AstraZeneca

Clinical Study Report

Drug Substance	Budesonide
Study Code	D5252C00006
Edition Number	1
Date	19 October 2007

An open-label, randomised crossover study of budesonide pharmacokinetics and the effect of budesonide on 24-hour plasma/urine cortisol concentrations when administered via HFA pMDI, CFC pMDI and Turbuhaler® for 6.5 days in healthy volunteers

Study dates: First subject enrolled: 08 March 2007
Last subject completed: 26 June 2007

Phase of development: Clinical Pharmacology (I)

This study was performed in compliance with Good Clinical Practice.

Drug Substance	Budesonide	**SYNOPSIS**	
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An open-label, randomised crossover study of budesonide pharmacokinetics and the effect of budesonide on 24-hour plasma/urine cortisol concentrations when administered via HFA pMDI, CFC pMDI and TurbuhalerP®P for 6.5 days in healthy volunteers

Study centre

Quintiles AB, Uppsala, Sweden

Publications

None at the time of this clinical study report.

Study dates		**Phase of development**
First subject enrolled	08 March 2007	Clinical pharmacology (I)
Last subject completed	26 June 2007	

Objectives

The primary objective of this study was to compare the systemic effects of budesonide HFA pMDI to Pulmicort® CFC pMDI using measurement of 24-hour plasma cortisol concentrations.

The secondary objectives of the study were:

- to compare the systemic effects of budesonide HFA pMDI to Pulmicort CFC pMDI using measurement of 24-hour urine cortisol concentrations

- to compare the systemic effects of budesonide HFA pMDI to Pulmicort Turbuhaler using measurement of 24-hour plasma/urine cortisol concentrations
- to establish pharmacokinetic (PK) parameters for budesonide HFA pMDI, Pulmicort CFC pMDI and Pulmicort Turbuhaler at steady state
- to compare PK parameters for budesonide HFA pMDI, Pulmicort CFC pMDI and Pulmicort Turbuhaler following administration of a single dose with a charcoal block
- to assess safety through reports of adverse events (AEs)

Study design

This was an open-label, randomised, three-way crossover study. Budesonide was administered from budesonide HFA pMDI, Pulmicort CFC pMDI and Pulmicort Turbuhaler, twice daily (BID) for 6.5 days. There was a screening visit to assess the acceptability for enrolment into the study followed by a baseline visit at which plasma and urine cortisol concentrations were determined. Study drug was administered at the Clinical Pharmacology Unit (CPU) on the 1st treatment day and then on an outpatient basis for the remainder of the first 6 days. For each period, on Day 1, subjects received the first dose in the morning with activated charcoal to block oral absorption; plasma samples for determination of budesonide were obtained over 12 hours post-dose. On Day 6, the subjects were admitted to the CPU prior to administration of the evening dose followed by plasma cortisol sampling (every 2 hours) and urine collection over 24 hours. Following the morning dose on Day 7, plasma budesonide samples were obtained over 12 hours post-dose. There was a washout of 12 to 30 days between each period.

Target subject population and sample size

Healthy male and female subjects at least 18 years of age, N = 30

Investigational product, dosage, mode of administration and batch numbers

Budesonide HFA pMDI 200 µg/actuation; 4 actuations BID x 6.5 days, Batch no. 6C726A

Comparator, dosage and mode of administration and batch numbers

Pulmicort CFC pMDI 200 µg/actuation; 4 actuations BID x 7 days, Batch no. 61203
Pulmicort Turbuhaler 200 µg/actuation; 4 actuations BID x 7 days, Batch no. HE1380

Duration of treatment

6.5 days for each of 3 treatments

Criteria for evaluation (main variables)

Pharmacokinetic

– Primary: $AUC_{0\text{-}inf}$ after single dose and $AUC_{0\text{-}12h}$ at steady state

- Secondary: AUC_{0-t}, C_{max}, t_{max}, MRT, $t_{1/2}$

Pharmacodynamic

- Primary: Plasma cortisol AUC_{0-24h}
- Secondary: 24-hour urinary cortisol and cortisol/creatinine ratio

Safety

- Reports of AEs

Statistical methods

Plasma cortisol AUC_{0-24h} was subjected to a multiplicative (i.e. the AUC values were log-transformed) analysis of variance (ANOVA) model with fixed factors for subject, period and treatment. Pairwise treatment comparisons were performed based on estimates obtained from the ANOVA model and estimates of the pairwise differences and 2-sided 95% confidence intervals (CIs) for these differences were presented on the linear scale and expressed as ratios of treatment effects (i.e. ratios of geometric means). Urine cortisol was assessed in a similar fashion.

