Sponsor

Novartis

Generic drug name

Fluticasone propionate

Trial indication(s)

Moderate-severe bronchial asthma

Protocol number

CQAE397A2202

Protocol title

A randomized open label study to assess the utility of measuring markers of inflammation, to detect transition from optimal to sub-optimal inhaled corticosteroid therapy in moderate-severe bronchial asthma

Clinical trial phase

Phase II

Study Start/End Dates

27 Jul 2006 to 20 Oct 2006

Study Design/Methodology

This was an open label, randomized study with 4 visits. Patients with moderate-severe asthma, well controlled on therapy with inhaled corticosteroid (ICS) of fluticasone propionate at least 500mcg (total daily dose), or equivalent of other licensed ICS were randomized into two cohorts. Cohort 1: the patients continued on previously prescribed medication. Cohort 2: the patients had their ICS therapy reduced to 250mcg fluticasone propionate once daily (QD). Inflammatory markers and lung function were measured in both cohorts at baseline, 2 weeks post baseline (Visit 3) and 4 weeks post baseline (study completion).

Centers

Germany (1).

Objectives:

Primary objective(s)

To assess the change in inflammatory parameters in response to a decrease in inhaled corticosteroid (ICS) compared to no change in therapy after 2 and 4 weeks.

Test Product (s), Dose(s), and Mode(s) of Administration

Patients received fluticasone propionate 250mcg dry powder through oral inhaler QD for 29 days.

Reference therapy, Dose and Mode of Administration

Patients usually prescribed inhaled steroid (asthma medication).

Statistical Methods

Descriptive summary statistics of the efficacy data are provided together with a summary of the change from baseline, and graphical summary over the course of the study. The data were subject to linear effects analysis of covariance with fixed effects for treatment group and a continuous baseline value.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Male and/or female moderate to severe asthmatic patients aged 18-75 years.
- Patients with no concomitant lung disease or significant medical conditions
- Patients who treated with 500mcg fluticasone propionate daily or greater, (or an equivalent dose of another medication (i.e. mometsaone 800 mcg, triamcinolone 2000 mcg, flunisolide 2000 mcg, budesonide DPI 800 mcg, beclomathasone HFA 500 mcg, beclomethasone CFC 1000 mcg)
- Patients who had forced expiratory volume in 1 second (FEV1) at screening ≥ 70% of the normal predicted
- Patients with evidence of asthma, demonstrated by one of the following: Historical evidence confirmed by their treating physician or demonstration of ≥ 12% reversibility of FEV1 using a standard dose of salbutamol (up to 400 µg) within 30 minutes
- Female patients of child bearing potential used two forms of contraception or postmenopausal women had no regular menstrual bleeding for at least 2 years prior to inclusion
- Patients with body mass index between 18 and 30 and less than 100 kg body weight

Exclusion criteria:

- Smokers were not eligible for participation
- Patients who used any other medications during the course of the study except for the short acting β_2 –agonists for symptom relief and long acting β_2 –agonists (LABAs) medication associated with study procedures
- Patients with a history of clinically significant drug allergy; any significant medical condition
- Any surgical or medical condition which might significantly alter the distribution, metabolism or excretion of the drug
- Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation.
- Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing or longer if required by local regulation.
- Significant illness within the two weeks prior to dosing.
- A past personal or close family medical history of clinically significant cardiac abnormalities
- Patients with a history of fainting, orthostatic hypotension, sinus arrhythmia, etc.
- A known hypersensitivity to fluticasone propionate or drugs similar to fluticasone propionate.
- Patients with history of immunocompromise, including a positive HIV test result.

- Patients with a history of drug or alcohol abuse within the 12 months prior to dosing

Other protocol-defined inclusion/exclusion criteria may apply

Patient Flow Table

Patients disposition	Total
Enrolled	24
Completed	24
Discontinued	0

Baseline Characteristics

Not available

Summary of Efficacy

Primary Outcome Result(s):

Descriptive analysis & change from baseline of exhaled nitric oxide (NO) average (ppb)

