AstraZeneca

Exploratory Study Report Synopsis

Drug Substance	Budesonide
Study Code	D5252M00001
Edition Number	1
Date	19 October 2010

A phase I, randomized, open-label, 5-way crossover, single centre study in healthy subjects to assess the lung deposition of inhaled budesonide delivered via different inhalation devices

Study dates: First subject enrolled: 8 September 2009
Last subject last visit: 3 November 2009

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre

The study was performed at 1 centre in Sweden.

Publications

None at the time of writing this report synopsis.

Objectives and criteria for evaluation

The primary objective of the study was to assess the lung deposition of inhaled budesonide from 5 different inhalation devices. A semi simultaneous intravenous infusion of budesonide was used as an absolute reference. Lung deposition estimates were based on analysis of budesonide in plasma. The primary variable was the area under the budesonide plasma concentration curve from zero to infinity (AUC).

The secondary objective of the study was to estimate the pharmacokinetics of budesonide in plasma after the 5 treatments. Secondary pharmacokinetic variables were maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}) and mean residence time (MRT).

Study design

This was an open, randomized, 5-way crossover, single centre study. Sixteen healthy subjects were to be randomized to have at least 12 evaluable subjects completing the study.

The study comprised of 1 screening visit, 5 treatment visits and 1 follow-up telephone call. All subjects were to inhale single doses of budesonide at 5 different occasions separated by a washout of minimum 3 days and a maximum of 28 days.

On the treatment visits subjects were to ingest activated charcoal to adsorb any study drug swallowed after inhalation, so that only budesonide absorbed from the lungs would be measured in plasma. On the last treatment visit, a semi simultaneous intravenous infusion of budesonide was given.

Target subject population and sample size

Healthy, non-smoking subjects able to inhale from Turbuhaler, pMDIs with and without spacer and Spira nebuliser were included.

The number of healthy subjects was not based on statistical considerations. Twelve (12) subjects were considered sufficient to get reliable estimates of the pharmacokinetic parameters.

Investigational product and comparators: dosage, mode of administration and batch numbers

The following inhaled treatments were used.

- Pulmicort pMDI (HFA), 4 inhalations of 200 µg budesonide, metered dose

- Budesonide pMDI (HFA), 4 inhalations of 160 µg budesonide, delivered dose
- Budesonide pMDI (HFA) + Aerochamber Zero-stat spacer, 4 inhalations of 160 µg budesonide, delivered dose
- Pulmicort Respules, inhalation of 3 x 2 mL of 0.5 mg/ml budesonide via Spira Nebuliser (corresponds to inhalation of approximately 800 µg budesonide)
- Pulmicort Turbuhaler (M2), 4 inhalations of 200 µg budesonide, metered dose

At the last visit, a semi-simultaneous intravenous infusion of 200 µg budesonide was given 4 hours after the inhaled dose. Since this was a crossover study, all subjects received all treatments, unless they did not complete the study. A single batch of each treatment used, as listed in the CSR.

Duration of treatment

Single doses were given on 5 occasions separated by at least a 3 and a maximum 28 days washout.

Statistical methods

Pharmacokinetic parameters for plasma budesonide were estimated with standard non-compartmental methods.

AUC = $AUC_{0-\infty}$ was calculated using the trapezoidal method up to last measurement above the lower limit of quantification (LOQ), and then the tail was calculated by mono-exponential extrapolation using the last measurement above LOQ and estimated k_{el}. AUMC was calculated by integrating the function $t \times C(t)$ in the same way as C(t) was integrated for AUC. The mean residence time (MRT) was then found as AUMC/AUC. In computations, each treatment was assumed to give a nominal dose of 800 µg budesonide.

The k_{el} estimated after the iv administration of budesonide was used for extrapolation of each subjects inhaled treatments (at the last visit extrapolation started from 4 hours). The AUC following the iv administration was estimated as the total AUC from the start of infusion (4 hours after inhaled dose), and subtracting the extrapolated part of the inhaled treatment from 4 hours. The lung deposition, F, was calculated as the dose-normalized AUC ratio of inhaled over iv treatment. The dose of the iv administration was estimated from the syringe weight before and after infusion.

Analysis was done using multiplicative or additive analysis of variance (ANOVA) models with subject, period and treatment as factors. In the multiplicative models the variability was expressed as a coefficient of variation. p-values less than 0.05 were considered statistically significant.

Subject population

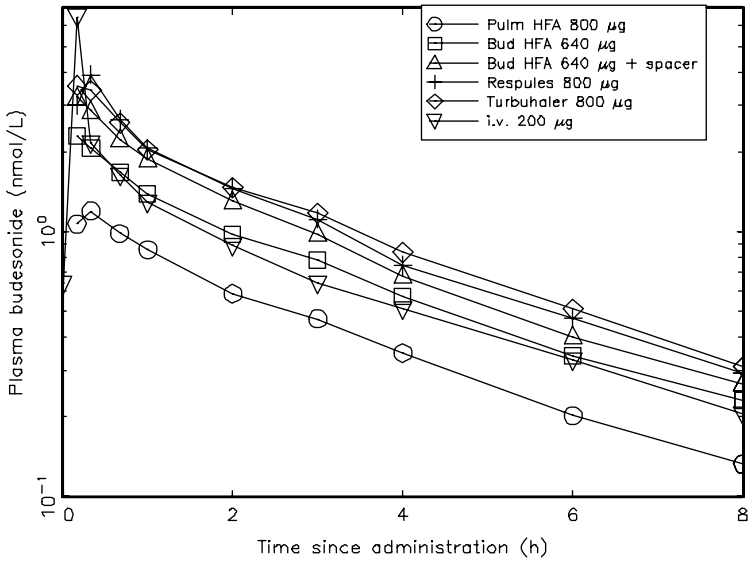
A total of 29 subjects were enrolled at 1 centre in Sweden. Sixteen (16) subjects were randomized at Visit 2. All randomized subjects completed the study and were included in the pharmacokinetic analysis. One subject did not perform 1 of the study days and thus the Pulmicort Turbuhaler data are missing for that subject.

