AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Symbicort® Turbuhaler®
Study Code	D589LC00003
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A comparison of tolerability of 10 inhalations of Symbicort® Turbuhaler® 160/4.5 µg and 10 inhalations of terbutaline Turbuhaler 0.4 mg on top of Symbicort Turbuhaler 160/4.5 µg 1 inhalation bid, randomized, double-blind, cross over, phase III study in Japanese adults asthma patients

Study dates: First subject enrolled: 24 January 2009
Last subject last visit: 9 July 2009

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

25 patients were enrolled at 2 study centres in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective of the study was to compare the tolerability of Symbicort® Turbuhaler® 160/4.5 µg 10 inhalations with terbutaline Turbuhaler® 0.4 mg 10 inhalations for 3 days on top of Symbicort® Turbuhaler® 160/4.5 µg 1 inhalation bid in Japanese adult asthma patients.

Study design

This was a randomized, double-blind, active comparator and cross-over study.

Target patient population and sample size

The subject population includes patients with asthma aged 16-65 years and ECG and S-potassium/blood glucose levels within normal reference ranges. 24 patients were to be randomised in order to have 20 evaluable patients into this study.

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

Table S 1 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
Symbicort® Turbuhaler® 160/4.5 µg	Dry powder inhaler budesonide 160 µg + formoterol fumarate 4.5 µg /inhalation 120 inhalations/Turbuhaler®	AstraZeneca, Sweden	H 1868-01-01	H 1868-01-01-02
Terbutaline Turbuhaler® 0.4 mg	Dry powder inhaler terbutaline sulphate 0.4 mg/inhalation 120 inhalation/Turbuhaler®	AstraZeneca, Sweden	H 1970-01-01	H 1970-01-01-01

The dose and treatment regimens of the investigational products were as follows:

- Symbicort® Turbuhaler® 160/4.5 µg
  Symbicort® Turbuhaler® 160/4.5 µg 10 inhalations/day for 3 days on top of Symbicort® Turbuhaler® 160/4.5 µg 1 inhalation bid as a maintenance treatment

- Terbutaline Turbuhaler® 0.4 mg
  Terbutaline Turbuhaler® 0.4 mg 10 inhalations/day for 3 days on top of Symbicort® Turbuhaler® 160/4.5 µg 1 inhalation bid as a maintenance treatment

Duration of treatment

Symbicort® Turbuhaler® 160/4.5 µg 1 inhalation bid was given from the second day of Run-in period to the end of Treatment period 2 (excluding the last day). After 7 to 10 days of run-in period, either Symbicort® Turbuhaler® 160/4.5 µg 10 inhalations or terbutaline Turbuhaler® 0.4 mg 10 inhalations were added for 3 days in Treatment period 1. Sequentially, after 7 to 14 days of washout, either Symbicort® Turbuhaler® 160/4.5 µg 10 inhalations or terbutaline Turbuhaler® 0.4 mg 10 inhalations were added for 3 days in Treatment period 2.

Criteria for evaluation (main variables)

- Adverse events (AEs)
- Clinical laboratory variables
- 12-Lead ECG
- Vital signs (blood pressure, pulse rate and body temperature)

Statistical methods

Safety variables were summarized using the descriptive statistics for each investigational product. In addition, average, maximal and minimal concentrations and effects were analysed separately using additive analysis of variance models with patient as a random effect, visit and treatment as fixed factors and the pre-drug value as a covariate.

Patient population

In total, 28 patients were enrolled at 2 centres in Japan. Of those 25 patients were randomised to either of the two treatment groups at Visit 3. All of 25 randomised patients received at least 1 study treatment and were included in safety analysis set. Of 25 patients in safety analysis set, 2 patients did not receive terbutaline due to adverse events lead to discontinuation. Therefore, data from 25 patients for Symbicort® and 23 patients for terbutaline were used for the safety evaluation.

