1. SUMMARY

The objective of this study was to compare the efficacy and tolerability of bambuterol (Bambec®) 20mg tablets administered once every evening with controlled release (CR) salbutamol tablets (Volmax®) 8mg twice daily in adult asthmatics suffering from nocturnal asthma symptoms.

This multicentre study was performed in general practice surgeries and hospital outpatient clinics throughout the UK. The study was an open, randomised, cross-over trial. Each treatment period was for three weeks with three clinic visits. In addition, patients aged ≥ 65 years received a four-week follow-up period with bambuterol 20mg nocte and an additional clinic visit (Clinic Visit 4).

Patients aged ≥16, currently receiving inhaled steroids ≥800μg/day with nocturnal asthma and with demonstrable reversibility of ≥15% in peak expiratory flow rate (PEFR) after an inhaled bronchodilator, were randomised to bambuterol 20mg nocte (B) followed by salbutamol CR 8mg bd (S) treatment or S followed by B. During the study, patients completed daily diary cards on which they recorded: compliance with therapy, morning and evening PEFRs, bronchodilator use and asthma symptoms. At the end of each week, patients also recorded the severity (0-3 scale) and duration (number of days) of side effects (i.e. tremor, headache, restlessness, palpitations, other) experienced that week. At the 3-weekly clinic visits, asthma symptoms, lung function and adverse events were recorded. Patients who crossed over to receive both treatments completed a treatment preference questionnaire at visit 3.

A total of 152 patients (mean age 54.7 years, range 17-87) were randomised into the study. One hundred and thirty two patients crossed over to receive both treatments and 116 patients completed the study. Thirty-three patients aged ≥ 65 entered the 4 week follow-up period of whom 31 completed.

Both treatments produced significant improvements over baseline lung function measurements and asthma symptoms, although no
statistically significant differences between treatments were observed in either lung function (PEFR, Forced Vital Capacity - FVC, or Forced Expiratory Volume in 1 second - FEV₁) or asthma symptoms recorded at the clinic visits.

At clinic visits, all asthma symptom severity scores were lower with bambuterol treatment compared to salbutamol, although individually none of these reached statistical significance. On diary cards, the proportion of days with wheeze was significantly lower with bambuterol (p<0.05).

During the first week of treatment, both the severity and duration of tremor was significantly (p<0.0001 for both) lower with bambuterol. The duration of palpitations in the first week was also significantly lower with bambuterol (p<0.01). This advantage in tremor with bambuterol treatment, was still maintained during the second (severity p<0.01; duration p<0.05) and third weeks of treatment (severity p<0.05, duration p<0.01). The severity of restlessness was significantly lower (p<0.05) with bambuterol during the second week. No other differences between treatments were observed at any stage of the study for the side effects of headache or restlessness.

Significant period effects were noted for both severity and duration of tremor (p<0.0001 for both) in the first week and for severity in the second week (p<0.05), with reductions in the second period, regardless of treatment. This tachyphylactic response to β₂- agonist induced side effects is a known characteristic of this class of drug (11).

The reported incidence of side effects during the first week of the study, showed that bambuterol produced tremor in significantly fewer patients than salbutamol treatment (47% and 70% of patients, respectively, p<0.01).

Patients considered bambuterol to cause less 'shakiness' (p<0.01) than salbutamol and overall treatment preference was 49% bambuterol, 36% salbutamol and 15% no preference (ns between treatments).
Once-daily was significantly \( p<0.0001 \) preferred over twice-daily treatment.

A total of 36 patients withdrew during the study due to asthma exacerbations (12), adverse events (11), side effects (8) and non-compliance (5). During the follow up period, one patient withdrew because of side effects and one due to non-compliance. Three serious adverse events were reported during the study, all during salbutamol treatment: one death due to pulmonary embolism and two hospitalisations (one due to an asthma exacerbation and one due to non-obstructive jaundice). In addition, one patient also died from a cerebrovascular accident 9 days after completing the study.

The tolerability of bambuterol and salbutamol was good with a similar incidence and type of adverse event reported (no. adverse events/ no. patients reporting: 115/69; 116/75 respectively).

In conclusion, bambuterol and salbutamol CR are equally effective in controlling nocturnal asthma symptoms. The incidence, severity and duration of side effects, particularly tremor are significantly reduced with bambuterol. Patients preferred taking their medication once-daily.