Of the 16 subjects included in the study, 14 (88%) were males and 2 (13%) were females. Their average age, at enrolment (Visit 1), was 28.4 years (range: 20–44). All subjects were white.

Summary of pharmacokinetic results

Mean plasma concentration-time curves of budesonide for the 5 inhaled treatments and the (unadjusted) iv-infusion of budesonide (given 4 hours after inhaled treatment) are shown on semi-logarithmic scale in Figure 1.

Figure 1 Mean plasma concentration curves of budesonide



Descriptive statistics for the computed pharmacokinetic parameters for C_{max}, AUC and F are given in Table 1 and for t_{max} and MRT in Table 2. The adjusted means for F for the inhaled treatments is given in Table 3.

Administration of budesonide via Pulmicort Turbuhaler resulted in statistically significant higher exposure (AUC and C_{max}) as compared with Pulmicort HFA and Budesonide HFA inhalers. The average F for Pulmicort Turbuhaler was estimated to 39% of nominal dose, compared to 27% for the Budesonide HFA and 15% for the Pulmicort HFA inhalers.

MRT was statistically significantly longer after administration via Pulmicort HFA and Budesonide HFA inhalers compared with Pulmicort Turbuhaler, with estimated mean

differences of 12 to 15 minutes. Absorption was fast with a median t_{max} of 10 to 20 minutes for all inhalers.

Table 1 Statistical summary of pharmacokinetic parameters of budesonide, inhaled treatments (geometric means)

Variable	Treatment	n	GMean	CV	Min	Median	Max
C_{max} (nmol/L)	Pulm HFA 800 µg	16	1.144	54.6	0.46	1.21	2.40
	Bud HFA 640 µg	16	2.246	36.4	1.20	2.20	4.79
	Bud HFA 640 µg + spacer	16	3.191	37.2	1.60	3.47	5.61
	Respules 800 µg	16	3.751	34.6	1.76	3.90	6.26
	Turbuhaler 800 µg	15	3.966	20.4	2.75	4.23	5.22
AUC (nmol*h/L)	Pulm HFA 800 µg	16	3.752	40.6	2.07	4.08	7.24
	Bud HFA 640 µg	16	6.751	21.6	4.17	7.11	8.49
	Bud HFA 640 µg + spacer	16	8.488	22.4	5.74	8.21	12.12
	Respules 800 µg	16	9.497	23.0	5.81	9.50	13.11
	Turbuhaler 800 µg	15	9.834	19.3	7.33	9.47	14.17
F (%)[a]	Pulm HFA 800 µg	16	15.09	41.3	6.7	16.2	29.3
	Bud HFA 640 µg	16	27.15	34.2	13.2	28.7	46.4
	Bud HFA 640 µg + spacer	16	34.14	30.7	19.2	33.2	63.4
	Respules 800 µg	16	38.19	40.9	21.5	35.6	102.2
	Turbuhaler 800 µg	15	40.60	26.1	29.1	40.4	65.0

[a] For all treatments, F is expressed as percent of the nominal dose of 800 µg budesonide

Table 2 Statistical summary of pharmacokinetic parameters of budesonide, inhaled treatments (arithmetic means)

Variable	Treatment	n	Mean	SD	Min	Median	Max
t_{max} (min)	Pulm HFA 800 µg	16	20.9	8.6	10	20	41
	Bud HFA 640 µg	16	15.4	8.3	9	11	41
	Bud HFA 640 µg + spacer	16	17.3	10.1	9	11	41
	Respules 800 µg	16	21.9	4.9	18	21	40
	Turbuhaler 800 µg	15	16.6	6.6	9	20	31
MRT (h)	Pulm HFA 800 µg	16	3.90	0.46	3.0	3.9	4.8
	Bud HFA 640 µg	16	4.03	0.94	2.6	3.8	6.1
	Bud HFA 640 µg + spacer	16	3.62	0.51	2.9	3.6	4.6
	Respules 800 µg	16	3.74	0.70	2.1	3.7	4.9
	Turbuhaler 800 µg	15	3.53	0.56	2.7	3.6	4.5

Table 3 Adjusted mean F with 95% confidence intervals

	Estimate of F[a]	
Treatments	**(%)**	**95% C.I.**
Pulm HFA 800 µg	15.1	(13.5 - 17.0)
Bud HFA 640 µg	27.1	(24.2 - 30.4)
Bud HFA 640 µg + spacer	34.2	(30.5 - 38.4)
Respules 800 µg	38.3	(34.1 - 42.9)
Turbuhaler 800 µg	39.3	(34.8 - 44.2)

[a] For all treatments, F is expressed as percent of the nominal dose of 800 µg budesonide

Summary of safety results

Only serious adverse events (SAE) and discontinuations due to adverse events (DAE) were collected in this study. There were no SAEs or DAEs.