AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Terbutaline Turbuhaler®
Study Code	D589LC00002
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A study to investigate the relative efficacy of terbutaline Turbuhaler® 0.4 mg and Salbutamol pMDI 200 µg - a single blind, single dose, randomized, crossover, phase III study in Japanese adult asthma patients

Study dates: First subject enrolled: March 2010
Last subject last visit: July 2010

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)

37 patients were enrolled at one centre in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary		
To investigate relative efficacy of terbutaline Turbuhaler® 0.4 mg and salbutamol pMDI 200 μg in Japanese adult asthma patients.	**Primary variable** • $AUC_{0\text{-}4hr}$ of FEV_1 **Secondary variables** • percent change from pre-dose measurement at each time point • maximum percent change • time to peak measurement • number of patients with percent change more than or equal 15% • time to change more than or equal 15% (time to onset response)	Efficacy
Secondary		
To investigate safety of terbutaline Turbuhaler® 0.4 mg in Japanese adult asthma patients by means of adverse events (AEs) and vital signs (blood pressure, pulse rate).	• Adverse events • Vital sign (blood pressure, pulse rate)	Safety

Study design

This was a single blind, single dose, crossover study to investigate the relative efficacy of terbutaline Turbuhaler® 0.4 mg in relation to salbutamol pMDI 200 μg in Japanese adult asthmatic patients.

Target subject population and sample size

The subject population includes Japanese patients (16 years of age or older) with asthma who need treatment with inhaled Glucocorticosteroids (ICS). 24 patients were to be randomised in order to have 22 evaluable patients into this study.

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

Table S 2 Identity of investigational product

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Terbutaline Turbuhaler® 0.4 mg	Dry powder inhalerTerbutaline sulphate 0.4 mg/dose120 doses/Turbuhaler	AstraZeneca Sweden	21-000-82	09-004976AZ
Placebo Turbuhaler	Dry powder inhaler120 doses/Turbuhaler	AstraZeneca Sweden	21-003-57	09-002660AZ
Salbutamol pMDI 100 µg	Aerosol in pMDI,Salbutamol 100 µg/actuation,Ca 200 actuations	GlaxoSmithKline	-	F1128
Placebo pMDI	Aerosol in pMDI, Ca 120 actuations	AstraZeneca UK	FDN 174	08-003148AZ

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

- Placebo pMDI 2 inhalations followed by terbutaline Turbuhaler® 0.4 mg 1 inhalation per dose.

Or

- Placebo Turbuhaler 1 inhalation followed by Salbutamol pMDI 100 µg 2 inhalations per dose.

Duration of treatment

The study was single dose 2-way crossover study with 7 to 14 days of run-in period and 1 to 13 days of wash-out period between the treatments.

Statistical methods

The analysis set for efficacy was based on the Full Analysis Set (FAS) in line with the International Conference on Harmonisation (ICH) E9 guidelines. Efficacy variable, FEV_1, was summarised with the descriptive statistics for each treatment, and the comparisons between treatments were performed with the primary and secondary variables. An analysis was also performed with a multiplicative Analysis of Variance (ANOVA) model including patient, period and treatment as fixed factors. The estimate and 95% confidence interval for the mean difference between treatments were computed from the model. For the safety data,

the descriptive statistics of incidences of AEs and vital signs were calculated for each treatment.

Subject population

In total, 37 patients were enrolled at 1 centre in Japan. Of those 24 patients were randomised to either of the two treatment sequences at Visit 3. Of 24 randomised patients, 2 patients (1 from each treatment sequence) were discontinued from the study before the start of their second treatment because they did not fulfil inclusion criteria 8. Therefore, data from 22 and 24 patients were included in efficacy and safety analysis sets, respectively.

The demographic and key baseline characteristics of study subjects are summarised in Table S 3. Of the 24 randomized patients, 7 patients (29.2%) were male, 17 patients (70.8%) were female and 13 patients (54.2%) were never smokers. The mean age was 42 years (range: 24 to 55) and the mean duration of disease was 26 years (range: 3 to 55). The mean total daily dose of ICS was 375.0 µg. The mean FVC, FEV_1 and FEV_1 % of predicted normal at entry were 3.23 L (range: 1.88 to 5.37), 2.16 L (range: 1.25 to 3.46) and 74.8% (range: 58 to 94), respectively.