The demographic and key baseline characteristics of study subjects are summarised in Table S 2. Of the 25 randomized patients, 15 (60%) were male, 10 (40%) were female and 13 (52.0%) were never smokers. The mean age was 44.3 years (range: 20 to 62) and the mean duration of asthma from screening was 11.4 years (range: 0.5 to 31.2). The mean FVC, FEV_1 and FEV_1 % of predicted normal at screening were 3.88 L (range: 2.48 to 7.17), 2.98 L (range: 1.89 to 5.01) and 96.6% (range: 74.2 to 130.5), respectively. The patient population enrolled into the study was considered to be consistent with those defined by the study protocol and to be adequately representative of the target population to Symbicort® SMART regimen.

Table S 2 Demographic characteristics (All randomised patients)

Demographic characteristic		Number (%) of patients N=25
Sex	Male (%)	15 (60.0)
	Female (%)	10 (40.0)
Race	Asian (%)	25 (100.0)
Age (years)	Mean (SD)	44.3 (14.8)
	Range	20 to 62
Smoking status N (%)	Never	13 (52.0)
	Current	0
	Former	12 (48.0)
Smoking pack years	N	12
	Mean (SD)	4.6 (2.0)
	Range	2 to 8
Height (cm)	Mean (SD)	166.0 (10.6)
	Range	147 to 193
Weight (kg)	Mean (SD)	67.2 (12.6)
	Range	51 to 97
BMI (kg/m^2)	Mean (SD)	24.26 (2.90)
	Range	19.0 to 30.6
Duration of asthma from screening (days)	Mean (SD)	4178.0 (3476.1)
	Range	186 to 11384
Total ICS dose (µg)*	Mean (SD)	404.0 (53.9)
	Range	200 to 500
FVC (L)	Mean (SD)	3.882 (1.071)
	Range	2.48 to 7.17
FEV_1 (L)	Mean (SD)	2.984 (0.755)
	Range	1.89 to 5.01
FEV_1% of predicted normal (%)**	Mean (SD)	96.589 (17.790)
	Range	74.21 to 130.50

* ICS: ATC code = R03AK 5205, R03BA 5205
** Predicted normal FEV1 value will be calculated according to ERS (Quanjer et al 1993).

Summary of safety results

A summary of adverse events (AEs) in each category is presented in Table S 3. In the study, 14 AEs were reported for 12 of the 25 patients (48.0%) during treatment with Symbicort® and 24 AEs were reported for 14 of the 23 patients (60.9%) during treatment with terbutaline. The majority of AEs were of mild intensity. No severe AEs were reported in the study. No SAEs were reported in the study. However, adverse events leading to discontinuation of treatment (DAE) were reported in 3 patients. Of the 3 DAEs, 1 event, Electrocardiogram T wave inversion, during treatment with terbutaline was considered causally related to investigational product by the investigator(s). There was no OAE identified in this study.

AEs summarised by system organ class and preferred term in the study are shown in Table S 4. During treatment with Symbicort®, the most common AEs by preferred term (>10%) were tremor in 3 (12.0%) of the patients. During treatment with terbutaline, most common AEs (>10%) were tremor in 4 (17.4%) of the patients, and palpitations, tachycardia, and blood potassium decreased, all in 3 (13.0%) of the patients. AEs reported with similar incidence in both treatment were tremor (3 patients in Symbicort®, 4 in terbutaline), nasopharyngitis (2 patients in each group), blood potassium decreased (2 patients in Symbicort®, 3 in terbutaline) and headache (1 patient in each group). AEs reported in the study were predictable and consistent with the safety profiles of both Symbicort® and β_2-agonists or commonly occurring health problems in the studied population.

