AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8848
Study Code	D0540C00003
Edition Number	1
Date	25 January 2010

A double-blind, placebo controlled, randomized, parallel group study to investigate the tolerability, safety, pharmacodynamics and pharmacokinetics of repeated weekly doses of AZD8848 administered intranasally to seasonal allergic rhinitis patients

Study Dates	First patient enrolled: 29 September 2008 Last patient completed visit 8: 31 March, 2009
Phase of development	Clinical pharmacology (I)

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

Study Centres

Three centres in Sweden enrolled patients into this study, at the Clinical Pharmacology Unit, AstraZeneca R&D Lund, Sweden and at the hospitals in Helsingborg and Lund, Sweden.

Publications

None at the time of finalising this report.

Objectives and criteria for evaluation

Table 1 Study objectives and variables

Objective		Outcome variables
Primary	To investigate the tolerability and safety of five weekly doses of AZD8848 administered intranasally to seasonal allergic rhinitis patients out of season	-Incidence and nature of adverse events -Instantaneous total nasal symptoms score (TNSS) and peak nasal inspiratory flow (PNIF) during treatment -In part A: pulse, blood pressure, body temperature, clinical chemistry, haematology, urinalysis, ECG parameters, telemetry. -In part B: clinical chemistry, haematology
Secondary	To demonstrate effect of AZD8848 on nasal symptoms in an allergen challenge model. Systemic and local biomarkers were evaluated regarding effect	-Reflective TNSS (-10 min) (-12 h) and PNIF during allergen challenge -Neopterin in nasal lavage -IL-1Ra in plasma -Diary card data on nasal symptoms during subsequent natural pollen season
	To investigate the pharmacokinetics after weekly doses of AZD8848	Plasma concentration of the sum of AZD8848 and its acid metabolite
	To investigate the influence of butyrylcholinesterase genotype on pharmacokinetics (and pharmacodynamic response where appropriate)	Analysis of the butyrylcholinesterase gene[a]

(Continued)

Table 1 Study objectives and variables

	Objective	Outcome variables
	To evaluate exploratory biomarkers in blood, plasma and nasal lavage	-Part A only; Cellularity in nasal lavage -Part A only; mRNA in nasal lavage[a] -Part A only; lymphocytes in blood -Part A only; Lymphocyte cell surface markers in blood -Immune/inflammatory factors in nasal lavage/plasma[a] -Myeloperoxidase, α_2-macroglobulin, tryptase, ECP in nasal lavage -mRNA in blood[a] -Anti-infective antibody levels in blood[a]
Pharma-coge-netic	To collect optional blood samples for possible future pooled analysis	DNA from blood[a]

a Not reported in this CSR

Study design

This was a double-blind, placebo-controlled, randomized, parallel group study in seasonal allergic rhinitis male patients out of season. The study was conducted in 2 parts; part A and part B. In both parts, AZD8848 or placebo were given as 5 weekly doses during 1 month, thereafter a 7-day allergen challenge period was performed. **Part A:** AZD8848, 30 and 60 µg respectively, were tested in 2 parallel groups. The lower dose group started. **Part B:** After completion of part A, the AZD8848 60 µg dose level was tested in part B.

Patients attended a formal screening visit (visit 1) where their eligibility to take part in the study was checked and where an allergen challenge dose of birch or grass pollen was individually titrated until predetermined symptom levels were reached. This dose was then used in the allergen challenge period. Eligible patients were randomized at visit 2 and then dosed 5 times (every week at the clinic up to visit 6). At visit 7, approximately 24 hours after the last dose, patients started a 7-day daily allergen challenge period. Patients were followed up at 11 to 16 days after last study drug administration (visit 8). Long term safety follow up 5 to 7 months (visit 9) and 11-13 months (visit 10) after last study drug administration were still ongoing at the preparation of this report (data from these visits will be reported in an addendum to this report).

During the study patients were not allowed to go on immunotherapy, use topical or systemic glucocorticosteroids or any other medication, including herbal medicines and nutritial

supplements. Occasional use of paracetamol was however allowed. Also single doses of antihistamines during allergen challenge was allowed.

Target patient population and sample size

Male seasonal allergic rhinitis patients, otherwise healthy, aged 18 to 45 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 nasal blockage or runny nose. Also they should be able to metabolize AZD8848.

A sample size of 30 patients in each group was determined to have an 80% chance to detect a difference of 1 unit in TNSS between AZD8848 and placebo assuming a standard deviation of 1.5 unit in TNSS (both morning and evening) using a one-sided test at a 5% significance level.

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

Patients were randomized to the following treatments:

- Part A, AZD8848 nasal spray, 30 μg, one spray of 15 μg (50 μL) per nostril once weekly. Batch nr 08-001184AZ
- Part A and B, AZD8848 nasal spray, 60 μg, one spray of 30 μg (50 μL) per nostril once weekly. Batch nr 08-001168AZ
- Part A and B, Placebo nasal spray, one spray (50 μL) per nostril once weekly. Batch nr 08-001169AZ.

Duration of treatment

In total, 5 doses once weekly were given during 1 month.

Statistical methods

P-values in tables refer to 2-sided hypothesis testing (divide by 2 to get 1-sided p-values).