Table S 3 Demographic characteristics (All randomised patients)

Demographic characteristic		Number of patients (N=24)
Sex	Male (%)	7 (29.2)
	Female (%)	17 (70.8)
Race	Asian (%)	24 (100.0)
Age (years)	Mean (SD)	41.7 (7.4)
	Range	24 to 55
Smoking status	Never (%)	13 (54.2)
	Current (%)	0
	Former (%)	11 (45.8)
Smoking pack years	N	11
	Mean (SD)	4.1 (1.9)
	Range	1 to 7
Height (cm)	Mean (SD)	161.6 (8.8)
	Range	150 to 181
Weight (kg)	Mean (SD)	64.5 (11.9)
	Range	46 to 84
Body mass index (BMI) (kg/m^2)	Mean (SD)	24.6 (3.8)
	Range	18 to 33
Duration of disease (year)	Mean (SD)	25.8 (14.0)
	Range	3 to 55
Total daily ICS dose (µg) [1)]	Mean (SD)	375.0 (170.0)
	Range	200 to 800
FVC (L)	Mean (SD)	3.230 (0.864)
	Range	1.88 to 5.37
FEV_1 (L)	Mean (SD)	2.163 (0.551)
	Range	1.25 to 3.46
FEV_1% of predicted normal [2)] (%)	Mean (SD)	74.797 (11.229)
	Range	58.40 to 93.95

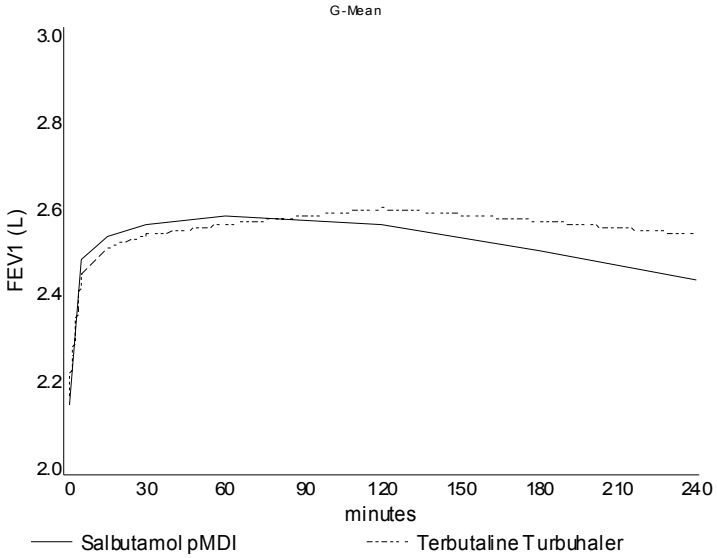
1) Label dose recorded in the CRF.
2) Predicted normal FEV_1 value (pre-bronchodilator) was used.
Data derived from Table 11.1.3 and 11.1.8, Section 11.

Summary of efficacy results

Primary variable AUC_{0-4hr} of FEV_1

Mean plots for % change of FEV_1 from pre-dose at treatment period is presented in Figure S 1. The figure showed that both terbutaline treatment and salbutamol treatment had similar effect on lung function, with a rapid onset of effect that was maintained throughout the 4-hour test period.

Figure S 1 G-mean plots for FEV_1 (L) at treatment period (Efficacy analysis set)



Data derived from Figure 11.2.14, Section 11.

Summary of AUC_{0-4hr} of FEV_1 and comparison between treatment groups for AUC_{0-4hr} of FEV_1 with ANOVA are shown in Table S 4. The G-mean of $AUC_{0-4\ hr}$ of FEV_1 for terbutaline treatment and salbutamol treatment were 634.6 mL·min and 617.6 mL•min, respectively. No statistically significant difference was seen between the two treatments in $AUC_{0-4\ hr}$ of FEV_1 (ANOVA; adjusted salbutamol/terbutaline ratio: 0.97; 95%CI: 0.935 to 1.013, p=0.17).

Table S 4 Descriptive statistics in AUC_{0-4hr} of FEV_1 (Efficacy analysis set)

	Salbutamol pMDI (N = 22)					Terbutaline Turbuhaler® (N = 22)				
Variable	**G-Mean**	**CV**	**Min**	**Median**	**Max**	**G-Mean**	**CV**	**Min**	**Median**	**Max**
$AUC_{0-4\ hr}$ of FEV_1 (mL•min)	617.556	25.253	352.57	603.905	974.45	634.637	25.417	356.68	626.945	1016.46

AUC (calculated with the trapezodial method) of actual time for each treatment period.
Data derived from Table 11.2.3, Section 11.