Table S 3 Summary of adverse events in any category (Safety analysis set)

Category	Symbicort® Turbuhaler® 160/4.5 µg, 10 inhalation/ day N=25	Terbutaline Turbuhaler® 0.4 mg, 10 inhalation/day N=23
Number of patients who had at least 1 AE in each category N(%)		
All adverse events	12 (48.0)	14 (60.9)
Adverse events with severe intensity	0	0
Adverse events with moderate intensity	1 (4.0)	1 (4.3)
Adverse events with mild intensity	11 (44.0)	13 (56.5)
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	0	0
Adverse events leading to discontinuation of treatment	2 (8.0)	1 (4.3)
All other significant adverse events	0	0
Total number of events		
All adverse events	14	24
Adverse events with severe intensity	0	0
Adverse events with moderate intensity	1	1
Adverse events with mild intensity	13	23
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	0	0
Adverse events leading to discontinuation of treatment	2	1
All other significant adverse events	0	0

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Table S 4 Number (%) of patients who had at least 1 adverse event by system organ class and preferred term (Safety analysis set)

System organ class and Preferred term*	Number (%) of patients	
	Symbicort® Turbuhaler® 160/4.5 µg, 10 inhalation/day N=25	Terbutaline Turbuhaler® 0.4 mg, 10 inhalation/day N=23
INFECTIONS AND INFESTATIONS	4 (16.0)	2 (8.7)
NASOPHARYNGITIS	2 (8.0)	2 (8.7)
INFLUENZA	1 (4.0)	0
PHARYNGITIS	1 (4.0)	0
NERVOUS SYSTEM DISORDERS	4 (16.0)	5 (21.7)
TREMOR	3 (12.0)	4 (17.4)
HEADACHE	1 (4.0)	1 (4.3)
CARDIAC DISORDERS	3 (12.0)	5 (21.7)
PALPITATIONS	1 (4.0)	3 (13.0)
SUPRAVENTRICULAR EXTRASYSTOLES	1 (4.0)	0
TACHYCARDIA	1 (4.0)	3 (13.0)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0	1 (4.3)
INVESTIGATIONS	2 (8.0)	4 (17.4)
BLOOD POTASSIUM DECREASED	2 (8.0)	3 (13.0)
ELECTROCARDIOGRAM T WAVE AMPLITUDE DECREASED	0	1 (4.3)
ELECTROCARDIOGRAM T WAVE INVERSION	0	1 (4.3)
VASCULAR DISORDERS	1 (4.0)	0
HOT FLUSH	1 (4.0)	0
GASTROINTESTINAL DISORDERS	0	2 (8.7)
NAUSEA	0	1 (4.3)
TOOTHACHE	0	1 (4.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	3 (13.0)
FATIGUE	0	1 (4.3)
FEELING COLD	0	1 (4.3)
MALAISE	0	1 (4.3)

* MedDRA version 12.0

There were no clinically significant changes in mean values between screening and follow-up in any clinical chemistry variable. However, elevations of glucose and decreases of serum potassium were observed during treatment with both investigational products. The incidence and magnitudes of these findings were considered higher during treatment with terbutaline than with Symbicort®. These changes in glucose and potassium were considered reversible as they resolved at pre-dose measurements in the morning after completion of daily 10 inhalations of investigational products.

Mean value of supine pulse elevated after the start of treatment with both investigational products. Individually, the elevations of supine pulse were observed in the majority of the patients during treatment with terbutaline. However, the elevations were considered reversible as they resolved at pre-dose measurements in the morning after completion of daily 10 inhalations of investigational products and there were no patients who experienced continuously elevations of supine pulse through 3 days of the treatment period.

Slight increase of mean QTcF was observed during treatment with both investigational products. The increase resolved at pre-dose the next morning. The time profiles of mean QTcF were similar for both investigator products. There were no significant differences in the pattern of shifts in QTcF between both treatments. QTcF prolongation, > 30 ms of change from pre-dose, was observed in 6 patients during treatment with both treatments (1 patient during treatment with Symbicort®, 3 patients during treatment with terbutaline and 2 patients during both treatments). These QTcF prolongations recovered within 10 hours after the onset and were considered transient findings.

Overall, there were no serious adverse events or significant findings for clinical laboratory values, vital signs or ECG that gave any reason for concern regarding the safety and tolerability of Symbicort® Turbuhaler®.