AstraZeneca

D5252C00001

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Pulmicort HFA pMDI

ACTIVE INGREDIENT: budesonide

Trial title (number): A pharmacokinetic comparison of orally inhaled budesonidedelivered via SkyePharma HFA metered dose inhaler and marketed CFC metered dose inhaler (Pulmicort® , AstraZeneca) in healthy male and female volunteers.(D5252C00001)

Developmental phase: I
First subject recruited: 04 June 2002
Last subject completed: 15 August 2002
Approval date: 05 Feb 2003

OBJECTIVES

Primary objective:
To compare the single-dose pharmacokinetics of budesonide at three dose levels in healthy volunteers using two formulations delivered by the SkyePharma (SKP) hydrofluoroalkane (HFA) metered dose inhaler (MDI) (100 µg/actuation and 200 µg/actuation)a with a marketed chlorofluoroalkane (CFC) MDI [Pulmicort® , Astra Zeneca (AZ) CFC MDI, 200 µg/actuation].

Secondary objective:
To evaluate the dose proportionality and relative bioavailability of the two SKP HFA MDI budesonide formulations (100 µg/actuation and 200 µg/actuation) in comparison to the reference product.

METHODS

This study was a randomised, open-label, four-way crossover, singledose study. A total of 40 subjects divided into eight groups (n=5) was to be dosed with 400, 800 or 1600 µg budesonide from either SKP HFA MDI or AZ CFC MDI.
Each subject was to receive a single dose on four occasions each followed by a wash out period of at least 2 and maximally 7 days between the four treatments. Subjects were institutionalised at the investigating facility (FOCUS) the night prior to drug administration and remained at the clinical facility until 12 hours post-dose on each of the four study periods.
A total of 40 male and female subjects divided into eight groups (n=5) were enrolled in this study.

Caucasian, healthy volunteers aged 18-45 years.
Body weight above 50 kg with an acceptable range of -10% to +15% of ideal body weight as determined by Metropolitan Life Insurance Company (see Appendices D and E of the protocol).
Normal findings in general physical examination.
Normal findings in spirometry (FEV1 $\geq$ 80% of predicted values).
Non-smoking.
Absence of viral hepatitis and HIV infection as indicated by negative serological markers.
Negative urine drug screen.
Negative pregnancy test in female subjects.
Signed written consent.

Each subject had to dose him or herself.
Doses contained 400, 800 or 1600 µg of budesonide and were administered by 4-8 puffs using the SKP HFA MDIs with 100 or 200 µg/actuation.
Groups A, B, C, and D received 400 and 800 µg budesonide via SKP HFA (100 µg/actuation).
Groups E, F, G, and H received 800 and 1600 µg budesonide via SKP HFA (200 µg/actuation).

Each subject dosed him-or herself.
Doses contained 400, 800 or 1600 µg budesonide and were administered by 2-8 puffs using the AZ CFC MDIs with 200 µg/actuation. Groups A, B, C, and D received 400 and 800 µg budesonide via AZ CFC MDIs (200 µg/actuation).
Groups E, F, G, and H received 800 and 1600 µg budesonide via AZ CFC MDIs (200 µg/actuation).
Pulmicort CFC MDI 200 µg/actuation. The sequence of treatment was different for each group.
Each volunteer underwent a medical screening examination within 21 days prior to dosing (day 1).
Eligible subjects were institutionalised at the clinic facility of FOCUS the night prior to drug administration and remained at the clinic until 12 hours post-dose on each of the four study periods.
Each volunteer underwent a medical examination for follow up within 7 days after the last dosing day.
The study duration for each volunteer was approximately two months including pre-study and post-study assessments.

Criteria of evaluation:

Pharmacokinetics:

Plasma samples were collected for budesonide concentration measurement at pre-dose and 10, 20, 30, 40, 60, and 90 minutes and at 2, 2.5, 3, 4, 6, 8, 10 and 12 hours after dosing.
The following pharmacokinetic parameters were calculated for budesonide:
C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf} and t1/2

Pharmacodynamics:

Blood samples were collected for cortisol plasma concentration measurement at pre-dose and 30 and 60 minutes, and at 2, 3, 4, 6, 8, 10 and 12 hours after dosing and at follow up examination.
The following parameter was calculated for cortisol:
AUC_{0-12}

Safety:
Adverse events were monitored at every visit pre-dose, 30 minutes, 6 and 12 hours after dosing and at the follow up examination. Subjects were also asked to spontaneously report any AEs during the study. Vital signs (blood pressure, heart rate and respiratory rate) were determined at screening, pre-dose, 30 minutes and 12 hours post-dose on each dosing day and at the follow up medical examination. Spirometry tests (FEV1, VC and FEV1/FVC) were performed at screening, in the afternoon on the days before the dosing days and at the follow up medical examination. Laboratory monitoring (haematology, clinical chemistry including urinalysis) was carried out at screening and at follow up medical examination.

Statistical methods: The primary statistical analysis concerned AUC and Cmax for budesonide. This analysis was performed separately for the two test products (100 µg and 200 µg HFA). The primary variables were dose normalised, logarithmically transformed and then subjected to Analysis of Variance (ANOVA) taking into account the factors “treatment” (test or reference), “period”, “sequence” (4 sequences for each test product), “dose” and “subject within sequence”. Based on these analyses, the 90% confidence interval (CI) of the ratio “Reference / Test ” was calculated for both primary parameters. Bioequivalence of the test and reference products was concluded if the 90% confidence interval for the ratios both fell within the pre-specified interval of 0.70-1.43 although establishment of bioequivalence was not a primary objective for this study.