For budesonide pharmacokinetics, log transformed AUC_{0-inf} and C_{max} after a single dose were compared between treatment regimens using an analysis of variance model with fixed factors subject, period and treatment. Results were backtransformed to the linear scale giving differences between regimens as ratios of geometric means. 90% two-sided CIs were constructed for the ratios between the HFA and CFC regimens, and the HFA and Turbuhaler regimens. The same analysis was performed for steady state AUC_{0-12h} and C_{max}.

All tests were 2-sided and p-values less than or equal to 0.05 were considered statistically significant.

Subject population

In total 50 subjects were screened, 28 subjects were randomised to treatment and 26 subjects completed the study. Two (2) subjects discontinued the study between Treatment Periods 2 and 3 (one due to an AE and one due to withdrawal of consent). All 28 randomised subjects completed at least 2 treatment periods and were thus included in the comparative analysis (pharmacodynamic/pharmacokinetic [PD/PK] data set). All 28 randomised subjects were included in the safety analysis set.

Pharmacodynamic results

The estimated treatment ratio for plasma cortisol AUC was 1.018 (95% CI 0.934 to 1.110, p=0.6736) for budesonide HFA vs Pulmicort CFC pMDI indicating that there was no statistically significant difference between these 2 products on plasma cortisol. The estimated treatment ratio for plasma cortisol AUC was 1.373 (95% CI 1.258 to 1.499, p<0.0001) for budesonide HFA treatment vs Pulmicort Turbuhaler and 1.349 (95% CI 1.237 to 1.470,

p<0.0001) for Pulmicort CFC pMDI vs Pulmicort Turbuhaler, indicating that both pMDI products had significantly less effect on plasma cortisol than Pulmicort Turbuhaler. Similar treatment effects were estimated for 24-hour urinary cortisol, with and without correction for creatinine.

Table S 1 AUC of plasma cortisol from 24-hour sampling at steady state, ratios of treatment effects (geometric means) from ANOVA model in logarithmic scale - PD/PK data set

		95% confidence interval		
Ratio	**Estimate**	**Lower**	**Upper**	**p-value**
Budesonide HFA pMDI / Pulmicort CFC pMDI	1.018	0.934	1.110	0.6736
Budesonide HFA pMDI / Pulmicort Turbuhaler	1.373	1.258	1.499	<0.0001
Pulmicort CFC pMDI / Pulmicort Turbuhaler	1.349	1.237	1.470	<0.0001

Pharmacokinetic

Systemic exposure to budesonide at steady state was similar after treatment with budesonide HFA pMDI and Pulmicort CFC pMDI. This was supported by the treatment ratios for budesonide HFA pMDI vs Pulmicort CFC pMDI which were close to 1 for both AUC_{0-12h} and C_{max}. After treatment with the pMDI products, budesonide exposure was approximately one-half of that for Pulmicort Turbuhaler. The treatment ratios for budesonide HFA pMDI vs Pulmicort Turbuhaler were 0.512 (AUC_{0-12h}) and 0.363 (C_{max}) and for Pulmicort CFC pMDI vs Pulmicort Turbuhaler were 0.497 (AUC_{0-12h}) and 0.406 (C_{max}).

Systemic exposure to budesonide after single dose administration with charcoal block differed between the 3 treatments. Treatment ratios for AUC_{0-inf} were 0.595 (p<0.0001) for budesonide HFA pMDI vs Pulmicort CFC pMDI, 0.413 (p<0.0001) for budesonide HFA pMDI vs Pulmicort Turbuhaler and 0.695 (p<0.0001) for Pulmicort CFC pMDI vs Pulmicort Turbuhaler. Similar treatment ratios were estimated for C_{max}. Safety results

No safety concerns were raised during the study. There were no deaths, SAEs or other significant AEs during the study. There were 2 severe AEs (fainting). All other events were mild or moderate. One (1) subject discontinued the study due to an AE that was not considered causally related to study treatment (cervicitis). The most common AEs judged as causally related to treatment were dysphonia (4 events), nausea (4 events), headache (3 events) and dry mouth (3 events).

Date of the report

19 October 2007