SYNOPSIS

INN : TRIAMCINOLONE ACETONIDE

Study number : RG5029Y-315

Study title : A Phase III, Single Center, Randomized, Cross-Over Pediatric Trial With Nasacort AQ Nasal Spray Assessing Short Term Growth In Patients With Allergic Rhinitis

CSR date : 15 August 2007

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.
SYNOPSIS

Study: RG5029Y-315

Title of the study:
A Phase III, Single Center, Randomized, Cross-Over Pediatric Trial With Nasacort AQ Nasal Spray Assessing Short Term Growth In Patients With Allergic Rhinitis

Investigators:
David Skoner, MD

Study Center(s):
One

Publications (reference):
None


Objectives:

Primary: To determine the effect of Nasacort AQ on lower leg short term growth velocity at doses of 110 and 220 µg/day compared to placebo

Secondary: To determine the effect of Nasacort AQ (110 and 220 µg) and Flonase Nasal Spray (200 µg) on lower leg short term growth velocity and overnight urine cortisol/creatinine ratios compared to placebo; to compare the adverse event reports for all treatment periods.

Methodology:
Randomized, 4-way cross-over, with placebo and active comparators

Number of Patients (total and for each treatment):
Total Randomized – 59 patients, each to receive four treatments in cross-over design; 49 patients completed all four treatment periods.

Diagnosis and criteria for inclusion:
Allergic Rhinitis with sufficient symptoms to justify intranasal steroid use, prepubescent patients ages 4 to 10/10.5 years.
**Test product, dose and mode of administration, batch №.:**

Nasacort AQ Nasal Spray 110 µg (2 sprays) and 220 µg (4 sprays) administered intranasally once daily,
Lot No. 9806830, Exp 01-Feb-00.

**Duration of treatment:**

Planned duration of the study: Four 2 week treatment periods, three 2 week washout periods and a 1 week follow-up period

Planned enrollment duration: 60 days (including baseline period)

**Reference therapy, dose and mode of administration, batch №.:**

Placebo 2 and 4 sprays intranasally to match the Nasacort AQ treatments,
Lot No. 5029/24-2E1, Exp 01-Feb-00.

Flonase (fluticasone propionate) Nasal Spray 200 µg (4 sprays) administered intranasally once daily,
Lot No. 9805810, Exp 01-Feb-00.

**Criteria for evaluation:**

Short term lower leg growth rate measured by knemometry

**Statistical methods:**

**Knemometry:** The principal objective of the study was to assess the effect of the two Nasacort AQ dosage regimens on lower leg growth compared with placebo. An assessment of the relative effects of Nasacort AQ compared with Flonase was a secondary objective. The primary variable was growth velocity. This was estimated as the actual growth during the period divided by the length of the treatment period (mm/week) and as the slope obtained by fitting a regression line (mm regressed on time) to the three knemometry values for each patient during a given treatment period. A fixed effects analysis of variance was performed including effects for patient, period, treatment and carryover.

Patients who completed at least two treatment periods were included in the analysis. An additional analysis was performed on data from patients who completed the entire trial.
**Urine Cortisol/Creatinine Ratio:** The change in overnight urine cortisol/creatinine ratio from beginning to end of each treatment period was to be statistically analyzed using the same analysis of variance methods used for the growth velocity data. Since the cortisol data was found to be not normally distributed, two similar nonparametric approaches were undertaken. In both approaches, the change in the ratio was ranked within each patient across all treatment groups. In the first approach, the rank values were analyzed using a fixed effects analysis of variance with effects for patient, period, treatment and carryover. In the second approach, the sum of the ranks for each treatment group was determined and a Friedman’s test was applied.

**Summary - Conclusions:**

**Efficacy results - N/A**

**Safety Results**

Knemometry Results, ITT Population; Patients Completing at Least Two Treatment Periods

Mean growth velocity during each treatment period and the treatment effect compared to placebo treatment were as follows:

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Adjusted Mean Lower Leg Growth Velocity (mm/week)</th>
<th>Treatment Effect Compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Nasacort AQ Nasal Spray 110 µg</td>
<td>0.37</td>
<td>27.5%</td>
</tr>
<tr>
<td>Nasacort AQ Nasal Spray 220 µg</td>
<td>0.34</td>
<td>33.3%</td>
</tr>
<tr>
<td>Flonase Nasal Spray 200 µg</td>
<td>0.38</td>
<td>25.5%</td>
</tr>
</tbody>
</table>

The treatment effects compared to placebo for all three active treatment periods were less than 50%. A treatment effect of 50% or greater was defined in the protocol as clinically significant.

Very similar results were found in analyses of the evaluable population which excluded 2 patients who progressed to Tanner Stage II at the end of the study.

**Overnight Urine Cortisol Results; ITT Population; Patients Completing at Least 2 Treatment Periods**

Mean change in urine cortisol/creatinine from beginning to end of each treatment period and the p-values of the treatment comparison to placebo were as follows:
### Urine Cortisol/Creatinine Ratio, Rank ANOVA
**Patients Who Completed At Least Two Treatment Periods**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Mean Change During Treatment (µg/g)</th>
<th>P-Value of Comparison to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.52</td>
<td></td>
</tr>
<tr>
<td>Nasacort Nasal Spray AQ 110 µg</td>
<td>3.92</td>
<td>0.175</td>
</tr>
<tr>
<td>Nasacort Nasal Spray AQ 220 µg</td>
<td>3.21</td>
<td>0.271</td>
</tr>
<tr>
<td>Flonase Nasal Spray 200 µg</td>
<td>-3.59</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Comparisons between Nasacort AQ treatment periods and Flonase were statistically significant for the 220 µg treatment period (p=0.037) but not for the 100 µg treatment period (p=0.076).

**Conclusion**

Nasacort AQ at doses of 110 µg or 220 µg once daily did not have a clinically significant effect on lower leg growth. The effects of Flonase Nasal Spray 200 µg once daily on lower leg growth were very similar to those of TAA Nasal Spray. Two week treatment periods with Nasacort AQ Nasal Spray 110 µg or 220 µg once daily did not significantly affect HPA axis function as measured by overnight urine cortisol/creatinine ratio. Flonase Nasal Spray 200 µg once daily for two weeks produced a statistically significant mean decrease in urine cortisol/creatinine ratio compared to placebo.