Clinical Study Report Synopsis

Drug Substance	AZD8848
Study Code	D0540C00001
Edition Number	1
Date	29 October 2008

A Double Blind, Placebo Controlled, Randomised, First Time In Man Study to Investigate the Tolerability, Safety, Pharmacokinetics and Pharmacodynamics of Single Ascending Doses of AZD8848 Administered Intranasally to Healthy Male Volunteers and Seasonal Allergic Rhinitis Male Patients Out of Season

Study Dates	First healthy volunteer/patient enrolled: 14 January 2008 Last healthy volunteer/patient completed: Visit 3, 22 May 2008
Phase of development	Clinical pharmacology (I)

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

Study centre

This study was conducted at the Phase One Unit, Lund University Hospital, SE-221 85 Lund, Sweden. Selected study activities were performed at the Clinical Pharmacology Unit, AstraZeneca R&D Lund, SE-221 87 Lund, Sweden and Department of Otorhinolaryngology, Lund University Hospital SE-221 85 Lund, Sweden.

Publications

None at the time of writing this report.

Objectives

The primary objectives were:

Part A: to investigate the tolerability and safety of single ascending doses of AZD8848 administered intranasally to healthy subjects

Part B: to investigate the tolerability and safety of single doses of AZD8848 administered intranasally to seasonal allergic rhinitis patients out of season

Part C: to investigate the tolerability and safety of single doses of AZD8848 administered intranasally to allergen-challenged seasonal allergic rhinitis patients out of season and to examine tolerability to allergen post drug administration.

The primary variables of Part A, B, and C were assessment of:

- Incidence and nature of adverse events
- Clinically significant abnormalities in pulse, blood pressure, body temperature, spirometry, clinical chemistry, haematology, urinalysis, and ECG parameters
- Nasal symptoms and peak nasal inspiratory flow

The secondary objectives were:

To investigate the pharmacokinetics after single ascending doses of AZD8848 by determination of plasma concentration of the sum of AZD8848 and acid metabolite (AZ12432045), and if possible AZD8848 alone

To investigate the pharmacodynamic effect of AZD8848 by assessments of biomarkers in blood and nasal lavage fluid

To investigate the influence of butyrylcholinesterase genotype on pharmacokinetics (and pharmacodynamic response where appropriate).

Study design

This was a double blind, placebo controlled, randomised, first time in man study to investigate the tolerability, safety, pharmacokinetics and pharmacodynamics of single ascending doses of AZD8848 administered intranasally to healthy male volunteers (Part A) and seasonal allergic rhinitis male patients out of season without or with allergen challenge (Part B and Part C, respectively). The 3 study parts all consisted of 4 visits and a telephone contact, and the assessments performed at the visits were similar in the 3 parts. The study was designed with a long-term follow-up for possible retrospective analysis of autoantibodies. However, the long-term follow-up was not completed at the finalisation of this Clinical Study Report and will be reported separately.

Target healthy volunteer/patient population and sample size

The study was conducted in a total of 89 subjects divided in 3 parts (A, B and C). Part A consisted of 9 dose levels administered in healthy volunteers. Part B of 2 dose levels administered in allergic rhinitis patients out of season. Part C of 2 dose levels administered in allergen challenged seasonal allergic rhinitis patients out of season.

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

Single doses of AZD8848 or placebo were administrated as a nasal spray solution (50 µL in each nostril). The nasal spray solution was delivered as a bulk solution. The concentrated solution (60 mg/g, batch no. DIL411/07-012564AZ) was diluted with 0.9% sodium chloride for parenteral use, to achieve the concentration needed for each dose levels. In Part A the doses were 0.3, 1, 3, 10, 30, 100, 300, 600, and 170 µg. In Part B, 30 and 100 µg and in Part C, 30 and 60 µg. Sodium chloride solution (9 mg/mL, batch no. 07IV26) was use as placebo.

Duration of treatment

Part A: single doses in healthy volunteers, 9 dose levels.

Part B: single doses in seasonal allergic rhinitis patients out of season, 2 dose levels.

Part C: single doses in allergen challenged seasonal allergic rhinitis patients out of season, 2 dose levels.