		Exhaled NO average (ppb)							Difference from baseline (ppb)						
Treatment	Time point	N	Mean	SD	Min	Q25	Median	Q75	Max	N	Mean	SD	Min	Q25	Median	Q75	Max
Continuation of medication as per run-in																	
	BAS (Day 1)	12	24.22	12.65	1.70	16.55	19.15	35.80	41.40								
	WEEK3 (Day 15)	12	21.62	12.10	1.00	13.35	19.00	33.50	41.50	12	-2.60	5.93	-15.1	-5.40	-2.05	0.10	8.00
	EOS (Day 29)	12	21.31	11.30	1.00	15.69	19.99	25.30	46.00	12	-2.91	9.60	-20.7	-9.25	-1.17	3.15	12.50
Reduction of fluticasone to 250 mcg QD																	
	BAS (Day 1)	12	26.27	20.31	9.30	11.00	18.05	40.05	75.30								
	WEEK3 (Day 15)	12	33.95	37.86	8.00	13.50	21.00	35.99	144.0	12	7.67	36.89	-21.3	-8.49	0.63	4.00	120.6
	EOS (Day 29)	12	32.31	22.12	10.30	13.29	24.34	50.00	72.00	12	6.04	16.65	-15.3	-0.22	0.95	13.74	48.60

Descriptive analysis & change from baseline of calculated methacholine (MCH) PC20 (mg/mL)

		Calculated MCH PC20 (mg/mL)							Difference from baseline (mg/mL)						
Treatment	Time point	N	Mean	SD	Min	Q25	Median	Q75	Max	N	Mean	SD	Min	Q25	Median	Q75	Max
Continuation of medication as per run-in																	
	BAS (Day 1)	12	1.92	4.39	0.09	0.26	0.78	0.99	15.80								
	WEEK3 (Day 15)	12	4.17	8.37	0.11	0.25	0.75	2.33	27.66	12	2.25	5.03	-0.78	-0.35	0.06	1.42	13.85
	EOS (Day 29)	12	3.02	4.74	0.16	0.40	0.79	4.09	16.00	12	1.10	2.14	-0.53	-0.00	0.22	1.44	6.46
Reduction of fluticasone to 250 mcg QD																	
	BAS (Day 1)	12	11.49	24.54	0.15	0.32	0.85	2.74	64.00								
	WEEK3 (Day 15)	12	7.80	18.90	0.11	0.34	0.72	1.09	64.00	12	-3.70	11.58	-40.3	-1.08	-0.14	-0.04	1.20
	EOS (Day 29)	12	8.11	19.46	0.09	0.20	0.36	0.87	64.00	12	-3.38	9.92	-34.7	-1.28	-0.12	-0.03	0.18

Descriptive analysis & change from baseline of sputum eosinophils (%)

		Sputum eosinophils (%)							Difference from baseline (%)						
Treatment	Time point	N	Mean	SD	Min	Q25	Median	Q75	Max	N	Mean	SD	Min	Q25	Median	Q75	Max
Continuation of medication as per run-in																	
	BAS (Day 1)	12	2.30	2.97	0.00	0.70	1.60	1.75	10.20								
	WEEK3 (Day 15)	12	2.22	2.56	0.20	0.80	1.20	3.05	9.60	12	-0.08	1.37	-3.10	-0.60	-0.40	0.80	2.10
	EOS (Day 29)	12	2.15	2.02	0.30	0.75	1.55	3.25	7.30	12	-0.15	1.73	-2.90	-1.35	-0.35	1.45	2.00
Reduction of fluticasone to 250 mcg QD																	
	BAS (Day 1)	12	3.99	5.71	0.00	0.55	1.80	5.65	20.30								
	WEEK3 (Day 15)	12	6.53	6.49	0.80	2.15	3.65	10.00	21.50	12	2.54	6.67	-10.5	-0.20	1.50	6.20	15.50
	EOS (Day 29)	12	10.79	13.88	0.80	1.80	8.85	11.80	51.40	12	6.80	14.25	-8.40	0.55	2.70	8.25	49.10

Descriptive analysis & change from baseline of sputum absolute eosinophils (10E9/L)

