A randomised, double-blind, placebo-controlled study of the efficacy, tolerability, and cost-effectiveness of formoterol Turbuhaler® 4.5 µg and 9 µg b.i.d. in six to eleven year old children with symptomatic asthma.

INVESTIGATOR
Barry Zimmerman et al. Names and addresses for all principal investigators can be found in Appendix 16.1.4.1.

STUDY CENTRE(S)
Multicentre study in Canada (27 centres).

PUBLICATION (REFERENCE)

<table>
<thead>
<tr>
<th>STUDY PERIOD</th>
<th>PHASE OF DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- DATE OF FIRST subject ENROLLED: 25 March, 1999</td>
<td>III b, therapeutic use</td>
</tr>
<tr>
<td>- DATE OF LAST subject COMPLETED: 16 February, 2001</td>
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</tr>
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</table>

OBJECTIVES
The primary objective was to study the clinical efficacy of adding 4.5 µg or 9 µg formoterol (Oxis) Turbuhaler b.i.d., compared to the addition of placebo b.i.d., to the usual dose of inhaled corticosteroid (IGCS) in children six to 11 years old and whose asthma was not well-controlled while taking their current dose of IGCS. The secondary objectives were to investigate the safety, quality of life and cost-effectiveness of these treatment strategies.

N.B. Cost-effectiveness will be analysed and evaluated in a separate report and will not be part of this clinical report.

STUDY DESIGN
Double-blind, randomised, placebo-controlled, parallel groups, multicentre.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Children with asthma, 6-11 years old, on treatment with inhaled steroids at a stable dose were enrolled. At baseline, $\text{FEV}_1$ should be between 50-90% of predicted value and a post-bronchodilator increase in $\text{FEV}_1$ of $\geq 15\%$ or $\geq 9\%$ predicted value had to be demonstrated. At randomisation, the children had to demonstrate a post-bronchodilator increase in $\text{FEV}_1$ of $\geq 12\%$ or a diurnal variation in PEF of $\geq 15\%$ on any five of the last ten days during run-in. During the last ten days of the run-in, subjects also had to demonstrate either:
- need of rescue use of short-acting $\beta_2$-agonist $\geq 4$ inhalations or,
- a sum of day-time and night-time symptoms of $\geq 4$ or,
- night-time awakening on $\geq 1$ night or,

Subjects with any significant disease or laboratory test results, as judged by the investigator, were excluded. Criteria regarding asthma medicine not allowed or requirements regarding stable dosing were other reasons for exclusion. A respiratory tract infection during the run-in period or change in present asthma medication was not accepted at randomisation.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Formoterol Turbuhaler 4.5 $\mu$g/ 9 $\mu$g b.i.d., for inhalation. Strength: 4.5 $\mu$g/dose (Batch Nos. AH18, ZE17) or 9 $\mu$g/dose (Batch Nos. AD25, ZE23).

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Placebo Turbuhaler, b.i.d. for inhalation (Batch Nos. AF22, AI23, ZF15).

DURATION OF TREATMENT

Three-month treatment periods with b.i.d. treatment on top of regular IGCS.

MAIN VARIABLE(S):

- Efficacy

The primary variable was the change in morning Peak Expiratory Flow (PEF) from baseline to treatment.

$\text{FEV}_1$, evening PEF, asthma symptoms, use of short-acting $\beta_2$-agonist, time to first severe exacerbation were used as secondary variables.

- Safety

Safety was assessed through a physical examination, the collection of adverse events and by monitoring of heart rate and blood pressure.

- Quality of Life

The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) was used.
- COST-EFFECTIVENESS

Cost-effectiveness parameters were: cost per episode-free day, total cost of therapy. The outcome of these will be presented and discussed in a separate report and will not be commented upon in this clinical report.

STATISTICAL METHODS

The change in morning PEF from run-in to the treatment period was compared between treatments using an analysis of variance model adjusting for treatment and region and using the run-in mean as a covariate. Treatments were compared pairwise: first formoterol 9 \( \mu \text{g} \) was compared to placebo, if statistically significant then formoterol 4.5 \( \mu \text{g} \) was compared to placebo, and finally the two active treatments were compared.

Secondary variables from the diary (evening PEF, asthma symptoms, terbutaline consumption, nocturnal awakenings, episode-free days, PEF \( \text{E}_{\text{av}} \), PEF \( \text{E}_{\text{max}} \)) and from the clinic visits (FEV\(_1\), vital signs, PAQLQ) were compared using similar analysis of variance models. As baseline covariate, either the run-in mean or the value from visit 2 was considered. The time to first severe asthma exacerbation and time to withdrawal from study medication were compared between treatments using survival analysis (Kaplan-Meier) and a Cox proportional hazards model.