RESULTS

Summary of pharmacokinetics:
Similar pharmacokinetic parameters were obtained for budesonide following administration of the test SkyePharma and reference Astra Zeneca MDI device. Slightly higher systemic plasma concentrations of budesonide were generally observed from the HFA inhalers. Nevertheless, the systemic availability of budesonide from the new HFA inhalers under test could be shown to be bioequivalent to the availability from the marketed CFC inhaler since the 90% confidence intervals for the ratios of both C_{max} and AUC fell within the predefined limits of 0.70 – 1.43. Good dose proportionality was apparent for both the test and the reference inhalers over the dosing range of 400 to 1600 µg. Summary tables of the main pharmacokinetic parameters for budesonide obtained following the various treatment schedules are shown below:

Summary of pharmacokinetic parameters for budesonide for treatment groups A to D (n=20):

	Formulation/Dose			
	400 µg		800 µg	
	SKP HFA	AZ CFC	SKP HFA	AZ CFC
	100 µg	200 µg	100 µg	200 µg**
AUC0-inf	1.155 ±0.406	1.021 ±0.475	2.256 ±0.892	2.091 ±0.875
(ng.h/mL)	1.063 (49.3%)	0.919 (51.1%)	2.082 (44.7%)	1.881 (56.0%)
AUC0-t	0.988 ±0.390	0.831 ±0.477	2.075 ±0.871	1.862 ±0.823
(ng.h/mL)	0.879 (63.6%)	0.701 (69.4%)	1.891 (48.8%)	1.623 (68.4%)
Cmax	0.360 ±0.173	0.303 ±0.141	0.656 ±0.275	0.570 ±0.248
(ng/mL)	0.319 (58.2%)	0.269 (57.4%)	0.596 (50.5%)	0.509 (56.4%)
tmax	0.583	0.500	0.583	0.500
(h)				
t1/2	2.208 ±0.373	2.441 ±0.573	2.400 ±0.309	2.838 ±1.062
(h)				
	Arithmetic mean ±SD and			
	geometric mean (CVb%) are displayed for AUC and Cmax.			
	Arithmetic mean ±SD is displayed for t1/2.			
	Median is displayed for tmax.			
	**data also included from treatment groups E to H (ie. n=40)			

	Summary pharmacokinetic parameters for budesonide for treatment			
	groups E to H (n=18 to 20*):			
	Formulation/Dose			
	800 µg		**1600 µg**	
	SKP HFA	**AZ CFC**	**SKP HFA**	**AZ CFC**
	200 µg	**200 µg****	**200 µg**	**200 µg****
AUC0-inf	2.309 ±1.016	2.091 ±0.875	4.213 ±1.697	4.030 ±1.760
(ng.h/mL)	2.075 (53.9%)	1.881 (56.0%)	3.877 (45.5%)	3.698 (44.4%)
AUC0-t	2.079 ±1.011	1.862 ±0.823	3.900 ±1.591	3.701 ±1.673
(ng.h/mL)	1.798 (68.1%)	1.623 (68.4%)	3.580 (46.3%)	3.375 (46.2%)
Cmax	0.567 ±0.226	0.570 ±0.248	1.042 ±0.373	0.990 ±0.474
(ng/mL)	0.513 (55.2%)	0.509 (56.4%)	0.969 (43.1%)	0.841 (82.5%)
tmax	0.667	0.500	0.667	0.500
(h)				
t1/2	3.044 ±0.851	2.838 ±1.062	3.176 ±0.957	3.619 ±1.018
(h)				
	Arithmetic mean ±SD and geometric mean (CVb%) are displayed for AUC and			
	Cmax.			
	Arithmetic mean ±SD is displayed for t1/2.			
	Median is displayed for tmax.			
	*n variations due to subjects 7 (LOQ plasma concentrations) and 25 (drop out)			
	** data also included from treatment groups A to D (ie. n=40)			

Summary of pharmacodynamics:

The following table shows AUC_{0-12} (µg.h/dL) values of cortisol. No relevant differences of cortisol levels were observed in the different treatment sequences.

	Summary of the AUC0-12(µg.h/dL) values of cortisol			
Treatment groups	**Treatment**	**Dose (µg)**	**Mean (SD)**	**Geom. Mean (CV%)**
A-D	SKP HFA 100	400	68.3 (19.0)	66.1 (26.7)
		800	70.2 (28.8)	65.7 (38.3)
	AZ CFC 200	400	74.7 (24.7)	71.4 (31.3)
		800**	59.2 (15.0)	57.5 (24.3)
	SKP HFA 100 vs. AZ CFC 200	Estimated ratio	1.02	
		(CI)*	(0.95, 1.09)	
E-H	SKP HFA 200	800	62.4 (21.5)	59.7 (30.0)
		1600	47.6 (12.6)	46.1 (26.4)
	AZ CFC 200	800**	59.2 (15.0)	57.5 (24.3)
		1600	61.1 (31.8)	55.1 (46.8)
	SKP HFA 200 vs. AZ CFC 200	Estimated ratio	0.95	
		(CI)*	(0.88, 1.04)	
	* For ratio the estimated value and corresponding 90% confidence interval are displayed. ** The values of all 40 subjects are summarized.			

Summary of safety:

In total, 32 adverse events were reported in 19 subjects. The majority of adverse events were mild in intensity and spontaneously disappeared without specific therapy.

The most common adverse event was headache. Pulmonary tolerability was excellent despite two episodes of slight cough, which were reported shortly after dose administration. These events possibly occurred due to irritation of the airways.

There were no clinically significant effects of budesonide on vital signs or ECG parameters. The only clinically significant finding was an asymptomatic increase of blood alpha-amylase value in one subject at follow up medical examination.

All other laboratory values including complete blood cell count, standard blood biochemistry panel and urinalysis showed no findings of clinical relevance.

REFERENCE

Abstract ERS 2005

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Pulmicort™ (budesonide), Healthcare Professionals should view their specific country information.