		Sputum absolute eosinophils (10E9/L)							Difference from baseline (10E9/L)						
Treatment	Time point	N	Mean	SD	Min	Q25	Median	Q75	Max	N	Mean	SD	Min	Q25	Median	Q75	Max
Continuation of medication as per run-in																	
	BAS (Day 1)	12	0.08	0.14	0.00	0.02	0.04	0.07	0.52								
	WEEK3 (Day 15)	12	0.07	0.08	0.01	0.02	0.06	0.09	0.31	12	-0.01	0.07	-0.21	-0.03	0.00	0.02	0.08
	EOS (Day 29)	12	0.11	0.17	0.00	0.02	0.06	0.09	0.61	12	0.03	0.06	-0.06	-0.02	0.03	0.06	0.14
Reduction of fluticasone to 250 mcg QD																	
	BAS (Day 1)	12	0.21	0.36	0.00	0.02	0.05	0.28	1.27								
	WEEK3 (Day 15)	12	0.19	0.16	0.02	0.04	0.17	0.30	0.53	12	-0.01	0.25	-0.74	-0.03	0.03	0.10	0.26
	EOS (Day 29)	12	0.36	0.46	0.02	0.06	0.27	0.49	1.66	12	0.16	0.56	-0.83	0.02	0.05	0.26	1.61

Descriptive analysis & change from baseline of blood eosinophils (%)

		Blood eosinophils (%)							Difference from baseline (%)						
Treatment	Time point	N	Mean	SD	Min	Q25	Median	Q75	Max	N	Mean	SD	Min	Q25	Median	Q75	Max
Continuation of medication as per run-in																	
	BAS (Day 1)	12	3.74	2.16	1.60	2.00	2.95	5.25	7.90								
	WEEK3 (Day 15)	12	3.54	2.04	1.80	1.90	3.05	3.95	8.30	12	-0.20	1.34	-4.00	-0.60	0.10	0.50	1.20
	EOS (Day 29)	12	2.83	1.55	0.90	1.65	2.45	4.00	6.00	12	-0.92	1.66	-5.40	-1.45	-0.50	0.05	0.80
Reduction of fluticasone to 250 mcg QD																	
	BAS (Day 1)	12	4.97	3.09	1.20	2.35	4.45	7.10	11.60								
	WEEK3 (Day 15)	12	6.07	3.95	1.00	2.80	6.75	8.15	15.00	12	1.10	3.30	-5.10	-0.60	0.85	3.40	6.90
	EOS (Day 29)	12	6.31	3.46	2.00	3.35	6.05	8.50	12.00	12	1.34	2.82	-3.50	-0.50	0.90	3.80	6.50

Descriptive analysis & change from baseline of blood absolute eosinophils (10E6/L)

		Blood absolute eosinophils (10E6/L)							Difference from baseline (10E6/L)						
Treatment	Time point	N	Mean	SD	Min	Q25	Median	Q75	Max	N	Mean	SD	Min	Q25	Median	Q75	Max
Continuation of medication as per run-in																	
	BAS (Day 1)	12	209.2	107.7	90.00	125.0	175.0	270.0	410.0								
	WEEK3 (Day 15)	12	204.2	104.2	100.0	130.0	185.0	245.0	470.0	12	-5.00	58.08	-140	-30.0	-10.0	40.00	80.00
	EOS (Day 29)	12	165.0	84.48	10.00	110.0	145.0	225.0	290.0	12	-44.2	83.72	-250	-80.0	-15.0	10.00	30.00
Reduction of fluticasone to 250 mcg QD																	
	BAS (Day 1)	12	318.5	192.9	50.00	175.0	260.0	485.0	630.0								
	WEEK3 (Day 15)	11	338.0	260.7	60.00	160.0	290.0	500.0	970.0	11	42.36	227.8	-290	-80.0	10.00	80.00	570.0
	EOS (Day 29)	12	364.3	217.7	120.0	195.0	340.0	445.0	870.0	12	45.75	192.3	-230	-50.0	59.50	95.00	470.0

Summary of Safety

Safety Results:

Summary of Adverse events

Body System	Preferred term	Continuation of medication as per run-in N = 12 n (%)	Reduction of fluticasone to 250 mcg QD N = 12 n (%)
General disorders and administration	Fatigue	0 (0.0)	1 (8.3)
Infections and infestations	Nasopharyngitis	1 (8.3)	0 (0.0)
	Urinary tract infection	1 (8.3)	0 (0.0)
Nervous system disorders	Headache	2 (16.7)	0 (0.0)
Reproductive system and breast disorders	Breast pain	1 (8.3)	0 (0.0)

Deaths, other serious and other significant adverse events

- No deaths reported during the study
- No serious adverse events reported during the study
- No clinically significant changes in vital signs or laboratory safety tests were observed in this study.

Other Relevant Findings

None

Date of Clinical Trial Report

20 Oct 2007