For the primary efficacy variable, morning PEF, ITT and PP analyses were performed. In the ITT approach, all randomised subjects treated with study drug and having values from both the run-in and treatment periods were included. All data collected that were not considered defective were used in the analysis, i.e. also data collected after termination of study medication. In the PP approach, subjects with important protocol deviations were excluded, as well as subjects non-compliant to their IGCS regime or recording of morning PEF in the diary. For secondary efficacy variables only an ITT analysis was performed. All tests were two-sided at a 5% significance level.

Adverse events and data from physical examinations, including weight and height, were analysed by means of descriptive statistics and qualitative analysis.

SUBJECTS

Summary of subject demographics, number included in efficacy/safety analysis and distribution between treatment groups.
**SUMMARY - CONCLUSION(S)**

**- EFFICACY RESULTS**

The primary variable, mean morning PEF, increased in all treatment groups. After three months treatment there was a statistically significant difference between the formoterol groups and placebo (formoterol 9 \( \mu \)g vs placebo, \( p=0.0045 \), formoterol 4.5 \( \mu \)g vs. placebo, \( p=0.035 \)). Descriptive statistics for period means for morning and evening PEF are shown in Table 1 below. Also for evening PEF and FEV\(_1\) there were statistically significant differences compared with placebo after 3 months treatment, for both groups of formoterol.

**Table 1.** Descriptive statistics for period mean for morning and evening PEF.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>N</th>
<th>Run-in period Mean</th>
<th>(Range)</th>
<th>Treatment period Mean</th>
<th>(Range)</th>
<th>Adjusted Mean change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Placebo</strong></td>
<td></td>
<td><strong>Formoterol 4.5 ( \mu )g</strong></td>
<td></td>
<td><strong>Formoterol 9 ( \mu )g</strong></td>
</tr>
<tr>
<td><strong>PEF (L/min)</strong></td>
<td></td>
<td></td>
<td><strong>morning</strong></td>
<td></td>
<td><strong>evening</strong></td>
<td></td>
<td><strong>morning</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Placebo</strong></td>
<td>97</td>
<td>204.8</td>
<td>(80 - 345)</td>
<td>210.7</td>
<td>(73 - 354)</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td><strong>Formoterol 4.5 ( \mu )g</strong></td>
<td>105</td>
<td>207.9</td>
<td>(84 - 390)</td>
<td>221.4</td>
<td>(88 - 391)</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td><strong>Formoterol 9 ( \mu )g</strong></td>
<td>94</td>
<td>204.5</td>
<td>(107 - 374)</td>
<td>221.7</td>
<td>(127 - 415)</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td><strong>Placebo</strong></td>
<td>97</td>
<td>210.2</td>
<td>(91 - 342)</td>
<td>213.5</td>
<td>(77 - 356)</td>
<td>4.0</td>
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<tr>
<td></td>
<td><strong>Formoterol 4.5 ( \mu )g</strong></td>
<td>105</td>
<td>213.5</td>
<td>(80 - 478)</td>
<td>225.5</td>
<td>(93 - 384)</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td><strong>Formoterol 9 ( \mu )g</strong></td>
<td>94</td>
<td>210.8</td>
<td>(113 - 378)</td>
<td>223.4</td>
<td>(128 - 416)</td>
<td>13.2</td>
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</tbody>
</table>

Final 9 May, 2001
For all other diary variables and quality of life, no statistically significant differences were shown. In the subgroup of subjects performing serial PEF at home, a statistically significant difference was seen between formoterol 9 μg and placebo after one and three months.

- **SAFETY RESULTS**

The reported AEs were evenly distributed between the treatment groups, including four SAEs and 17 DAEs, and no clinically important drug related safety findings were identified in the study.

- **QUALITY OF LIFE**

No statistically significant differences were shown between the three treatment groups for any of the domains or the total score.

- **CONCLUSION(S)**

In conclusion, formoterol Turbuhaler 4.5 μg and 9 μg were shown to be effective and well tolerated after three months regular (b.i.d.) treatment in children on a stable dose of IGCS. There was a statistically significantly difference in the improvement of the lung function after three months treatment for both strengths of formoterol Turbuhaler, compared with placebo.

**DATE OF THE REPORT**

9 May, 2001