An open, randomized, two-way crossover study evaluating the pharmacokinetics of budesonide and formoterol from Symbicort® pMDI versus Oxis® Turbuhaler® plus Pulmicort® Turbuhaler® when given to children with asthma aged 6 to 11 years

Principal Investigator

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Study center(s)
This was a single-center study.

Publications
None at the time of writing this report.

Study dates

First patient enrolled: 19 October 2004
Last patient completed: 12 November 2004

Phase of development
Clinical pharmacology (I)
Objectives

Primary objective:

- To compare the systemic availability of budesonide after inhalation from Symbicort® pMDI (pressurized metered dose inhaler) and Pulmicort® Turbuhaler® in asthmatic children 6 to 11 years of age.

Secondary objectives:

- To compare the systemic availability of formoterol after inhalation from Symbicort pMDI and Oxis® Turbuhaler in asthmatic children 6 to 11 years of age.

- To assess the safety and tolerability of single doses of Symbicort pMDI and Oxis Turbuhaler plus Pulmicort Turbuhaler in asthmatic children 6 to 11 years of age.

Study design

This was an open-label, randomized, single-center study to evaluate the pharmacokinetics, safety, and tolerability of Symbicort pMDI and Oxis Turbuhaler plus Pulmicort Turbuhaler when given as single doses in a crossover fashion.

Target subject population and sample size

Outpatients of either sex, aged 6 to 11 years, having a documented clinical diagnosis of asthma as defined by the American Thoracic Society (ATS) for at least 6 months prior to enrollment (Visit 1), and using a constant daily dose of inhaled glucocorticosteroid. The patients were required to demonstrate proper use of a pMDI without spacer and a Turbuhaler dry-powder inhaler.

Twenty-four (24) patients were to be randomized in order to obtain 20 evaluable patients. To insure an equal distribution of ages, at least 10 patients were to be 6 to 8 years of age and 10 patients were to be 9 to 11 years of age.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

A. Symbicort pMDI 160/4.5 µg (nominal delivered dose) per actuation, 4 actuations given as a single dose of 640/18 µg. Batch number: P6722.

B. Oxis Turbuhaler 4.5 µg (nominal delivered dose) per inhalation, 4 inhalations given as a single dose of 18 µg. Batch number: FD 585. Plus:
Pulmicort Turbuhaler 200 µg (nominal metered dose, US marketed product) per inhalation, 4 inhalations given as a single dose of 800 µg, corresponding to a delivered dose of 640 µg. Batch number: FE 2003.
The products were administered in the order they are presented.

**Duration of treatment**

Two single-dose treatments separated by a washout period of at least 5 but not more than 14 days.

**Criteria for evaluation (main variables)**

- **Pharmacokinetics**
  Plasma samples were analyzed to determine the pharmacokinetics (area under the plasma concentration versus time curve from time zero to infinity (AUC), area under the plasma concentration versus time curve from time zero to the last concentration above the limit of quantification $AUC_{0-t}$, maximum plasma concentration ($C_{max}$), time for maximum plasma concentration ($t_{max}$), mean residence time (MRT), and half-life ($t_{1/2}$)) of budesonide in plasma, with AUC being the primary outcome variable. The fraction of formoterol excreted unchanged into urine over 24 hours ($fe_{0-24h}$) was also determined.

- **Safety**
  Safety and tolerability were assessed by means of incidence and severity of all Adverse Events (AEs), vital signs, and laboratory parameters.

**Statistical methods**

This study is descriptive. There were no predefined statistical hypotheses and no predetermined tests or decision rules. Pharmacokinetic and AE data are presented.

All analyses were based on the full analysis set, comprising all randomized patients with data.

The AUC for budesonide was compared between treatments using a multiplicative (ie, log-transformation) analysis of variance (ANOVA) model with treatment, period, and patient as fixed factors. Mean treatment ratios were estimated and 90% confidence limits were calculated from the model.

The $AUC_{0-t}$, $C_{max}$, and $t_{1/2}$ for budesonide and $fe_{0-24h}$ for formoterol were analyzed and described in the same way as AUC. Budesonide MRT was analyzed in the same way but with an additive model. Budesonide $t_{max}$ was described for both treatments.

The AEs were to be analyzed by means of descriptive statistics and qualitative analysis.

**Subject population**

A total of 25 asthmatic patients were enrolled at one center. One patient voluntarily discontinued the study before randomization. The other 24 patients (11 males (46%) and
13 females (54%) were randomized and allocated to a treatment sequence at Visit 2. Their mean age was 8 years (range: 6 to 11). All patients except one (Caucasian) were Black. All randomized patients completed the study. The first patient was enrolled in the study on 19 October 2004 and the last patient completed the study on 12 November 2004. All 24 randomized patients were analyzed for pharmacokinetics and safety.

