-
  - astemizole in the previous 6 weeks.
  - systemic steroids in the previous 4 weeks.
  - ketotifen in the previous 2 weeks.
  - topical steroids (nasal or ocular) in the previous week.
  - disodium cromoglycate (nasal or ocular) in the previous week.
  - nasal decongestants or oral anti-histamines in the 2 days prior to screening.
- a current graduated course of desensitization therapy.
- participation in another clinical study in the previous three months.
- recent or foreseeable changes in lifestyle, e.g. moving house, holidays, regular weekend trips, during the trial period, to places where the patient may not be exposed to the allergen(s) for which he/she was being treated.

- the likelihood of poor compliance.

C. **The Treatments**

1. **Study Medications**

   The medications which were compared during the course of this study were:-

   Cetirizine 1 mg/ml oral solution (batch no. 80) and placebo (batch no. 79P).

   Astemizole 1 mg/ml oral suspension (batch no. 86A29/F16) and placebo (batch no. 305.016).

   Patients fulfilling the inclusion criteria and not meeting any of the exclusion criteria were randomly allocated to receive one of the following dosage regimens once daily in the evening for 28 days:-

   The **cetirizine group** received 10 ml (10 mg) of cetirizine and 5 ml of placebo astemizole. The **astemizole group** received 5 ml (5 mg) of astemizole and 10 ml of placebo cetirizine. All study medication was to be taken one hour prior to the evening meal, over the four week study period, commencing in the evening of the day of enrolment.
D. **Conduct of the Study**

1. **Clinical Assessments**

   The study involved three clinical assessment visits. The initial evaluation was on day 1; eligible patients entered the study following this screening assessment. The intermediate clinical assessment was scheduled between days 12 and 18 and the final visit to the clinic was between days 26 and 32.

2. **Diary Cards**

   The patient, with parental assistance, was to complete a diary card each evening during the study, which recorded severity of the five rhinitis symptoms (itchy nose, sneezing, runny nose, blocked nose and itchy eyes).
E. Evaluation of Efficacy

1. Investigator Assessments

At each visit to the clinic the investigator evaluated the severity of the patient's symptoms of perennial allergic rhinitis, namely; sneezing, rhinorrhea, blocked nose and nasal and ocular pruritis on a 4 point scale, where 0 = symptom not present, 1 = mild, 2 = moderate and 3 = a severe symptom which disrupted sleep and/or the patient's normal daily activities. At the final visit the investigator made a global assessment of the response to the treatment, on a five point scale where 0 = deterioration, 1 = no change, 2 = slight improvement, 3 = marked improvement and 4 = a complete resolution of the symptoms.
2. **Patient Assessments**

The patients, with parental assistance, made a daily evaluation of the perennial allergic rhinitis symptoms based upon a 4 point scale where 0 = not at all, 1 = slightly, 2 = a great deal and 3 = unbearable. The first diary entry referred to the symptoms of the day prior to enrolment, and the second entry was based upon the symptoms on the enrolment day, prior to taking the medication; the scores of these first two evaluations were utilized as a baseline.

F. **Evaluation of Tolerance**

1. **Laboratory Tests**

The toleration of the treatment regimens was assessed in part by comparisons of pre- and post-study laboratory measurements of biochemical and haematological parameters and in part by the occurrence of adverse events. The haematology safety evaluations included the following measures: erythrocytes, haemoglobin, haematocrit, leucocytes, neutrophils, lymphocytes, monocytes, basophils and eosinophils. The biochemical parameters assessed consisted of total bilirubin, SGOT, SGPT, urea and creatinine.

2. **Adverse Events**

At clinic visits 2 and 3 the investigator elicited information on the toleration of the medication by asking the standard question "Have you noticed anything in particular which concerns the health of your child?". In addition, the parent was asked to record in the daily diary any events experienced by the child.

For all adverse events, irrespective of cause, the investigator had to complete a full record containing descriptive details of the event, its onset, frequency, course, intensity, outcome and relationship to treatment.
The severity of each adverse event was graded by the investigator on a three point scale where 1 = mild, 2 = moderate and 3 = severe. The relationship of the adverse event to study drug was rated on a five point scale where 1 = none, 2 = unlikely, 3 = possible, 4 = probable and 5 = certain.

