AstraZeneca

Drug Product	Oxis	**Synopsis**	(For national authority use only)
Drug substance(s)	Formoterol fumarate dihydrate		
Document No.	SD-037-CR-0738	Referring to part of the dossier	
Edition No.	1		
Study Code	SD-037-0738		
Date	18 December, 2002		

Tolerability of high dose formoterol vs. high dose terbutaline in asthmatic children after inhalation via Turbuhaler

Publications

None at the time of writing this report.

Study dates

Study Dates First subject entered: 27 March, 2002
Last subject completed: 30 September, 2002

Synopsis Document No. SD-037-CR-0738 Study Code SD-037-0738	(For national authority use only)

Objectives

Primary: To evaluate the high dose tolerability of formoterol (Oxis) (18+9+9+9=45 µg, delivered dose) compared with the high dose tolerability of the short-acting ß $_2$-agonist terbutaline (Bricanyl) (2+1+1+1=5 mg, metered dose), both cumulatively inhaled via Turbuhaler. The evaluation was based on selected cardiovascular and metabolic effects, and reported adverse events.

Secondary: To assess relative systemic dose potency between inhaled formoterol(Oxis) and terbutaline (Bricanyl). The primary variable for the secondary objective was plasma potassium concentration 30 minutes after each dose increment.

Study design

The tolerability and systemic effects of formoterol (Oxis) and terbutaline (Bricanyl) inhaled via Turbuhaler were compared in a double-blind (active treatments), placebo-controlled (a day of no treatment), crossover, randomized single-dose study in asthmatic children.

Target subject population and sample size

Children 6-11 years of age with a diagnosis of asthma were recruited. Main exclusion criteria were cardiovascular disorders, e.g. arrhythmia, clinically relevant ECG abnormalities, treatment with potentially arrhythmogenic (e.g., terfenadine, promethazine, and monoamine oxidase inhibitors), or potassium depleting drugs (diuretica).

A total of approximately 30 subjects at three centres were to be enrolled, 20 subjects were to be randomised to ensure that at least 15 evaluable subjects completed the study.

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

Investigational Product

Formoterol fumarate dihydrate (Oxis) Turbuhaler 4.5 µg/dose. Cumulative administration via inhalation of a total dose of 45 µg divided as 4 x 4.5µg + 2 x 4.5µg + 2 x 4.5µg + 2 x 4.5µg at times zero, 0.5h, 2h and 2.5h. Batch number: CC22

Comparator

Terbutaline sulphate (Bricanyl) Turbuhaler 0.5 mg/dose. Cumulative administration via inhalation of a total dose of 5 mg divided as 4 x 0.5mg + 2 x 0.5mg + 2 x 0.5mg + 2 x 0.5mg at times zero, 0.5h, 2h and 2.5h. Batch number: CE21

Duration of treatment

Two single doses and one day of no treament at intervals of at least one week.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable

The primary evaluation was based on individual and overall interpretations of cardiovascular and metabolic effects, and safety assessment (see below).

Systemic effects:
- Cardiovascular effects: Systolic and diastolic blood pressure and ECG
- Metabolic effects: Plasma potassium, plasma glucose and lactate.

- Secondary variables

The secondary evaluation of relative systemic dose potency between formoterol (Oxis Turbuhaler) and terbutaline (Bricanyl Turbuhaler) was based on plasma concentration of potassium 30 minutes after each dose increment.

Safety

Safety assessment:
- Frequency and nature of adverse events
- Cardiovascular and metabolic effects as described above.

Statistical methods

Maximum/minimum and average values were compared between the three study days - treatment vs. no treatment and Oxis Turbuhaler vs. Bricanyl Turbuhaler - using analysis of variance models with fixed factors subject, treatment and period, and using the pre-dose measurement as covariate.

Relative systemic dose potency was evaluated using an analysis of variance model with fixed factors subject, period, treatment, dose number, an interaction between dose number and treatment, and using the pre-dose measurement as covariate. Straight lines were fitted to the adjusted mean values at 30 min after each dose fraction of Oxis Turbuhaler or Bricanyl Turbuhaler on the log-dose scale using weighted least square regression. Relative systemic dose potency was assessed from the horizontal shift between the straight lines, and the 95% confidence intervals for the estimate were calculated using Fieller's method.

