AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8848
Study Code	D0540C00004
Edition Number	1
Date	29 June 2011

A double-blind, placebo controlled, randomised, parallel group phase IIa study to investigate the efficacy, tolerability and safety of 8 doses of AZD8848 administered intranasally once weekly in mild to moderate allergic asthma patients challenged with an inhaled allergen

Study dates:	First patient enrolled: 21 October 2009 Last patient completed Visit 18: 8 March 2011
Phase of development:	Therapeutic exploratory (II)

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

Study centre(s)

The study was performed at 2 centres in the United Kingdom. The national coordinating investigator was Dr. Brian Leaker at the Heart Lung Centre, Respiratory Clinical Trials Ltd at Queen Anne Street Medical Centre in London, United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the efficacy of AZD8848 on the late asthmatic response (LAR) compared with placebo after 8 doses of once weekly intranasal administration in mild to moderate allergic asthma patients challenged with inhaled allergen (Main part only).	FEV_1 (late asthmatic response)	Efficacy
Secondary	**Secondary**	
To evaluate the efficacy of AZD8848 compared with placebo after 8 doses of once weekly intranasal administration in mild to moderate allergic asthma patients challenged with inhaled allergen as measured by the early asthmatic response (EAR), bronchial hyperreactivity and sputum biomarkers (Main part only).	FEV_1 (early asthmatic response) PC_{20} (methacholine challenge) Sputum cellularity and cytokines	Efficacy
To investigate tolerability and safety of AZD8848 after 8 doses of once weekly intranasal administration in allergic asthma patients (Pilot and Main part).	Vital signs, ECG, clinical chemistry, haematology, urinalysis, physical examination, clinical inspection of the nose, spirometry (FEV_1), auto-antibodies[a], adverse events (AEs)	Safety
To investigate plasma concentrations of the acid metabolite around C_{max} after the first and last dose of AZD8848 administered intranasally (concentrations represent the sum of AZD8848 and acid metabolite), Main part only.	Concentration of acid metabolite in plasma (representing the sum of the concentration of AZD8848 and acid metabolite)	Pharmaco kinetic
To investigate the influence of butyrylcholinesterase genotype on pharmacokinetic and pharmacodynamic responses (Main part only) [a]	Butyrylcholinesterase gene	Pharmaco genetic

a The results will be reported separately and are not included in the Clinical Study Report.

Study design

This was a double-blind, placebo-controlled, randomised, parallel group study of intranasal administration of AZD8848 in patients with mild to moderate allergic asthma.

The study started with a Pilot part in which patients with allergic asthma were randomised to receive 8 weekly doses of either 30 µg AZD8848 or placebo. The Pilot part focused on tolerability and safety (ie, no efficacy measurements). In the Main part of the study, the patients were randomised to receive 8 weekly doses of either 60 µg AZD8848 or placebo and allergen and methacholine challenges were then performed 1 and 4 weeks after last dose. In addition, sputum samples were collected for the assessment of biomarkers.

Target subject population and sample size

Male and female patients with allergic asthma (according to GINA guidelines) since >6 months, otherwise healthy, aged 18 to 55 years, with a prebronchodilator FEV_1 >70% of predicted normal value, an Early Asthmatic Response (EAR) corresponding to ≥20% FEV_1 decrease within 2 hours post-allergen challenge and a methacholine PC_{20} <16 mg/mL (ie, the provocative concentration of methacholine causing a 20% fall in FEV_1). Also they should be able to metabolize AZD8848.

The sample size for the Main part of the study, 20 evaluable patients per group, was selected based on previous similar studies from scientific literature, powered not to miss a 40% attenuation of the AUC based LAR with 80% power. The background data was on a linear scale and was based on a difference of 10% and a standard deviation of 12%. In the Pilot part, 9 patients (6 active and 3 placebo) were included.

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

Patients were randomized to the following treatments:

- Pilot part: AZD8848 nasal spray, 30 µg, one spray of 30 µg (50 µL) in the left nostril once weekly. Batch no 09-006098AZ
- Main part: AZD8848 nasal spray, 60 µg, one spray of 30 µg (50 µL) per nostril once weekly. Batch no 09-006098AZ
- Placebo nasal spray, one spray (50 µL) in the left nostril (Pilot part) or per nostril (Main part) once weekly. Batch no 09-006100AZ and 10-003166AZ

Duration of treatment

Each patient received 8 weekly doses of AZD8848 or placebo.

Statistical methods

The primary outcome variable for the allergen challenge test was area under the curve (AUC) based average mean fall from the pre-dose value of FEV1 during the 4–10 hour interval post allergen assessment (LAR). EAR was computed as the average fall over the time interval 0-2 hours after administration of allergen

The primary analysis consisted of a comparison of the active vs. placebo treatment groups with respect to change in response to allergen challenge 1 week after the treatment period. The statistical model used was analysis of variance (ANOVA) on the outcome variable with treatment as factor and pre-treatment LAR as covariate. The results were presented as a ratio of means, with confidence intervals obtained by using Fieller's method. The secondary outcome variable AUC based EAR was analysed in the same way as AUC based LAR. The biomarkers in sputum and metacoline PC_{20} were measured both prior to allergen challenge and post challenge, at visits before treatment, and 1 and 4 weeks after treatment period and analysed with ANOVA on log-transformed data with treatment, centre and baseline measurement as factors.