In the event of a serious adverse event, the investigator was to notify the study monitor immediately and institute appropriate treatment for the patient.

If deemed absolutely necessary, the investigator could open the appropriate envelope and discover the treatment allocated to the patient experiencing the adverse event, in which case the patient would be excluded from the study.
H. Statistical Methods

1. General

An "intention to treat analysis" was conducted, all patients who were randomized and received treatment being included.

At each clinic visit, the variables recorded in the daily diary cards by the patient were compared for each treatment, as were the variables recorded in the Case Record Form by the investigator.

Final Version/HCC/HJD/220692
When analysing the rhinitis symptoms recorded in the diary card, all comparisons were made to reference baselines, which were the maximum of the values recorded for the day before enrolment, and for the first day of the study, immediately pre-treatment.

The baseline for the comparison of the variables recorded by the investigator in the Case Record Form was the value for each individual parameter at the initial clinical assessment on visit 1.

All the tests which were applied were two tailed and the level of significance was 5%.

The statistical analysis was conducted using the SAS, software version 6.06, under licence from SAS Institute Inc.

2. Estimation of Missing Data

An estimation of missing data of rhinitis symptoms at each visit was made if the patient was a "treatment failure" (= withdrawn from the study for inefficacy or/adverse events). The scores at visit 3 were estimated by the score at visit 2. (This was done for one patient: 433/045).

3. Daily Diary Cards

Throughout the study commencing on the day of first medication, the patient recorded a severity score for the rhinitis symptoms.
4. Rhinitis Symptoms Recorded at Clinic Visits

For each patient at each visit, a maximum and a mean for each score of the five rhinitis symptoms were calculated. The maximum and mean scores were subjected to summary statistics by treatment group and by visit. From the summary statistics of the mean scores, bar charts were constructed for each treatment group for each clinic visit. The differences in the groups' maximum and mean scores between visit 1 and visit 2 and between visit 1 and visit 3 were analysed. An inferential analysis of the maximal score compared the groups' frequency distribution at visit 3 and visit 2 in relation to the maximal score at visit 1, using the Cochran-Mantel-Haenszel test based on ranks.

5. Global Evaluations

The investigator's global evaluation of the response to treatment was analysed in terms of frequency and relative frequency distribution by treatment group.

The frequency distribution between the groups in terms of the global evaluation was compared using the Cochran-Mantel-Haenszel test based on ranks.
7. Safety Evaluation

Adverse Events

Adverse events were subjected to the following analyses:

- for each treatment group a frequency distribution of the number of patients with zero, one, two, three or more adverse events during the study was calculated. The numbers of patients in the two groups were compared by a Cochran-Mantel-Haenszel test based on ranks.

- a frequency distribution in each group of the number and the proportion of patients with at least one adverse event by body-system was prepared. If the same body-system was reported several times for the same patient, only one was retained.

- a frequency distribution for each treatment group, by body-system of the number and the proportion of patients, with at least one adverse event by COSTART term, was produced. If the same COSTART term was reported several times for the same patient, only one was retained, unless it was the same COSTART term reported under different body-systems.

- for each treatment, a frequency distribution of the number of patients by body-system, by COSTART term and by severity of adverse event was prepared. If the same COSTART term was reported several times for the same patient, the maximum severity was retained.
the frequency distribution of the number of patients in each treatment group by body-system, by COSTART term and by relationship of adverse event to the drug was compiled. If the same COSTART term was reported several times for the same patient, the maximum relationship was retained.

**Laboratory Tests**

Laboratory values were characterised in accordance with the following three-category ordinal scale status:-

-1 = measured value below the lower normal limit.
0 = measured value within the normal limits.
+1 = measured value above the upper normal limit.

The haematological and biochemical parameters were subjected to the following analyses:-

- for each patient for each parameter, the measured value, the laboratory normal range and units, status, and the clinical significance at laboratory 1 (initial clinic visit) and at laboratory 2 (final clinic visit) were tabulated.

- listings were made of patients, by parameter and by treatment, with abnormal values.

- for each parameter the following was calculated:-

- a frequency distribution of patient’s status by visit and by treatment

- a frequency distribution of patient’s status at laboratory 2 by treatment, controlling for status at laboratory 1. The distribution in the two groups was compared by the Cochran-Mantel-Haenszel test based on ranks.