Clinical data and diary card data

For plotting of variables collected in the diary daily mean values were calculated with imputation for missing data.

Nasal symptoms, TNSS, PNIF and biomarkers

For nasal symptoms, TNSS and PNIF an additive analysis of variance model (ANOVA) was used for comparisons between treatments with treatment and centre as factors. 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 (visit 2 pre dose) value as covariate (no covariate in analysis during challenge). If there was a value prefixed with "<" in this analysis it was estimated to half the value. Treatment differences were estimated from respective model and confidence intervals and p-values were calculated.

Safety data

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. AEs were analysed in terms of descriptive statistics.

Pharmacokinetics

Plasma concentrations of the AZD8848 acid metabolite are presented using descriptive statistics.

Subject population

A total of 103 patients were enrolled in the study at 3 centres. In part A totally 26 male seasonal allergic rhinitis patients were enrolled, 18 of them were randomized and all of them completed visits 1 to 8. Of the first 9 patients randomized to the lower dose level, 6 received AZD8848 30 µg and 3 placebo and of the next 9 patients, 6 received AZD8848 60 µg and 3 placebo. Part B of the study started with 77 patients enrolled. 56 patients were randomized, 28 patients received AZD8848 60 µg and 28 received placebo. All patients were male, all but 1 were white, the mean age was 27 years and the median time of seasonal allergic rhinitis diagnosis was 16 years. The mean BMI was 24 kg/m^2. Two patients from the AZD8848 group discontinued the study. The AZD8848 and placebo groups were well balanced in demographic and baseline disease characteristics.

Since AZD8848 60 µg and placebo were used both in part A and part B in total 68 patients were randomized to AZD8848 60 µg and placebo from both parts (34 to AZD8848 60 µg and 34 to placebo). The body of this report is mainly based on these 68 patients and this gave enough power in the efficacy analysis.

Summary of efficacy results

The study showed a prophylactic effect of AZD8848 on mean TNSS during allergen challenge measured at days 4 to 7 at 10 minutes after challenge (1-sided tests). The improvement in symptom scores was 0.74 compared to placebo. There were also effects

demonstrated for individual symptom scores itchy nose, sneezing and blocked nose (1-sided test) compared to placebo (Table 2). No effects could be demonstrated for TNSS in the evenings and mornings after allergen challenge. Also, no effects for PNIF could be demonstrated.

Table 2 **Treatment comparisons (AZD8848 60 µg vs. placebo) of period means (days 4 to 7) for reflective (at 10 min) clinic TNSS and PNIF post allergen challenge**

Variable	Mean diff.	95% CI[a]	P-value
Total nasal symptom score (TNSS)	-0.74	(-1.5, 0.063)	0.070
Blocked nose	-0.23	(-0.51, 0.045)	0.098
Runny nose	-0.10	(-0.47, 0.26)	0.57
Itchy nose	-0.49	(-0.90, -0.075)	0.021
Sneezing	-0.43	(-0.84, -0.016)	0.042
PNIF (L/min)	-4.8	(-23, 14)	0.61

a CI Confidence interval

The proof of mechanism marker (PoM) IL-1Ra mean levels in plasma (systemic reaction) increased during treatment in the AZD8848 group compared to placebo. A 5.5-fold elevation compared to placebo (p-value <0.001) was seen 24 hours after the last dose (visit 7, before allergen challenge), and levels were back to baseline within 1 week (day 8 of the allergen challenge period). There were no effects demonstrated for neopterin in nasal lavage (local reaction).

Summary of pharmacokinetic results

Pharmacokinetics was only performed in part A so this section is therefore based on all patients from part A. Due to the extensive and rapid metabolism of AZD8848 in human plasma to its acid metabolite also after a blood samples was drawn, it was not possible to measure AZD8848 at the time of sampling. Instead the levels AZD8848 acid metabolite was measured, representing the sum of AZD8848 and its acid metabolite. The plasma concentration of AZD8848 acid metabolite decreased with time, and after 4 hours concentrations were below LOQ for all patients in AZD8848 30 µg treatment group and very low or below LOQ in the AZD8848 60 µg. There was a time independent pharmacokinetics for the current dosing regimen. All patients exposed to AZD8848 had concentrations above LOQ but the variability between the patients were very high.

Summary of safety results

In the AZD8848 60 μg group, influenza like illness, epistaxis, pyrexia and headache were more frequent than in the placebo group. These influenza like symptoms were typically reported within 24 hours after dosing and generally resolved within 48 hours after dosing. The influenza like symptoms generally subsided when treated with paracetamol.

There was no deterioration in TNSS or PNIF, and no evidence of nasal ulcers, related to treatment with AZD8848. A transient reduction in blood lymphocytes was seen, but values normalized between dosing. The effect on lymphocytes was not driven by any of the different subtypes of lymphocytes, as shown by flow cytometry analysis. The biological response was similar between the first and the fifth dose (with respect to AEs and effects on lymphocytes) indicating that sensitivity to the drug neither increases nor decreases with repeated dosing. No clinically relevant ECG changes were seen and all absolute QTcF shifts were less than 30 milliseconds.

Date of the report

25 January 2010