1. SUMMARY

The objective of this study was to investigate the continued bronchodilating effect of bambuterol 10 and 20 mg tablets administered once daily in the evening for three months, to asthmatic children 6-12 years of age. Bambuterol was compared with placebo and terbutaline 2.5 mg tablets three times daily. The study was performed in Austria, Belgium, France, Germany and Great Britain. It was a double-blind, double-dummy, randomized, parallel groups, comparative study. A two-week run-in period initiated the study, followed by a three month treatment period. Out-patients with asthma bronchiale were to be included in the study. The patients were to have an FEV\(_{1.0}\) of 50% or more of predicted value and a reversibility in FEV\(_{1.0}\) of \(\geq 15\%\) after 0.5 mg inhaled terbutaline via pMDI or 0.2 mg salbutamol via pMDI. Inhaled \(\beta_2\)-agonists when necessary, inhaled corticosteroids, disodium cromoglycate and nedocromil sodium at a constant dose, were allowed to be used during the study. FEV\(_{1.0}\) 24 hours after study medication intake the evening before was recorded at the clinic. PEF, asthma symptoms, use of rescue medication (inhalation of \(\beta_2\)-agonists and/or anticholinergics), sleep disturbance, time of medication intake and adverse events (tremor specified) were recorded in a diary every morning and evening.

The estimated number of 480 patients which were to be randomized in order to be able to detect a difference of 0.18 L FEV\(_{1.0}\) and with a power of 80% between the treatments, was not achieved. Only 171 patients were randomized which led to a considerable loss of power in the statistical analysis.

The evening measurements of FEV\(_{1.0}\) performed at the clinic were originally planned to be the primary efficacy variables. However, the majority of children in this study were at school, making control of the midday dosage difficult; consequently a high percentage of the evening FEV\(_{1.0}\) measurements were invalidated by the timing of midday medication. For this reason, FEV\(_{1.0}\) (primary efficacy variable) was only analysed in the All Patient Treated Analysis (APT) and the morning PEF was upgraded to primary efficacy variable.

Two hundred and thirty-eight patients were enrolled into the study, from whom 171 were randomized: 67 girls and 104 boys, 6 to 12 years old. The groups allocated by randomization were 46 (placebo), 46 (bambuterol 10 mg), 40 (bambuterol 20 mg) and 39 (terbutaline 2.5 mg). Mean baseline FEV\(_{1.0}\) after run-in was 1.68, 1.73, 1.56 and 1.68 L in the placebo, bambuterol 10 mg, bambuterol 20 mg and terbutaline groups respectively. Mean morning PEF at baseline was 267, 254, 253 and 256 L/min in the same groups.
The mean percent of predicted FEV\textsubscript{1.0} at baseline was 78.1, 76.9, 78.2 and 78.1 respectively.

Mean FEV\textsubscript{1.0}, measured 24 hours after study medication intake, at the end of the study (visit 7) was 1.77, 1.78, 1.74 and 1.72 L, in the placebo, bambuterol 10 mg, bambuterol 20 mg and terbutaline groups, respectively. The changes from baseline were 0.08, 0.04, 0.15 and 0.03 L respectively.

In the APT analysis the morning PEF values at the end of the study (between visits 6 and 7) were 274, 282, 277 and 279 L/min, the changes from baseline being 6.8, 28.2, 24.0 and 23.1, respectively. The pairwise comparisons were significant between placebo and all 3 active treatments (p=0.0033, 0.0219 and 0.0214 respectively).

In the per protocol analysis (PP), the mean morning PEF at the end of the study (between visits 6 and 7) was 277, 286, 288 and 278 L/min in the placebo, bambuterol 10 mg, bambuterol 20 mg and terbutaline groups respectively. The change from baseline was 8.8, 32.2, 24.6 and 22.4 L/min, respectively. The pairwise comparison placebo versus 10 mg bambuterol was significant (p=0.0062).

The median of the tremor-free days and nights was compared rather than the mean, since the data was skewed with many patients reporting virtually no problems with tremor. The treatment groups were compared by means of a Kruskal-Wallis test and were not statistically significantly different.

Adverse events occurred in 88% of the patients receiving bambuterol 20 mg, 87% of the patients receiving terbutaline, 80% of the patients receiving bambuterol 10 mg and 80% of the patients receiving placebo. Overall the difference was not significant (p=0.284 on a Mantel-Haenszel chi-square test). The pairwise comparisons using Fisher's Exact test showed no statistical significance between the groups. The changes in mean values and individual values of haematology and clinical chemistry were small and clinically and statistically insignificant.

Vital signs showed little change from baseline to visit 7 in any of the treatment groups. There was a statistically significant pairwise difference for change in systolic blood pressure, between placebo and bambuterol 10 mg (p=0.0255). The change was unlikely to be of a clinical significance. Over the whole treatment period there were no clinically significant differences between the treatments regarding changes from baseline in the systolic and diastolic blood pressure, and pulse rate.

Three randomized patients experienced serious adverse events, one on placebo and 2 on bambuterol 10 mg. The placebo patient needed hospital treatment for a torsion of the right testis. The patients on bambuterol experienced GI symptoms needing hospital treatment.
Twenty-three patients withdrew from the study, six due to adverse events, six due to disease deterioration and 11 for other reasons (consent withdrawn, insurance reasons, compliance). No patient in the placebo group withdrew due to adverse events, but two withdrew from the 10 mg bambuterol group, one from the 20 mg group and three from the terbutaline group for this reason.

**Conclusions:** The increases in the morning PEF (APT) from baseline measured at home and recorded in the patient diary card were between 13 and 28 L/min for the three active treatments, and between 3.2 and 7 for placebo. The greatest increase was 28.2 L/min seen in the 10 mg bambuterol group between visit 6 and 7. On these occasions, the morning PEF values were statistically significantly higher in all three active treatment groups as compared to placebo. Further, for both morning and evening PEF there were statistically significant differences between some of the active treatments and placebo on other occasions. For FEV$_{1.0}$, the greatest difference between baseline and treatment was seen in the 20 mg bambuterol group at visit 7 and was 0.15 L, which was not statistically significant as compared to placebo. Finally, both treatments were generally well tolerated and the reported adverse events were mostly mild to moderate.