AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide
Study Code	D5252C00008
Edition Number	01
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A Phase 3, randomised, open-label, crossover study to compare HFA vs CFC pMDI formulations of budesonide on methacholine hyper-reactivity in patients with stable, persistent, mild to moderate asthma

Study dates: First patient enrolled: 15 April 2008
Last patient completed: 14 May 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)

The principal investigator was Dr Brian Lipworth, with patients being recruited from 2 centres in Scotland (Ninewells Hospital and Medical School [University of Dundee] and Perth Royal Infirmary).

Publications

None at the time of writing this report.

Objectives

The primary objective was to compare the relative dose potency (RDP) of HFA vs CFC pMDI budesonide on airway responsiveness to methacholine.

Secondary objectives included assessment of the effect of the two treatments on:

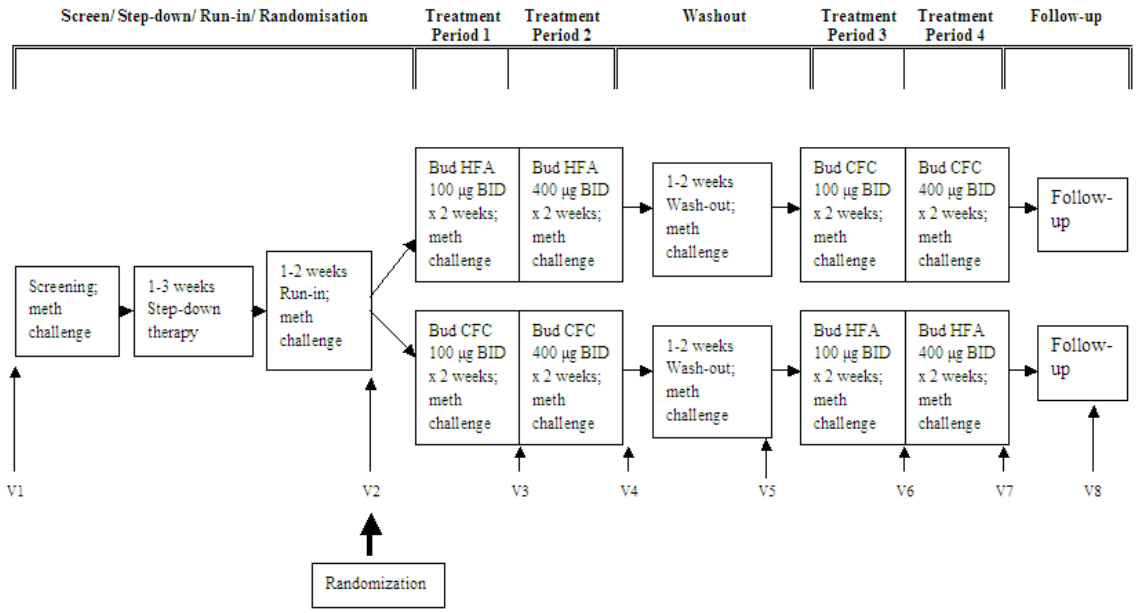
- Airway responsiveness to methacholine
- Spirometry
- Exhaled nitric oxide (eNO)
- Asthma symptoms
- Peak expiratory flow (PEF)
- Ratio of overnight urinary cortisol to creatinine.

Assessment of safety included reports of serious adverse events (SAEs) and discontinuations due to adverse event (DAE).

Study design

This was a randomised, open-label, crossover, multi-centre study with a 1 to 2 week run-in period followed by two treatment periods of 4 weeks each separated by a 1 to 2 week wash-out period. The overall schematic design of the study is presented in Figure S1.

Figure S1 Flow chart of study design



Target study population and sample size

Patients met the following key criteria for inclusion in the study run-in period:

1. Male or female patients between 18 and 65 years of age inclusive

2. Patients suffering from stable, persistent, mild to moderate asthma as defined by Global Initiative for Asthma (GINA) Guidelines and for whom $FEV_1 > 60$ %

3. ICS free or taking ≤ 1000 µg BDP per day, or equivalent

4. Methacholine PC_{20} $FEV_1 < 4$ mg/mL (if necessary this assessment could be repeated, but patients only needed to satisfy this criterion once before entering the run-in period. Also at the investigator's discretion, this assessment could be deferred until the patient was otherwise eligible to enter the run-in period, ie following ICS step-down)

For inclusion in the study treatment period patients had to fulfill all of the following criteria:

- Methacholine PC_{20} $FEV_1 < 4$ mg/mL
- FEV_1 at the end of the run-in period > 60% predicted

For feasibility reasons the number of patients were restricted to around 60 patients. 144 patients were enrolled and 99 patients were subsequently randomized and treated.