Subject population

Table S1. Subject population and disposition

		Total
Population		
N randomized and treated (N planned)		20 (20)
Demographic characteristics		
Sex (% of subjects)	Male	13 (65%)
	Female	7 (35%)
Mean Age (range)		9.4 (6-11)
Baseline characteristics		
Median time, years since asthma diagnosis (range)		8 (0-11)
N subjects on inhaled GCS (%)		13 (65%)
Disposition		
N (%) of subjects who	completed	17 (85%)
	discontinued	3 (15%)
N analyzed for safety		20
N analyzed for efficacy, primary objective		19
N analyzed for efficacy, secondary objective		17

Efficacy results

The distribution of average and minimum/maximum effects for plasma potassium and QTc for the different treatments are summarized in Figure S1. The treatment effects on these variables were more pronounced with Bricanyl Turbuhaler than with Oxis Turbuhaler.

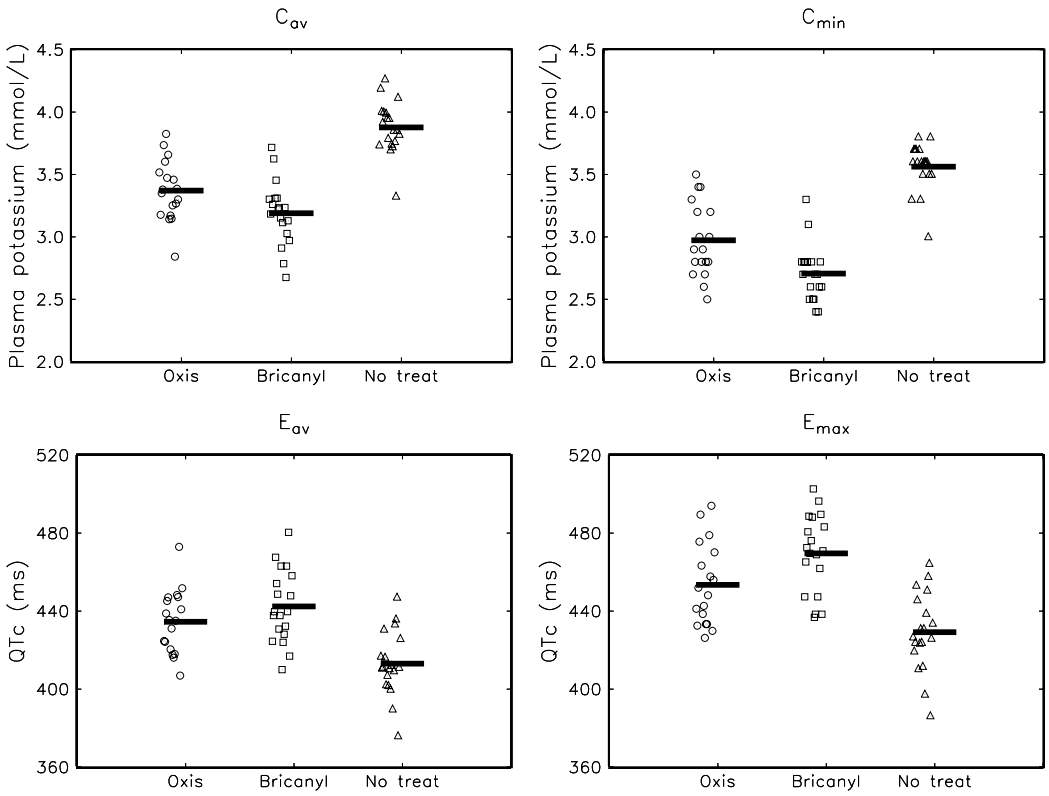

Figure S1. Distribution and means of pharmacodynamic parameters based on plasma potassium and QTc

Mean baseline (predose) and minimum/maximum values of plasma potassium and QTc after treatment with Oxis Turbuhaler or Bricanyl Turbuhaler or no treatment are shown in Table S2. Treatment comparisons of the same pharmacodynamic parameters are shown in Table S3.

