**NAME OF COMPANY:**
AstraZeneca R&D, Lund
S-221 87 Lund, Sweden

**TRADE NAME(S):**
Bambec®

**NAME OF ACTIVE INGREDIENT(S) INN:**
bambuterol hydrochloride

**STUDY CODE:** 09-3027

**REPORT NUMBER:** 09-CR-3027

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**CLINICAL STUDY SYNOPSIS**

**Title of the study:**
Bambuterol dose finding study in Asian children with asthma

**Principal investigators:**
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- **Centre 4:** Agnes R. Mendoza, St. Luke's Medical Centre, Quezon City, The Philippines
- **Centre 5:** Milagros S. Bautista, Philippine Heart Centre, Quezon City, The Philippines
- **Centre 6:** Miguel Javier, UP - Philippine General Hospital, Metro Manila, The Philippines
- **Centre 7:** Lee Bee Wah, Children Medical Centre, National University Hospital, Singapore
- **Centre 8:** Chay Oh Moh, Tan Tock Seng Hospital Pte Ltd, Singapore
- **Centre 9:** Jarungchit Ngampaiboon, Department of Paediatrics, Chulalongkorn Hospital, Bangkok, Thailand
- **Centre 10:** Pakit Vichyanond, Department of Paediatrics, Siriraj Hospital, Mahidol University, Bangkok, Thailand

**Study site(s):**
Multicentre study in South East Asia – Indonesia, Malaysia, The Philippines, Singapore, Thailand

**Publication (reference):** -

**Study period:**
October 1995 to June 1996

**Clinical phase:**
IIB

**Objectives:**
To compare the efficacy of two doses of bambuterol tablets (5 and 10 mg once daily) to placebo over two weeks in Asian children (6-12 years of age) with asthma.

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September 14, 1999/Lena Laxmyr
Clinical Study Synopsis
Study design:
Placebo controlled, double-blind, randomised, crossover design. A run-in period, followed by three treatment periods with washout periods in between the treatments. The three investigated treatments were bambuterol 5 mg, bambuterol 10 mg and placebo, all administered once a day in the evening. Placebo tablets were administered during the run-in and the washout periods. The total time of the study was around 12 weeks. Seven clinic visits were performed.

Number of patients (total and for each treatment):
Eighty-two (82) patients were enrolled in the study. Seventy patients were randomised to treatment and 62 completed the study.

Diagnosis and criteria for inclusion:
6 - 12 year old boys and girls with asthma (minimum duration of 6 months), reversibility in FEV₁ ≥15% 15 minutes after inhalation of 0.5 mg terbutaline sulphate (one inhalation of Bricanyl® Turbuhaler®), basal FEV₁ ≥ 1 litre (L) and ≥ 50% of predicted normal value, signed, informed consent given by parents/legal guardians and verbal informed consent by child.

Investigational drug:
Bambuterol hydrochloride (Bambec®) 5 mg (batch no. VA 101) and 10 mg (batch no. UL 183) tablets.

Reference treatment(s):
Placebo for bambuterol 5 mg (batch no. VA 4001) and 10 mg (batch no. VA 2003) tablets.

Duration of treatment:
All periods had a duration of 14 days with an additional 3 days, if needed.

Assessment methods:
At the clinic in the morning, at 08.00 a.m. (±1 hour) or 12 hours (±1 hour) after intake of study medication the day before the clinic visit, FEV₁, FVC, blood pressure, and pulse were measured. Adverse events were asked for by a standard question and compliance was checked by tablet counting. At home twice daily (recorded in a diary): PEF morning (primary efficacy variable) and evening, asthma symptoms, use of rescue medication, awakenings due to asthma and time awake and adverse events (active questioning for restlessness, headache, palpitation and tremor).

Statistical methods:
The study was analysed according to the "all patient treated" approach. Treatment differences were presented as mean ± SEM, and 95% confidence intervals (level of significance p< 0.05). The comparison was made using ANOVA with factors patient, period and treatment, followed by pairwise comparison of treatments. For all tests, two-tailed alternatives were considered. No adjustment of significance levels for multiple comparisons was made. No carry-over effects were assumed in the model, due to the long washout periods. No test for a treatment by centre interaction was carried out due to the imbalance of patients from each centre. Descriptive statistics (n, mean, standard deviation, min, and max) were performed for all variables, for each treatment. Diary card data from the last 10 days of each period were used.

Summary of results:
The 53 boys and 17 girls (68 Oriental/2 Caucasian) randomised, had a mean age of 9 years. Mean morning and evening PEF were 208 and 212 L/min, respectively. Mean FEV₁ was 1.3 L, mean predicted normal value of FEV₁ 83%, mean reversibility in FEV₁ 22% and mean FVC 1.6 L. Inhaled corticosteroids in a constant dose was used throughout the study by 71% of the patients and inhaled short-acting β₂-agonists as rescue medication by 77%.
A dose-response was seen in change from baseline for morning PEF (mean 12.2 L/min) but only the difference between bambuterol 10 mg and placebo was statistically significant. Evening PEF also showed a dose-response but the difference between treatments was not statistically significant. In FEV₁ and FVC there were no statistically significant treatment differences in change from baseline.

No statistics were performed on number of awakenings due to asthma, time awake and the number of days and nights supplementary inhaled β₂-agonists were used. Most patients did not wake up due to asthma (about 40) and most patients did not use rescue medication neither day nor night (about 50). The mean number of inhalations made per patient and the mean asthma symptom score were small in all treatment groups and no statistically significant treatment differences were shown, night or day.

The mean score was very low for all adverse events actively asked for. Only small changes were seen from baseline to treatment and most of them were not statistically significant. However, a small but statistically significant difference in mean score between placebo and bambuterol 5 mg treatments was seen for night-time tremor (p=0.05).

Blood pressure and pulse, on average 96/62 mmHg and 88 beats/min at enrolment, remained consistent throughout the study.

Five patients experienced serious adverse events; two during run-in, one during bambuterol 10 mg treatment and two during washout periods. All patients were hospitalised, which is by definition a serious adverse event. Four events was due to asthma deterioration and the one was due to pneumonia (washout period). All patients recovered completely and only the patients in the run-in period discontinued the study.

Three patients discontinued the study due to adverse events; one during run-in (acute mycoplasma bronchitis) and two during bambuterol 10 mg treatment (tremor and acute rhinitis). Four patients discontinued the study due to deterioration of asthma, all during the run-in period. Two of these were the patients who were hospitalised.

**Conclusion(s):**
- bambuterol 10 mg once in the evening statistically significantly improved morning PEF
- bambuterol was well tolerated, both evaluated as changes in vital signs and as adverse event recordings

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**Date:** 99-09-14

**Statistician:** Caro Badcock

**Date:** 99-09-22

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