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

The following treatments were administered during the active treatment periods:

- Budesonide HFA pMDI 100 µg/actuation; 1 actuation twice daily (BID) followed by budesonide HFA pMDI 200 µg/actuation; 2 actuations BID
- Pulmicort CFC pMDI 100 µg/actuation; 1 actuation BID followed by Pulmicort CFC pMDI 200 µg/actuation; 2 actuation BID.

Budesonide HFA pMDI (Batch number: 08-012718AZ). Budesonide HFA pMDI (Batch number: 08-012716AZ). Pulmicort pMDI (Batch number: 08-012712AZ). Pulmicort pMDI (Batch number: 08-012710AZ).

Duration of treatment

There was a 1 to 2 week run-in period followed by two treatment periods of 4 weeks each separated by a 1 to 2 week washout period. The overall schematic design of the study is presented in Figure S1.

Criteria for evaluation - efficacy (main variables)

Primary outcome variable:

Methacholine airway responsiveness measured as the PC_{20} FEV_1.

Secondary outcome variables:

- Clinical spirometry assessments (FVC, FEF_{25-75} , FEV_1 and PEF)
- Morning PEF / peak flow meters
- eNO
- Asthma symptom scores (day, night and total) and rescue use consumption (day, night and total)
- Overnight (2200h - 0800h) creatinine corrected urinary cortisol.

Criteria for evaluation - safety (main variables)

- SAEs
- DAEs.

Statistical methods

The primary analysis estimated the RDP and the 95% confidence interval (CI) for the RDP based on the change in natural log PC_{20} FEV_1 from the natural log pooled baseline. An analysis of variance (ANOVA) model with patient, period, dose level, and formulation was fitted to the change in log PC_{20} FEV_1 from the natural log pooled baseline.

RDP was estimated from the fitted model that estimates parallel regression lines for each formulation (ie same slopes but differing intercepts).

The change in the natural log PC_{20} FEV_1 from the natural log pooled baseline was also compared between formulation at each dose level and between dose levels using an ANOVA model with patient, period, dose level, formulation and the dose level / formulation interaction term.

Subject population

The full analysis set was used for reporting the efficacy analyses and comprised 89 patients. Ten patients were excluded from the FAS analysis set as they hadn't contributed PC_{20} FEV_1 data from at least one period (ie, data from both low and high dose of one inhaler). The safety analysis set was used for the reporting of the adverse event data and comprised 99 patients.

The demographic and key baseline characteristics of study patients are summarised in Table S1.

Table S1 Demography and key baseline characteristics (full analysis set)

	Budesonide HFA then CFC (N=44)	Budesonide CFC then HFA (N=45)	Total (N=89)
Age, yr			
Mean	40.0	39.5	39.7
Median (Range)	44 (19 to 65)	43 (18 to 64)	44 (18 to 65)
Sex, n (%)			
Male	20 (45.5%)	19 (42.2%)	39 (43.8%)
Female	24 (54.5%)	26 (57.8%)	50 (56.2%)
Race, n (%)			
Caucasian	42 (95.5%)	42 (93.3%)	84 (94.4%)
Black	0	0	0
Oriental	1 (2.3%)	0	1 (1.1%)
Other	1 (2.3%)	3 (6.7%)	4 (4.5%)
PC_{20} FEV_1 (mg/mL) (Geometric mean and CV)	0.76 (133.7%)	0.60 (148.1%)	0.67 (141.1%)

FEV_1 at end of run-in period >60% predicted

Table S1 Demography and key baseline characteristics (full analysis set)

	Budesonide HFA then CFC (N=44)	Budesonide CFC then HFA (N=45)	Total (N=89)
Yes	44 (100.0%)	45 (100.0%)	89 (100.0%)
FEV_1 (L) Mean (SD)	2.86 (0.74)	2.82 (0.63)	2.84 (0.68)

Note percentages are based on the number of patients in each treatment sequence.
CFC chlorofluorocarbon (a propellant); FEV_1 forced expiratory volume in 1 second; HFA hydrofluoroalkane (a propellant); PC_{20} FEV_1 provocative concentration of methacholine that causes a 20% drop in FEV_1. Data source: Table 11.1.4.1.