**III Results**

The results presented are contained in the statistical report RRCE91G1502.
A. Time-Frame/Enrolment
Fifty three patients were randomly allocated to receive astemizole and 51 cetirizine.
B. Demography

The demographic variables, age, height, weight, sex and race are summarized for both treatment groups in Table 3. The distribution of the patients in the treatment groups by age ranges is presented in Table 4. A detailed presentation of the demographic characteristics is to be found in Appendix 2 (of the Statistical Report). The two treatment groups in terms of the main demographic variables were well balanced with the exception of sex, there being a higher percentage of males 66.7% in the cetirizine group, compared to 54.7% on astemizole.
C. Medical History and Physical Examination

A detailed listing of relevant medical history by body-system is presented in Appendix 3 (of the Statistical Report). As is to be expected in this population of patients with rhinitis, there was a preponderance of abnormal respiratory parameters. There were no differences between the two treatment groups in this respect; only 2 patients in each group were recorded as having normal respiratory systems.

The two groups were well balanced in terms of the duration of their chronic perennial rhinitis, the mean and standard deviation being 3.8 ± 2.5 years for astemizole and 3.3 ± 2.1 years for cetirizine. All of the patients enrolled in this study had a history of perennial rhinitis of greater than one year’s duration.

The clinical examinations conducted at visit 1 revealed that all patients had nasal and sinus symptomatology; in addition 15 astemizole and 21 cetirizine patients had ocular symptoms associated with chronic perennial rhinitis. A full listing of the patients’ physical examination findings is presented in Appendix 3 (of the Statistical Report).

D. Analysis of Efficacy

1. Evaluation of Symptoms of Rhinitis - Daily Diary Cards

Full details and summary statistics for each of the five rhinitis symptoms, together with the maximum and mean score for all recordings in the diary card between day 0, i.e. the day before commencing treatment, to the last day of treatment are presented in Appendices 13, 14, 15 and 16 (of the Statistical Report).

The number of patients completing their daily diary cards declined over time; by day 28 approximately 40 patients in each treatment group were still completing their diaries.
A statistical comparison of the two treatments, based upon frequency distribution of maximal symptom scores day 2 to day 7 compared to baseline maximal scores (day 0 and day 1), revealed no significant differences. Both treatments were similar in terms of their onset of effect in this initial treatment period (Appendix 14 of the Statistical Report).

For each patient, the percentage of days (from day 2 to the last day of treatment) when the maximal symptom score was 0 (PDS0), percentage of days when the maximal symptom score was 1 or less (PDS1) and the percentage of days when maximum score was 2 or less (PDS2) were calculated. These results for both treatments are summarized in Tables 5, 6 and 7.
Summary statistics of the computed variables PDS0, PDS1 and PDS2 are presented in Appendix 15 (of the Statistical Report); comparison of each of these between the two treatment groups, using the Wilcoxon Rank Sum Test, revealed no statistically significant differences.

Differences of at least 15% between the median PDS0 and at least 20% between the median PDS1, for each treatment group, were deemed to be clinically relevant. As the actual differences observed in the study between cetirizine and astemizole were smaller than these and the 95% confidence limits for the difference of PDS0 were -3 to 0%, and for the difference of PDS1 were -16 to 6%, the two treatments may be considered to be, on this basis, clinically equivalent.

2. Evaluation of Symptoms of Rhinitis by the Investigator at each visit

Rhinitis Symptoms

The scores for all five symptoms of rhinitis, recorded by the investigator at the clinic visits for each treatment group, are summarized in Table 8. For all of the symptoms, a maximum and mean score for each treatment group at each clinic visit has been calculated. A more complete and detailed presentation is to be found in Appendix 11 (of the Statistical Report).

For both groups of patients, the individual scores recorded for all five rhinitis symptoms, the maximum scores and the mean scores were lower at visits 2 and 3 when compared to corresponding values at visit 1. The degree of this improvement in symptomatology was greater between visits 1 and 2 than between visits 2 and 3.
The maximum and mean scores for both treatments by visit are presented as bar charts in Figures 15 and 16. These figures illustrate very clearly the overall improvement of symptoms which was present by visit 2 and that this beneficial effect of the treatments is sustained at the final clinical assessment. Calculations based upon maximum scores revealed that there was no statistically significant difference between treatments at visit 2, however at visit 3 astemizole was statistically superior to cetirizine (p = 0.035).