Subject population

A total of 162 patients were enrolled in the study at the 2 centres in the United Kingdom, and 60 of them were randomised to treatment ie, 9 in the Pilot part (6 on AZD8848 and 3 on placebo) and 51 in the Main part (26 on AZD8848 and 25 on placebo). All but 8 patients completed Visits 1 to 18, ie, 4 patients on AZD8848 and 2 on placebo discontinued due to AEs, and 2 on placebo discontinued due to personal reasons. All patients were male in the pilot part and had allergic asthma since >1 year. In the Main part, all patients had allergic asthma since >1 year (median 20 years) as well; 37 were male, 14 were female and their mean age was 32 years. The mean BMI was 25 kg/m^2 and the mean FEV_1 in percent of predicted normal was 89 (Main part). The AZD8848 and placebo groups were well balanced in demographic and baseline disease characteristics.

No patient was excluded from the full analysis set, which thus consisted of 60 patients. For the primary efficacy variable (LAR), 45 of the 51 patients that were allocated treatment had data. The efficacy analysis was therefore based on these 45 patients.

Summary of efficacy results

At one week after last dose, AZD8848 attenuated the LAR as the average drop in FEV_1 was reduced by 27% compared with placebo. This effect on LAR was supported by an 18% reduction of the LAR maximum fall in FEV_1 compared with placebo. AZD8848 also appeared to attenuate the EAR (18% reduction compared with placebo), but this effect did not reach statistical significance. The effect of AZD8848 on LAR observed at 1 week after last dose was not maintained 4 weeks after last dose.

The treatment comparison of the PC_{20} values determined during the methacoline challenge showed a significant effect after the allergen challenge at 1 week post dose, but not before the

allergen challenge. The effect of AZD8848 on the bronchial hyperreactivity observed at 1 week after last dose was not maintained 4 weeks after last dose.

Table S2 Statistical description of efficacy variables

				Descriptive statistics				Comparison to placebo		
Variable	**Visit**	**Treatment**	**n**	**Mean**	**SD[a]**	**Min**	**Max**	**Ratio**	**95% CI**	**P-value**
Average LAR	2	AZD8848	22	0.814	0.450	-0.093	1.95			
	2	Placebo	23	1.01	0.784	-0.063	2.92			
	13	AZD8848	22	0.616	0.296	0.194	1.23	0.730	(0.527, 0.977)	0.035
	13	Placebo	23	0.970	0.641	0.201	2.54			
Max fall in FEV_1, LAR	2	AZD8848	22	1.25	0.537	0.350	2.63			
	2	Placebo	23	1.45	0.802	0.470	3.18			
	13	AZD8848	22	1.01	0.396	0.440	1.91	0.818	(0.647, 1.02)	0.076
	13	Placebo	23	1.37	0.741	0.330	3.16			
Average EAR	2	AZD8848	22	0.524	0.241	0.067	0.908			
	2	Placebo	23	0.611	0.362	-0.217	1.42			
	13	AZD8848	22	0.468	0.361	-0.108	1.41	0.822	(0.555, 1.18)	0.280
	13	Placebo	23	0.624	0.362	0.025	1.57			
PC_{20}[a] (mg/mL)	1	AZD8848	22	0.564	365	0.004	11.1			
	1	Placebo	23	0.609	252	0.063	5.69			
	3	AZD8848	22	0.425	136	0.123	6.25	1.17	(0.616, 2.22)	0.624
	3	Placebo	23	0.364	189	0.063	10.2			
	12	AZD8848	22	0.488	171	0.063	3.01	1.10	(0.563, 2.15)	0.774
	12	Placebo	21	0.454	177	0.063	8.25			
	14	AZD8848	21	0.691	177	0.063	9.13	2.20	(1.12, 4.33)	0.024
	14	Placebo	21	0.340	186	0.063	17.8			

a Standard deviation (SD) is reported for all parameters but PC_{20} for which the coefficient of variation is shown.
Visit 1 Methacholine challenge at screening, pre allergen challenge
Visit 2 Allergen challenge at screening
Visit 3 Methacholine challenge at screening, post allergen challenge
Visit 12 Methacholine challenge 1 week after end of treatment, pre allergen challenge
Visit 13 1 week after end of treatment
Visit 12 Methacholine challenge 1 week after end of treatment, post allergen challenge
CI confidence interval