Summary of efficacy results

The RDP (ratio of the doses of HFA and CFC estimated to provide the same effect) for PC_{20} FEV_1 was estimated to 1.104 with an associated 95% CI of 0.489, 2.660.

For both formulations, statistically significant differences in PC_{20} FEV_1 were observed between the dose levels (high vs low CFC or HFA); however, no such differences were seen when comparing the two formulations at a given dose level (eg high dose HFA vs high dose CFC). At each of the dose levels the 95% confidence interval for the ratio of the PC_{20} FEV_1 for the two formulations were contained within 0.5 to 2, ie contained within ± one doubling dose dilution (see Table S2).

Table S2 PC_{20} FEV_1 (full analysis set)

Comparison	Ratio (coefficient of variation %)	95% Confidence interval	p-value
HFA (high vs low dose)	1.399 (277.5107)	1.152, 1.699	0.0008
CFC (high vs low dose)	1.244 (281.8687)	1.023, 1.512	0.0287
HFA vs CFC (low dose)	0.925 (300.6476)	0.757, 1.130	0.4436
HFA vs CFC (high dose)	1.040 (307.7110)	0.850, 1.274	0.7002

CFC chlorofluorocarbon (a propellant); HFA hydrofluoroalkane (a propellant).

Table S3 summarises the RDP (ratio of the doses of HFA and CFC estimated to provide the same effect) for the secondary variables

Table S3 Relative dose potency: Secondary variables (full analysis set)

Relative Dose Potency (HFA/CFC)	Estimate	95% CI[a]
eNO	0.779	0.374, 1.470
FVC	31.585	Could not be calculated

Table S3 Relative dose potency: Secondary variables (full analysis set)

Relative Dose Potency (HFA/CFC)	Estimate	95% CI[a]
FEV_1	3.206	Could not be calculated
$FEF_{25-75\%}$	5.460	Could not be calculated
PEF	0.000	Could not be calculated
Morning PEF (from Diary)	1.186	0.611, 2.523
Asthma symptom score Morning	0.949	0.413, 2.117
Asthma symptom score Evening	0.913	0.481, 1.681
Asthma symptom score Total	0.929	0.483, 1.740
Use of rescue medication Morning	1.202	0.489, 3.542
Use of rescue medication Evening	1.267	0.489, 4.376
Use of rescue medication Total	1.502	0.665, 4.961
Cortisol/creatinine ratio	0.804	0.320, 1.776
Cortisol	0.776	0.367, 1.485

CFC chlorofluorocarbon (a propellant); HFA hydrofluoroalkane (a propellant).

Summary of safety results

An overview of SAEs and DAEs are provided in Table S4. No deaths or SAEs were reported during the study. Three patients discontinued due to non-serious AEs.

Table S4 Overview of SAEs and DAEs (safety analysis set)

	Budesonide HFA			Budesonide CFC		
	100 µg BID (N=86)	400 µg BID (N=81)	Total (N=86)	100 µg BID (N=85)	400 µg BID (N=79)	Total (N=85)
Any SAE or DAE	0	1 (1.2%)	1 (1.2%)	2 (2.4%)	0	2 (2.4%)
Fatal SAEs	0	0	0	0	0	0
Non-fatal SAE	0	0	0	0	0	0
Treatment related SAE	0	0	0	0	0	0
DAE (serious or non-serious)	0	1 (1.2%)	1 (1.2%)	2 (2.4%)	0	2 (2.4%)
Any event with an outcome of death	0	0	0	0	0	0

BID twice daily; CFC chlorofluorocarbon (a propellant); DAE discontinuation due to adverse event (treatment and/or study participation); HFA hydrofluoroalkane (a propellant); SAE serious adverse event.