3. Global Evaluation of Treatment by the Investigator

At the final clinic visit the investigator made an overall global evaluation of the response to treatment, based upon a five point scale where 0 = a deterioration, 1 = no change, 2 = slight improvement, 3 = marked improvement and 4 = no symptoms. In the astemizole treated patients, 47 out of 53 were rated as having experienced slight improvement, marked improvement or resolution of rhinitis symptoms. The equivalent figure for the cetirizine group was 39 out of 51.

This difference in the frequency distribution of the global evaluation scores for astemizole and cetirizine was statistically significant (p = 0.023) in favour of astemizole.
E. Analysis of Tolerance

1. Adverse Events

Sixteen patients in each treatment group were recorded as experiencing one or more adverse events during the course of the study. These adverse events, in terms of frequency, are summarized in Table 9. A full listing of adverse events, together with degree of severity and relationship to study medication, is presented in Tables 10 and 11. The 16 astemizole treated patients reported a total of 27 adverse events, 25 of which were rated as mild or moderate by the investigator. A total of 26 adverse events were reported by 16 patients taking cetirizine, of which 21 were considered by the investigator to be in the mild or moderate category.
The most frequently reported adverse event in both treatment groups was headache. Seven patients reported mild or moderate headaches on a total of 9 occasions in the astemizole group. In the cetirizine group, 3 patients reported headaches, 2 of which were described as severe and one moderate.

All adverse events recorded in this study, categorized by body-system, by COSTART term, by severity and by relationship to treatment are listed in Appendices 17, 18, 19 and 20 (of the Statistical Report).

2. Laboratory Tests

Blood samples were obtained from 52 of the astemizole treated patients at the initial visit and from 45 patients at the final clinic visit. For the cetirizine treated patients there were 48 blood samples from the initial and 44 from the final clinic visits.
The haematological and biochemical values measured for each patient at initial and final visit are listed in Appendix 21 (of the Statistical Report), together with the laboratory normal ranges.

The individual haematological and biochemical parameters which were either outside the laboratory normal range at the first laboratory assessment or subsequently moved outside the range are listed in Appendix 22 (of the Statistical Report). Patients with normal laboratory values at visit 1 and missing or normal values at final visit are not included. Similarly, patients with missing values at the first visit and missing or normal values at the final visit are not included.

In only one instance did an investigator attach any clinical significance to an abnormal final laboratory parameter; in the case of patient 284, receiving astemizole, the investigator reported the raised SGOT and SGPT as mild adverse events unlikely to be related to study medication.

The Cochran-Mantel-Haenszel test, utilized to compare the groups' status at the final laboratory analysis, controlling for status at the initial laboratory evaluation, revealed changes for haematocrit (p = 0.085) and monocytes (p = 0.015); however, these changes between the treatment groups for these parameters were not considered to be of clinical relevance.

These comparisons of frequency distribution of laboratory values by treatment group, by status at the final laboratory assessment, controlled for the initial assessment, are presented in Appendix 23 (of the Statistical Report).
IV Discussion
The 104 patients were randomly allocated such that 53 patients received astemizole and 51 patients received cetirizine. The two treatment groups were well balanced at inclusion in terms of demographic parameters, medical history, duration of symptoms of chronic perennial rhinitis and severity of the rhinitis.

Non-compliance with the treatment regimens was a problem in this age group, possibly due in part to the complicated dosage regime required to achieve blinding in this study.

Despite the non-compliance and protocol deviations which occurred during the course of this study, a decision was made to include all patients who received study medications in the analyses of efficacy and safety.
There was an improvement in both treatment groups by visit 2 (end of week 2 of treatment). This clinical improvement continued with both treatments between visit 2 and the end of the study visit 3. However, the degree of improvement in rhinitis symptoms was not as great over the latter period.

The global evaluation of response to treatment, made by the investigators at the end of the treatment period, revealed that both cetirizine and astemizole brought about an improvement in the patients’ condition. However, a higher proportion of the astemizole patients, 47 out of 53, was judged by the investigators to have had a slight improvement, a marked improvement, or resolution of symptoms at the end of the study. The corresponding figure for cetirizine was 39 out of 51. This difference in the investigators’ global evaluation between the two treatments was statistically significant (p = 0.023) in favour of astemizole.