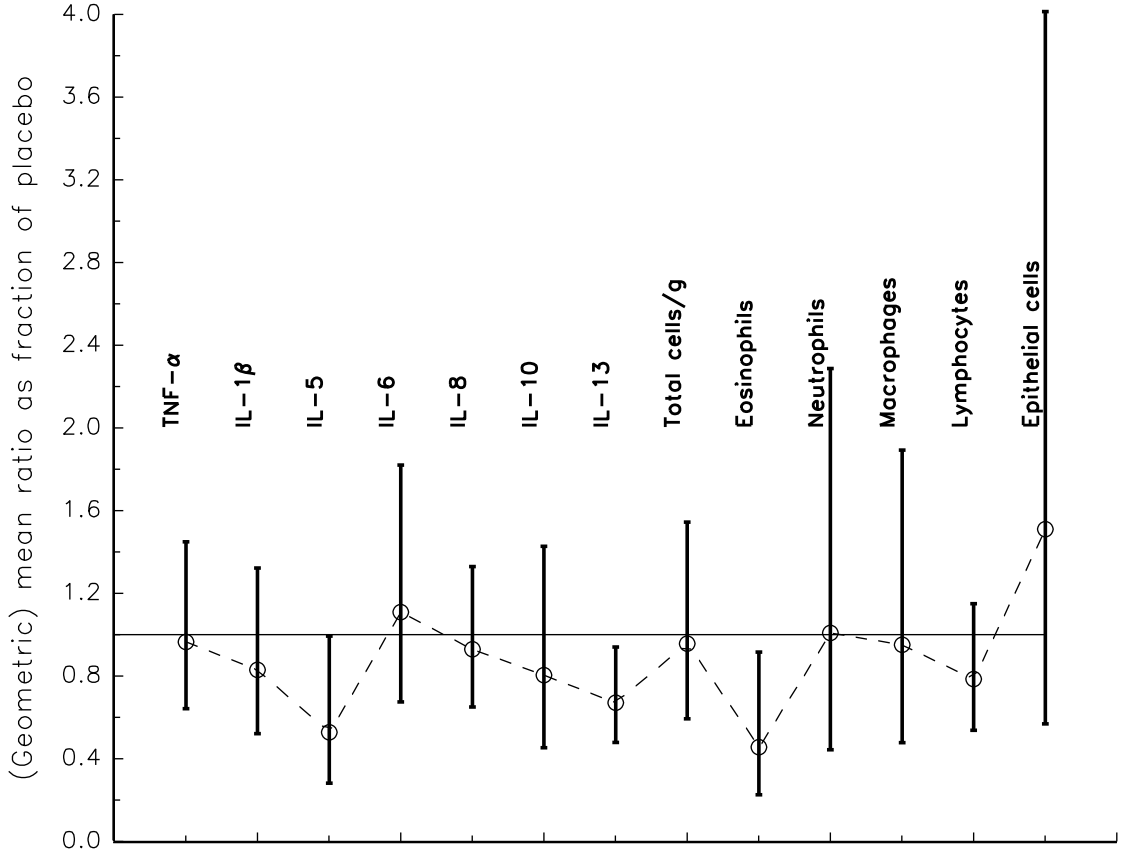
Summary of pharmacokinetic results

The plasma concentrations of the acid metabolite of AZD8848 ranged from <LOQ to approximately 1.2 nmol/L after the first dose and from <LOQ to approximately 1.3 nmol/L after the last dose of AZD8848.

Summary of pharmacodynamic results

While there were no changes observed in most of the cytokines measured, a trend towards a reduction in the Th2 biomarkers IL 5, IL-13 and in eosinophils was observed before the allergen challenge performed 1 week after treatment, which was close to significant on the 5% level for IL-13 and eosinophils (p=0.054 and p=0.068, respectively). No effect was observed after the allergen challenge. At 4 weeks after end of treatment, a trend towards a reduction in IL-13 was observed before the allergen challenge (p=0.070), whereas no effects were seen on IL-5 or eosinophils.

Figure S1 **Treatment effect on sputum biomarkers at Visit 12. Point estimate and 90% confidence limits are shown.**



Summary of safety results

Administration of AZD8848 was coupled to the appearance of mild to moderate influenza-like symptoms of a transient (12 to 48 hours post dose) and non-serious nature. These symptoms were more prevalent after administration of AZD8848 (58%) compared with placebo (24%).

Asthma-related events (asthma, exacerbation of asthma, wheezing, cough, chest discomfort, dyspnoea) reported from day 1 to 52 after first intake of investigational product were more frequent in the placebo group (32%) compared with AZD8848 (8%), whereas nasal symptoms (including epistaxis, rhinnorea, nasal congestion/obstruction, sneezing, nasal dryness, scab,

rhinalgia, nasal discomfort and nasal ulcer) reported from day 1 to 52 after first intake of investigational product were equally distributed between treatments.

No clinically relevant changes were seen in laboratory values, vital signs and ECG. There was no deterioration in FEV_1 related to treatment with AZD8848 during the treatment period. Three patients in the Pilot part, 2 on AZD8848 and 1 on placebo, had abnormal, new or aggregated findings at the nasal examination at follow-up. There were no findings upon the nasal examination performed in the Main part of the study.