SYNOPSIS

INN : TRIAMCINOLONE ACETONIDE

Study number : XRG5029C/1000

Study title : An open-label, repeat-dose, multicenter study to evaluate the safety and pharmacokinetics of single and multiple doses of intranasally administered triamcinolone acetonide (NASACORT® AQ) in pediatric allergic rhinitis patients 2 to 5 years of age compared to adult patients 18 to 50 years of age

CSR date : 18 August 2005

The study results and synopsis are supplied for informational purposes only.

Not all of the study results have necessarily been reviewed by the Regulatory Authorities.

The decision to prescribe and take a product should always be made on the basis of the most recent version of the product information and product package insert in the country of prescription.
STUDY SYNOPSIS

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Title
An open-label, repeat-dose, multicenter study to evaluate the safety and pharmacokinetics of single and multiple doses of intranasally administered triamcinolone acetonide (NASACORT® AQ) in pediatric allergic rhinitis patients 2 to 5 years of age compared to adult patients 18 to 50 years of age

Investigators, study sites
Multicenter study, 6 US sites

Study duration and dates The first subject was enrolled on 30 April 2003 and the last subject exited the study on 22 March 2004. Study duration was approximately 10 months. Phase I

Objectives
Primary:
• To characterize the single dose and steady-state pharmacokinetics (PK) of triamcinolone acetonide (TAA) in pediatric subjects 2 to 5 years of age compared with adult subjects 18 to 50 years of age following 5 days of intranasal dose administration
• To evaluate the safety and tolerability of 5 days of intranasal TAA in pediatric subjects

Study design
This was an open-label, repeat-dose, multicenter study with one treatment period for pediatric subjects and two treatment periods for adult subjects.

Number of subjects planned
24 subjects: 12 pediatric subjects (2 to 5 years of age); 12 adult subjects (18 to 50 years of age). Sites were permitted to over-enroll the study to ensure 12 evaluable subjects in each age group. Over-enrollment of the pediatric subjects was permitted to ensure completion of similar numbers of 2-, 3-, 4-, and 5-year olds. The chosen sample size was consistent with currently accepted standards for this type of investigation.

Inclusion criteria
Subjects included in the study were male or female 2 to 5 years of age (pediatric) or 18 to 50 years of age (adult), who had perennial allergic rhinitis (PAR) with or without seasonal allergic rhinitis (SAR), positive skin prick test to a perennial allergen (adult subjects only), and baseline morning serum cortisol (≥5 µg/dL [138 nmol/L]) confirmed by immunoassay.
Treatments

Pediatric subjects: TAA 110 µg intranasally once a day (qd) for 5 days.
Adult subjects: TAA 110 µg intranasally qd for 5 days. A 7-day washout period, followed by 220 µg intranasally qd for 5 days.

Pharmacokinetic data

- Subjects 2 to 5 years of age (pediatric):
  Peripheral venous blood samples were obtained for measurement of TAA plasma concentrations according to a staggered, sparse sampling strategy. Each subject was to have 4 blood samples collected on Study days 1 and 5, for 8 samples for the study. Each sparse sampling strategy specified a set of 4 sampling times on Study day 1 and a different set of 4 sampling times on Study day 5

- Subjects 18 to 50 years of age (adult):
  Peripheral venous blood samples were obtained for measurement of TAA plasma concentrations before TAA administration and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours postdose on Study days 1 and 5 for each of the 2 treatment periods

Safety data

Safety was assessed based on adverse events (spontaneous or elicited reports), clinical laboratory data (hematology, blood chemistry, and urinalysis), vital signs, and physical examination findings.

Statistical procedures

All subjects who received at least one dose of TAA were included in the safety evaluation. Subjects for whom adequate plasma TAA concentration-time data were obtained were included in the pharmacokinetic analysis.

Continuous data were summarized descriptively as the number of subjects (n), mean, standard deviation (SD), coefficient of variation (CV), median, minimum and maximum. Categorical data were summarized as the number of subjects (n) and percentage of subjects in each category.

The statistical analyses were performed on the SAS Software package, Release 8.02. Pharmacostatistical analyses were performed on WinNonlin® Professional Version 3.3 and NONMEM.

Interim analysis

No formal interim analysis was performed. However, a descriptive analysis was performed on the TAA plasma concentration data obtained from the first 5 pediatric subjects, compared with that obtained from the adult subjects. This descriptive analysis was performed to assess design assumptions and appropriateness of dose selection based on systemic exposure to TAA for a subsequent efficacy study (sponsor’s Study 3502), before that study’s initiation.

