AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8848
Study Code	D0540C00014
Edition Number	1
Date	22 June 2011

A double-blind, placebo controlled, randomised, parallel group phase IIa study to investigate the efficacy, tolerability, and safety of different dosing regimens of AZD8848 administered intranasally to seasonal allergic rhinitis patients out of pollen season in a nasal allergen challenge model

Study dates: First patient enrolled: 1 September 2010
Last patient completed Visit 16: 20 December 2010

Phase of development: Therapeutic exploratory (II)

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

Study centres

The study was conducted at 2 centres in Sweden. The national coordinating investigator was Lennart Greiff, Associate Professor, at the department of otorhinolaryngology, Skåne University Hospital, Lund, Sweden.

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 compare the efficacy of 60 µg AZD8848 once weekly with 20 µg 3 times weekly and with placebo when administered intranasally to seasonal allergic rhinitis patients out of season in a nasal allergen challenge model.	Reflective Total Nasal Symptom Score (TNSS) (recall period 12 h, twice daily during Visit 15) Reflective TNSS (recall period 10 min) after allergen challenge Peak Nasal Inspiratory Flow (PNIF) (twice daily during Visit 15) PNIF 10 min after allergen challenge	Efficacy
Secondary	**Secondary**	
To investigate the tolerability and safety of AZD8848 administered intranasally up to 3 times weekly for 1 month to seasonal allergic rhinitis patients out of season.	Incidence and nature of adverse events Instantaneous TNSS and PNIF during treatment Electrocardiogram parameters, blood pressure, pulse, physical examination, clinical chemistry, haematology, urinalysis, clinical inspection of the nose, auto-antibodies1	Safety
To investigate the pharmacodynamic effects of AZD8848 on systemic and local biomarkers.	CXCL-10 (IP-10) in nasal lavage and blood Myeloperoxidase, α2-macroglobulin, tryptase and eosinophilic cationic protein (ECP) in nasal lavage Soluble immune/inflammatory proteins in nasal lavage and blood[a], e.g. IFN-γ, Tumour Necrosis Factor (TNF), IL-10 mRNA expression in nasal lavage and blood[a], e.g. genes related to IFN-α, T-helper cell phenotypes and inflammatory functions	Pharmaco dynamic
To investigate the influence of butyrylcholinesterase genotype on pharmacodynamic responses where appropriate.	Butyrylcholinesterase genotypes[a]	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 phase IIa study performed out of pollen season in female and male patients with allergic rhinitis. The patients were randomised to one out of 3 treatment arms in a 1:3:1 ratio (60 µg once weekly: 20 µg 3 times weekly: placebo).

Target subject population and sample size

Male and female seasonal allergic rhinitis patients, otherwise healthy, aged 18 to 55 years, with a history of birch and/or timothy grass pollen allergy verified by a positive skin prick test, in need of treatment for their nasal symptoms during pollen season, and having a reaction to nasal allergen challenge with at lest 5 sneezes and/or recorded score of 2 or more on a scale from 1 to 3 on nasal blockage or runny nose. Also they should be able to metabolize AZD8848.

A planned total of 70 completed patients in proportions 1:3:1 for the treatments arms 60 µg AZD8848 once weekly, 20 µg 3 times weekly and placebo yields 14, 42 and 14 patients in the respective treatment arm. The efficacy data were pooled with the corresponding data from another study (Tol/PoP, D0540C00003), which included treatment arms with placebo (n=34) and 60 µg AZD8848 once weekly (n=34). Using a one-sided test at 5% significant level with a sample size of 42 patients in the 20 µg 3 times weekly arm and 14+34=48 patients in the 60 µg AZD8848 once weekly arm, with another 14+34=48 placebo patients contributing to the estimate of the standard deviation, then gave a 76% chance to detect a difference of 1 unit between the 2 AZD8848 arms.

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

Patients were randomized to the following treatments:

- AZD8848 nasal spray, 20 µg, one spray of 10 µg (50 µL) per nostril 3 times weekly. Batch no 10-003168AZ
- AZD8848 nasal spray, 60 µg, one spray of 30 µg (50 µL) per nostril once weekly. Batch no 10-001087AZ
- Placebo nasal spray, one spray (50 µL) per nostril 3 times weekly. Batch no 09-006100AZ, 10-003166AZ, 09-006100AZ.

Duration of treatment

Each patient received AZD8848 and/or placebo administered 3 times weekly during 1 month (13 doses), ie, 60 µg AZD8848 once weekly + placebo twice weekly, 20 µg AZD8848 3 times weekly or placebo 3 times weekly.

Statistical methods

For nasal symptoms, TNSS and PNIF an additive analysis of variance model (ANOVA) was used on pooled data for comparisons between treatments with study, treatment and centre as factors and the baseline value (Visit 2 pre-dose) as covariate for clinic PNIF measurements. A multiplicative model was used for biomarkers by log transformation on the response variable and the covariate, with treatment and centre as factors and the baseline value as covariate and the baseline value as covariate. The pairwise treatment differences between AZD8848 (once weekly and 3 times weekly, respectively) and placebo were estimated from respective model and confidence intervals and p-values were calculated.

Safety data was mainly analysed in terms of descriptive statistics and graphically illustrated over time. With the exception of AE data, the change from baseline to end of treatment was analysed statistically including summary statistics with confidence limits and p-values. Adverse events were analysed in terms of descriptive statistics.