Table S2. Descriptive statistics for minimum/maximum values of plasma potassium and QTc

Variable	Treatment	N	Baseline [1] mean	Baseline [1] (range)	Treatment mean	Treatment (range)
Plasma potassium (mmol/L)	Oxis Turbuhaler	17	3.91	(3.5 - 4.4)	2.98	(2.5 - 3.5)
	Bricanyl Turbuhaler	19	4.00	(3.7 - 5.6)	2.71	(2.4 - 3.3)
	No treatment	19	3.86	(3.3 - 4.3)	3.56	(3.0 - 3.8)
QTc (ms)	Oxis Turbuhaler	17	409.2	(379 - 455)	453.3	(426 - 494)
	Bricanyl Turbuhaler	19	411.5	(370 - 481)	469.6	(437 - 503)
	No treatment	19	403.2	(359 - 432)	429.2	(386 - 464)

1. value pre first dose

Table S3. Treatment comparisons of adjusted mean minimum/maximum values of plasma potassium and QTc

Variable	Contrast	Difference	95% conf. lim.	p-value
Plasma potassium (mmol/L)	Oxis Turbuhaler vs. No treatment	-0.58	(-0.70, -0.46)	<0.001
	Bricanyl Turbuhaler vs. No treatment	-0.87	(-0.99, -0.75)	<0.001
	Oxis Turbuhaler vs. Bricanyl Turbuhaler	0.29	(0.16, 0.41)	<0.001
QTc (ms)	Oxis Turbuhaler vs. No treatment	25.7	(16.1, 35.4)	<0.001
	Bricanyl Turbuhaler vs. No treatment	40.8	(31.4, 50.1)	<0.001
	Oxis Turbuhaler vs. Bricanyl Turbuhaler	-15.0	(-24.1, -5.9)	0.0021

Bricanyl Turbuhaler showed statistically significant effects relative no treatment on all variables. Oxis Turbuhaler showed statistically significant effects relative no treatment on all variables except diastolic blood pressure and QT interval. There were statistically significant larger effects after Bricanyl Turbuhaler than after Oxis Turbuhaler on plasma potassium and diastolic blood pressure (average and minimum) and on plasma glucose, plasma lactate, heart rate, QT interval and QTc (average and maximum).

The estimated relative dose-potencies between Oxis Turbuhaler and Bricanyl Turbuhaler are given in Table S4 expressed in two ways; firstly on a dose-to-dose basis (i.e. a relative dose-potency of 1 indicates that 4.5 µg Oxis Turbuhaler is equieffective systemically with 500 µg Bricanyl Turbuhaler), and secondly on a µg-to-µg basis.

Table S4. Dose-potency analysis: estimated relative dose-potency between Oxis Turbuhaler and Bricanyl Turbuhaler.

	By doses given		By µg	
Variable	mean	95% conf. int.	mean	95% conf. int.
Plasma potassium (mmol/L)	0.53	(0.40 - 0.64)	59	(45 - 71)
Plasma lactate (mmol/L)	0.48	(0.39 - 0.56)	53	(43 - 62)
QTc (ms)	0.52	(0.34 - 0.67)	57	(38 - 74)

Oxis Turbuhaler was estimated to be 50-60 times as potent systemically as Bricanyl Turbuhaler.

Safety results

In total, 78% of the subjects treated with Oxis Turbuhaler, 95% treated with Bricanyl Turbuhaler and 37% after the no treatment day, reported an AE in any category.

By far the most commonly reported AEs were reported in the SOC "Central and peripheral system disorders" with tremor as the most frequently reported event. For Oxis Turbuhaler, 13 subjects (72%) reported tremor and for Bricanyl Turbuhaler the corresponding figure was 17 (89%). No subjects reported tremor during the no treatment day. Tremor is a well known class effect of β_2-agonists, especially after high doses. Other well known class effects such as headache and tachycardia were reported by a low number of subjects and with a similar frequency during both active treatments.

The majority of the AEs were assessed as being of mild to moderate intensity. Two subjects had AEs of severe intensity. For Oxis Turbuhaler treatment, one subject experienced a β_2-agonist intoxication with vomiting and nausea and one subject experienced tremor and malaise, this subject also reported tremor after Bricanyl Turbuhaler treatment.

One SAE was reported after Oxis Turbuhaler, the subject experienced nausea, tremor, headache, vomiting, tachycardia and somnolence assessed by the investigator as a possible β_2-agonist intoxication. This subject was withdrawn from the study.

No clinically important differences between the treatments or changes over time were identified for clinical laboratory tests, vital signs or ECG measurements. The observed changes/abnormal findings on clinical laboratory values, vital signs and ECG measurements were in favour of Oxis Turbuhaler.

No new or unexpected safety findings were identified in this study.