Results – Study subjects and conduct

Of the 47 subjects screened, 16 subjects were pediatrics and 31 subjects were adults.
Of the 15 pediatric subjects enrolled, 8 were male and 7 were female; 8 were black, 4 were white, and 3 were multiracial. Of the 15 pediatric subjects, 2 were 2-year-olds, 4 were 3-year-olds, 6 were 4-year-olds, and 3 were 5-year-olds. Mean age was 3.7 years (range: 2 to 5 years) in
pediatric subjects. Mean body mass index (BMI) was 16.1 kg/m² (range: 15.0 to 17.6 kg/m²) and mean body surface area (BSA) was 0.7 m² (range: 0.58 to 0.87 m²) in pediatric subjects. Of the 15 adult subjects enrolled, 10 were male and 5 were female; 13 were black and 2 were white. Mean age was 32.3 years (range: 20 to 49 years) in adult subjects. Mean BMI was 26.2 kg/m² (range: 17.8 to 39.9 kg/m²) and mean BSA was 1.9 m² (range: 1.52 to 2.21 m²) in adult subjects.

Twenty-eight subjects (93.3%) completed the study according to the protocol. Two subjects (6.7%) discontinued the study: 1 pediatric subject (3.3%) discontinued as the site was unable to maintain intravenous access for PK sampling and 1 adult subject (3.3%) withdrew her consent. A total of 30 subjects (15 pediatric, 15 adult) comprised the evaluable study population.
Results – Pharmacokinetics

Individual TAA concentration-time data for pediatric subjects receiving 110 µg daily vs adult subject receiving 220 µg daily (Day 5)

![Graph showing plasma TAA concentration over time for both adult and pediatric subjects.]

One pediatric subject and one adult subject (Period 2) did not complete Day 5.

<table>
<thead>
<tr>
<th>PPK variable</th>
<th>Pharmacokinetic parameter estimates, based on the final PPK model</th>
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<tbody>
<tr>
<td></td>
<td>Pediatric&lt;sup&gt;a&lt;/sup&gt; (n = 15)</td>
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<tr>
<td></td>
<td>Adult&lt;sup&gt;a&lt;/sup&gt; (n = 15)</td>
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<tr>
<td>CL/F (L/hour)</td>
<td>Mean</td>
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<td></td>
<td>83.3</td>
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<tr>
<td>V/F (L)</td>
<td>164.0</td>
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</table>

<sup>a</sup> One pediatric subject and one adult subject (Period 2) did not complete Day 5. The available PK data from these two subjects were included in the PPK analysis.

CL/F = Apparent total body clearance
PPK = Population pharmacokinetics
V/F = Apparent volume of distribution
Supporting data are on file with the sponsor.
Results – Safety

There were a total of 3 pediatric subjects (20%) and 10 adult subjects (67%) with a TEAE in the total population (N=30). TEAEs in the pediatric subjects included (in decreasing order of frequency): nasal passage irritation, nasal dryness, pyrexia, abdominal pain, and UTI. All TEAEs were transient, mild in intensity with a short onset and duration (≤4 days), with the exception of the event of UTI. Action was not warranted for any TEAE. TEAEs in the adult subjects included (in decreasing order of frequency): headache, epistaxis, dizziness, dyspepsia, eye irritation, nasal congestion, nausea, pharyngolaryngeal pain, pollakiuria, and rash. TEAEs were mild or moderate (1 incident of headache only) and short in duration (≤4 days), with the exception of 1 incident of pharyngolaryngeal pain (21-day duration). All adult subjects recovered without sequelae; no event warranted an action.

TEAEs observed during the study that were considered related to investigational product by the investigator included (by age grouping): nasal dryness and nasal passage irritation (pediatric subjects only); dizziness, epistaxis, headache, nasal congestion, nausea, and pharyngolaryngeal pain (adult subjects). All TEAEs observed in the pediatric and adult subjects that were in the Nervous System Disorders and Respiratory, Thoracic, and Mediastinal Disorders classes were considered possibly related to investigational product by the investigator.

There was no apparent difference in the type, number, duration, severity, or resolution of TEAEs between doses (TAA 110 µg or 220 µg) in the adult subjects.

There were no overdoses, deaths, or other serious adverse events.

There were no clinically significant changes in laboratory test results in either pediatric or adult subjects following treatment with TAA.

There were no clinically significant changes in vital signs in either pediatric or adult subjects following administration of TAA.

Conclusions

NASACORT AQ 110 µg and/or 220 µg administered intranasally for 5 consecutive days was generally safe and well tolerated in all subjects studied. The overall safety profile was consistent with known adverse events previously reported for the use of NASACORT AQ in healthy subjects and patients with allergic rhinitis. In pediatric subjects 2 to 5 years of age with PAR and adult subjects with PAR, the pharmacokinetics of TAA following intranasal administration of NASACORT AQ were adequately described by a one compartmental model with first order input. The CL/F and V/F estimates for TAA in 2- to 5-year-old patients were lower than those in adult patients. Intersubject variability in CL/F was similar between the two groups, with CL/F most strongly correlated with study population (pediatric or adult). Body size, particularly weight, was strongly correlated with V/F. The overall exposure to TAA produced by the 110-µg dose in the pediatric subjects was similar to the overall exposure to TAA produced by the 220-µg dose in the adult subjects. No significant accumulation of TAA with multiple dosing in either pediatric or adult subjects was apparent.