Secondary variables - Percent change from pre-dose measurement at each time point

Percent change to pre-dose (ratio) of FEV_1 and comparison between treatment groups for FEV_1 at each time point is shown in Table S 5 and Table S 6. Although terbutaline treatment and salbutamol treatment differed statistically significantly with regard to effect on FEV_1 at 180 and 240 minutes (unadjusted for multiple comparisons), estimated treatment ratios were at all time points (t=5, 15, 30, 60, 120, 180 and 240 minutes) close to 1 with no indication of a clinically relevant difference at any time point.

Table S 5 Percent change to pre-dose (ratio) of FEV_1 (Efficacy analysis set)

	Salbutamol pMDI (N = 22)					Terbutaline Turbuhaler® (N = 22)				
Protocol schedule	**Mean**	**SD**	**Min**	**Median**	**Max**	**Mean**	**SD**	**Min**	**Median**	**Max**
Predose	2.145	24.844	1.26	2.090	3.34	2.168	24.607	1.31	2.125	3.43
5 min	115.583	8.241	102.80	115.551	137.95	112.801	7.140	100.00	111.556	134.85
15 min	118.147	8.070	105.11	117.634	142.16	115.688	7.621	103.27	115.935	138.59
30 min	119.420	9.240	103.28	119.029	147.32	117.022	8.462	99.59	118.146	139.83
60 min	120.279	9.477	102.19	119.650	149.19	118.112	8.988	102.86	117.839	144.40
120 min	119.539	8.811	97.45	119.945	149.73	119.794	8.902	103.27	119.336	150.21
180 min	116.680	9.335	92.70	115.802	142.70	118.479	9.677	100.68	117.240	146.06
240 min	113.592	8.735	87.96	111.511	132.67	117.049	9.347	97.96	116.864	139.00

Data derived from Table 11.2.2, Section 11.

Table S 6 Comparison between treatment groups for FEV_1 at each time point with ANOVA (Efficacy analysis set)

Multiplicative model			**95% CI**		
Difference	**Protocol schedule**	**Adjusted ratio**	**Lower**	**Upper**	**p-value**
Salbutamol pMDI / Terbutaline Turbuhaler®	5 min	1.013	0.986	1.042	0.3212
	15 min	1.010	0.982	1.039	0.4727
	30 min	1.009	0.982	1.038	0.4934
	60 min	1.007	0.981	1.034	0.5794

Table S 6 Comparison between treatment groups for FEV_1 at each time point with ANOVA (Efficacy analysis set)

Multiplicative model			95% CI		
Difference	**Protocol schedule**	**Adjusted ratio**	**Lower**	**Upper**	**p-value**
	120 min	0.987	0.956	1.019	0.3985
	180 min	0.974	0.950	0.998	0.0368
	240 min	0.960	0.927	0.994	0.0247

ANOVA model with period and treatment as fixed factors, and patient as random factor.
Data derived from Table 11.2.5, Section 11.

Secondary variables - Maximum percent change of FEV_1

The G-mean of maximum % change to pre-dose (ratio) of FEV_1 for terbutaline treatment and salbutamol treatment were 121.4% and 122.6%, respectively. No statistically significant difference was seen between the two treatments in maximum % change of FEV_1 (ANOVA; adjusted salbutamol/terbutaline ratio=1.01, 95%CI: 0.983 to 1.037, p=0.46).

Secondary variables - Time to peak measurement of FEV_1

No statistically significant difference was seen between the two treatments in time to peak measurement of FEV_1 (Wilcoxon signed rank test: p=0.054).

Secondary variables - Number of patients with percent change greater than or equal to 15% of FEV_1

Number of patients with % change greater than or equal to 15% of FEV_1 for terbutaline treatment and salbutamol treatment were 16 patients (72.7%) and 17 patients (77.3%), respectively. No statistically significant difference was seen between the two treatments in number of patients with % change greater than or equal to 15% of FEV_1 (McNemar test: p=0.65).

Secondary variables - Time to onset response of FEV_1

No statistically significant difference was seen between the two treatments in time to onset response of FEV_1 (Wilcoxon signed rank test: p= 0.59).

Summary of safety results

Only two AEs (nasopharyngitis and conjunctivitis) were reported for 2 patients during treatment with terbutaline (1 patient) and salbutamol (1 patient), respectively. Both AEs were mild intensity and not considered causally related to investigational products by investigator(s). No SAEs, adverse events leading to discontinuation of treatment (DAE) were reported in the study. There was no OAE identified in this study. No safety concerns were identified in the study.

There were no clinically significant findings for vital signs that gave any reason for concern regarding the safety in the study.