The patients’ response to treatment is apparent from the daily symptom severity scores, the fall in which clearly demonstrates that, with both treatments, improvement in rhinitis symptoms began after a few days and was sustained throughout the four week study period.

Not all of the symptoms of rhinitis were equally responsive to the treatments. Itchy eyes showed only a minimum improvement in either treatment group between visits 1 and 2, and no further improvement between visits 2 and 3. The daily symptom evaluation curves, plotted from the diary card records, are very similar for both cetirizine and astemizole. In the case of the symptom blocked nose, the cetirizine group was more severely affected at the outset; however, by the end of the first day of treatment the mean scores for this symptom were similar for both treatment groups.

Both treatments were well tolerated. The number of patients reporting adverse events was very similar for both treatments. The adverse events reported were, in the main, mild or moderate in nature and the majority was not considered to be related to study medication.
V Conclusion

In this study involving 104 children aged between 6 and 12 years suffering from perennial allergic rhinitis, both cetirizine and astemizole proved to be effective treatments.

The rapid onset of the beneficial response to astemizole and cetirizine is apparent from an inspection of the daily symptom severity scores, as recorded by the patients. The reduction in the daily symptom severity scores demonstrated clearly that both astemizole and cetirizine alleviated the rhinitis symptoms within the first few days of commencing treatment. This response to the treatments continued over the four weeks of the study period. The improvement in rhinitis symptoms observed in both treatment groups is confirmed by the investigators' symptom severity scores recorded at the clinic visits. The maximum response to the treatments occurred between visits 1 and 2.

Comparisons based upon the symptom severity scores recorded by the patients in the diary cards, revealed that cetirizine and astemizole were clinically equivalent in the treatment of perennial allergic rhinitis. This equivalence in clinical efficacy is confirmed by statistical analyses; there were no statistically significant differences between the treatments in terms of the symptom scores recorded by the patients.

There were statistically significant differences in favour of astemizole in both the investigators' global evaluation of response to treatment (p = 0.023) and the maximal symptom score recorded by the investigator at visit 3 (p = 0.035).

Both treatments were well tolerated and there were no statistically significant differences in frequency of reported adverse events, nor were there any clinically relevant laboratory changes associated with either treatment, at these doses, in this population of patients.
REFERENCES

1. Sabbah A.

Comparison of cetirizine and terfenadine in perennial allergic rhinitis.
Alergologia a Immunologia Clinica 1987 2/2 322 abstr. 431

2. Kurzeja A.

Comparative study of cetirizine, terfenadine and placebo in the treatment of patients with perennial allergic rhinitis.

3. Berman B.

Cetirizine therapy of perennial allergic rhinitis.

4. Broide D.H.

Evaluation of cetirizine in the treatment of patients with seasonal allergic rhinitis.

5. Bruttman G.

Antiallergic effectiveness of cetirizine in patients suffering from hay-fever and asthma.
6. Clinical Pharmacokinetics of cetirizine 5 mg p.o. in pediatrics patients with allergic rhinitis.
Pfizer report: D. Uden
Protocole 86-N-0002
Ref. interne UCB DE88A202

7. Etude de l’efficacité et de la tolérance de différentes doses de cetirizine dans la pathologie allergique de l’enfant d’âge scolaire souffrant de rhinite allergique chronique.
UCB rapport interne: Y. Baelde CF88L031.

8. Multicentre study of the efficacy and safety of cetirizine when given once or twice daily to children between the ages of 6 and 12 years suffering from seasonal allergic rhinitis.
UCB internal report: Y. Baelde CE89A104.

9. Sussman A.H., Sussman G.L., Kobric M.
The treatment of perennial rhinitis: An open, multicentre clinical trial of a new, non-sedating antihistamine, astemizole.

10. Holgate S.

11. Sanchez Borges, M.
The safety and efficacy of astemizole for the treatment of allergic rhinitis in children.
46th Annual Meeting of the American Academy of Allergy and Immunology, Baltimore, Maryland, USA.
12. Tiszler-Cieslik, E., Nowak, W., Krzeminska, I.

A double-blind trial comparing astemizole and ketotifen in perennial allergic rhinitis.