**Summary of pharmacokinetic results**

**Budesonide**

The mean plasma concentration of budesonide was lower after a single-dose treatment with Symbicort pMDI compared with a single-dose treatment with Pulmicort Turbuhaler plus Oxis Turbuhaler. The mean AUC ratio was 73% (90% confidence limits: 52% to 103%) and the mean $C_{\text{max}}$ ratio was 59% (90% confidence limits: 38% to 92%). The result for AUC$_{0-t}$ was similar to the result for AUC. Both MRT and $t_{1/2}$ were slightly longer after inhalation of a single dose of Symbicort pMDI compared with a single dose of Pulmicort Turbuhaler plus Oxis Turbuhaler. The median $t_{\text{max}}$ was 20 min for both treatments. The variability in data was large.

**Formoterol**

The mean f$_{0-24h}$ for formoterol was similar after a single-dose treatment with Symbicort pMDI and a single-dose treatment with Pulmicort Turbuhaler plus Oxis Turbuhaler. The mean f$_{0-24h}$ ratio was 113% (90% confidence limits: 80% to 158%). On average 3.5% of the formoterol dose was excreted unchanged in urine after inhalation of a single dose.

**Table S1**  Pharmacokinetic parameters for budesonide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbicort Mean</th>
<th>90% conf.lim.</th>
<th>Pulmicort + Oxis Mean</th>
<th>90% conf.lim.</th>
<th>Symbicort vs. Pulmicort + Oxis$^2$ Mean</th>
<th>90% conf.lim.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (nmol/L·h)</td>
<td>4.22</td>
<td>3.32 - 5.37</td>
<td>5.75</td>
<td>4.52 - 7.32</td>
<td>73</td>
<td>52 - 103</td>
</tr>
<tr>
<td>AUC$_{0-t}$ (nmol/L·h)</td>
<td>3.94</td>
<td>3.07 - 5.04</td>
<td>5.52</td>
<td>4.31 - 7.07</td>
<td>71</td>
<td>50 - 101</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>3.78</td>
<td>3.44 - 4.12</td>
<td>2.90</td>
<td>2.55 - 3.24</td>
<td>0.88</td>
<td>0.39 - 1.37</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>2.98</td>
<td>2.76 - 3.21</td>
<td>2.63</td>
<td>2.44 - 2.83</td>
<td>113</td>
<td>102 - 126</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (min)$^1$</td>
<td>20</td>
<td>10 - 240</td>
<td>20</td>
<td>10 - 62</td>
<td>59</td>
<td>38 - 92</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (nmol/L)</td>
<td>1.36</td>
<td>0.99 - 1.87</td>
<td>2.31</td>
<td>1.68 - 3.17</td>
<td>59</td>
<td>38 - 92</td>
</tr>
</tbody>
</table>

1 Median and range.
2 Ratios (%) for AUC, AUC$_{0-t}$, $C_{\text{max}}$, and $t_{1/2}$, and difference for MRT.
of Symbicort pMDI, compared with 3.1% after inhalation of a single dose of Pulmicort Turbuhaler plus Oxis Turbuhaler. The variability in data was large.

Table S2 Pharmacokinetic parameters for formoterol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbicort</th>
<th>Pulmicort + Oxis</th>
<th>Symbicort vs. Pulmicort + Oxis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean (%)</td>
<td>3.48</td>
<td>3.09</td>
<td>113</td>
</tr>
<tr>
<td>90% conf.lim.</td>
<td>2.73 - 4.43</td>
<td>2.43 - 3.93</td>
<td>80 - 158</td>
</tr>
</tbody>
</table>

¹ Ratio (%).

Summary of safety results

Single-dose treatments with budesonide and formoterol inhaled as Symbicort pMDI (640/18 µg) and Pulmicort Turbuhaler (800 µg) plus Oxis Turbuhaler (18 µg) were well tolerated in asthmatic children 6 to 11 years of age. No AEs were reported in this study and no clinically relevant findings were identified in clinical laboratory results, vital signs, or physical examination.

Conclusion(s)

- Both the systemic bioavailability (AUC) and Cmax of budesonide were numerically lower after inhalation from Symbicort pMDI than from Pulmicort Turbuhaler plus Oxis Turbuhaler. The mean AUC ratio was 73% (90% confidence limits: 52% to 103%) and the mean Cmax ratio was 59% (90% confidence limits: 38% to 92%).

- The systemic bioavailability of formoterol, based on the fraction of the dose excreted unchanged in urine during 24 h (fe0-24h), was similar after inhalation from Symbicort pMDI compared with Pulmicort Turbuhaler plus Oxis Turbuhaler. The mean fe0-24h ratio was 113% (90% confidence limits: 80% to 158%).

- All treatments were well tolerated and no new or unexpected safety findings were identified.