Subject population

A total of 93 patients were enrolled in the study at the 2 centres in Sweden, and 83 of them were randomised to treatment: 17 patients received AZD8848 60 µg once weekly, 50 received 20 µg 3 times weekly and 16 received placebo. All but 3 completed Visits 1 to 16, ie, 1 patient in each treatment group discontinued. All patients had allergic rhinitis since >2 years (median 16 years), 73 were male, 10 were female and their mean age was 30 years. The mean body mass index was 24 kg/m^2. 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 83 patients. Two patients discontinued the study before the efficacy measurements started and the efficacy analysis set consists of 81 patients from this study, ie, 16 patients for AZD8848 60 µg once weekly, 50 for AZD8848 20 µg 3 times weekly and 15 for placebo. The efficacy data were pooled with the corresponding data in the previous Tol/PoP study (D0540C00003), and the pooled efficacy analysis set consisted of 16+32=48 patients for AZD8848 60 µg once weekly, 50 for AZD8848 20 µg 3 times weekly and 15+34=49 for placebo, ie, 147 patients in total.

Summary of efficacy results

The study showed a prophylactic effect on mean TNSS at 10 minutes after challenge of 60 µg once weekly compared to placebo measured over the whole allergen challenge period and for both AZD8848 groups at days 4 to 7 (1-sided tests). The individual scores mainly contributing to this effect were itchy nose and sneezing, which were decreased for both active groups compared with placebo. The TNSS recorded at home was also improved in the mornings during the whole allergen challenge period after administration of 60 µg compared to placebo,

but this improvement was however not observed in the evening recordings. No effect on PNIF could be demonstrated.

Table S2 Treatment comparisons of period means for reflective nasal symptoms and PNIF during allergen challenge, pooled data

Period	Comparison	Mean diff.	95% CI	p-value[a]
TNSS Day 1-7	AZD8848 60 µg vs Placebo	-0.449	(-0.985, 0.0872)	0.100
	AZD8848 20 µg x3 vs Placebo	-0.532	(-1.20, 0.132)	0.115
	AZD8848 20 µg x3 vs AZD8848 60 µg	-0.0830	(-0.740, 0.574)	0.803
TNSS Day 4-7	AZD8848 60 µg vs Placebo	-0.805	(-1.42, -0.194)	0.0102
	AZD8848 20 µg x3 vs Placebo	-0.838	(-1.60, -0.0790)	0.0307
	AZD8848 20 µg x3 vs AZD8848 60 µg	-0.0329	(-0.784, 0.718)	0.931
TNSS Morning	AZD8848 60 µg vs Placebo	-0.345	(-0.754, 0.0634)	0.0970
	AZD8848 20 µg x3 vs Placebo	-0.171	(-0.682, 0.340)	0.508
	AZD8848 20 µg x3 vs AZD8848 60 µg	0.174	(-0.326, 0.674)	0.492

a 2-sided
CI Confidence interval

Summary of pharmacodynamic results

The levels of CXCL-10 increased substantially both locally (in saline nasal lavage) and systemically (in plasma) over the treatment period and then reverted back to baseline levels during the 7-day challenge period. Higher levels of CXCL-10 were detected locally than systemically. The increases were significant both locally and systemically after administration of AZD8848 compared with placebo. Moreover, administration of 60 µg once resulted in a 35% greater increase in systemic levels of CXCL-10 compared with administration of AZD8848 20 µg 3 times weekly, whereas local increases were similar for both groups.

Table S3 Treatment comparisons for CXCL-10 (pg/mL) in plasma and saline nasal lavage during treatment

Medium	Comparison	Mean ratio	95% CI	p-value[a]
Plasma	AZD8848 60 µg vs Placebo	4.86	(3.26, 7.24)	<0.000
	AZD8848 20 µg x3 vs Placebo	3.59	(2.58, 5.00)	<0.000
	AZD8848 20 µg x3 vs AZD8848 60 µg	0.740	(0.537, 1.02)	0.0661

Table S3 Treatment comparisons for CXCL-10 (pg/mL) in plasma and saline nasal lavage during treatment

Medium	Comparison	Mean ratio	95% CI	p-value[a]
Nasal lavage	AZD8848 60 µg vs Placebo	16.2	(7.29, 35.9)	<0.000
	AZD8848 20 µg x3 vs Placebo	18.0	(9.26, 35.1)	<0.000
	AZD8848 20 µg x3 vs AZD8848 60 µg	1.11	(0.593, 2.10)	0.734

a 2-sided

A decrease of about 50-60% in α2-macroglobulin levels was also shown during the challenge period after administration of AZD8848 compared with placebo when using histamine in the nasal lavage. No differences were observed between the 2 AZD8848 treatment groups, or for any of the other biomarkers in histamine nasal lavage.

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 20 µg 3 times weekly compared with 60 µg once weekly. AZD8848 20 µg 3 times weekly was also associated with an increased frequency of nasal AEs and an increase in instantaneous TNSS during treatment compared with baseline.

A transient reduction in blood lymphocytes was seen, but values normalized between dosing. No clinically relevant changes were seen on vital signs and ECG. There was no deterioration in TNSS or PNIF, and no evidence of nasal ulcers, related to treatment with AZD8848.

A numerical increase in blocked nose, itchy nose and TNSS as well as a numerical decrease was observed in the AZD8848 20 µg 3 times weekly group compared with the 2 other groups. These changes were small and of minor clinical relevance. One patient in the AZD8848 20 µg 3 times weekly group had a small synechia between the inferior nasal concha and the nasal septum on the left side upon the nasal examination at the follow-up visit.