Criteria for evaluation - safety and tolerability (main variables)

Adverse events, laboratory parameters (haematology, clinical chemistry and urinalysis), vital signs (blood pressure, pulse, body temperature), ECG, other safety measurements (spirometry, total nasal symptom score, peak nasal inspiratory flow).

Criteria for evaluation - pharmacokinetics (main variables)

AZD8848 (representing the sum of AZD8848 and acid metabolite) plasma concentrations and calculated pharmacokinetic (PK) parameters: AUC, C_{max}, t_{max}, $t_{½}$, CL/F, MRT, Vz/F.

Criteria for evaluation - pharmacodynamic (main variables)

The proof of mechanism biomarkers Neopterin and Interleukin-1 receptor antagonist (IL-1Ra) in plasma and nasal lavage. Exploratory biomarkers in plasma and nasal lavage (not reported in this Clinical Study Report).

Criteria for evaluation - Genetics

Pharmacogenetic samples (blood) for possible future pooled analysis. The butyrylcholinesterase gene will be analysed and reported separately.

Statistical methods

Safety and tolerability aspects of the study was mainly evaluated using descriptive statistics. The evaluation of pharmacodynamic data was focused on signals of response versus placebo and on dose-response patterns of the drug. Comparisons between active drug and placebo, were made using analysis of variance models.

Subject population

All of the 89 subjects allocated to treatment were males. Their average age was 25.0 years (range: 19-44) and all were white. Rhinitis patients in Part B and C had on average a rhinitis history for about 14 years.

Tables S1 to S3 contain treatment group comparisons of demographic and baseline characteristic data in terms of descriptive statistics.

Table S1 **Treatment group comparison of demographic data in Part A. For categorical data, frequencies are given, for other data mean values and ranges are presented**

	0.3 n=4	1 n=4	3 n=4	10 n=4	30 n=4	100 n=4	300 n=4	600 n=4	170 n=4	Pla-cebo n=18	All n=54
Sex											
Male	4	4	4	4	4	4	4	4	4	18	**54**
Age (yrs)	27.8 21-43	31.5 26-44	22.8 19-27	21.5 19-23	25.5 21-34	27.0 24-34	24.8 23-26	26.5 22-35	23.5 20-26	25.3 19-43	**25.5** **19-44**
Race											
White	4	4	4	4	4	4	4	4	4	18	**54**
BMI (kg/m^2)	21.9 20-24	24.1 22-26	22.4 20-26	24.3 20-27	24.3 23-27	23.2 22-24	23.3 21-24	25.2 21-27	23.2 23-24	24.1 20-29	**23.7** **20-29**
FEV_1 (L)	4.3 4-5	4.9 4-6	4.6 4-5	4.0 3-5	4.6 4-5	4.2 4-5	4.9 4-6	4.4 4-5	4.8 4-6	4.5 3-6	**4.5** **3-6**
FEV_1 (% p.n.)	98.3 85-116	108.1 95-120	101.1 93-107	94.6 83-105	102.7 93-109	92.7 85-108	105.7 94-113	99.3 92-109	102.7 90-112	97.9 74-129	**99.7** **74-129**

Table S2 **Treatment group comparison of demographic data in Part B. For categorical data, frequencies are given, for other data mean values and ranges are presented**

	30 n=4	**100 n=4**	**Placebo n=4**	**All n=12**
Sex				
Male	4	4	4	**12**
Age (yrs)	23.5	25.8	24.5	**24.6**
	22-24	22-28	23-26	**22-28**
Race				
White	4	4	4	**12**
BMI (kg/m^2)	22.9	24.3	23.7	**23.6**
	21-26	20-29	22-26	**20-29**
Rhinitis (yrs)[a]	11.7	13.8	16.3	**14.2**
	5-18	3-23	8-20	**3-23**
FEV_1 (L)	4.6	4.6	4.6	**4.6**
	5-5	4-5	4-5	**4-5**
FEV_1 (% p.n.)	98.5	101.3	101.5	**100.4**
	93-103	93-108	94-112	**93-112**

a Median

Table S3 **Treatment group comparison of demographic data in Part C. For categorical data, frequencies are given, for other data mean values and ranges are presented**

	30 n=8	60 n=7	Placebo n=8	All n=23
Sex				
Male	8	7	8	**23**
Age (yrs)	23.9	23.6	24.9	**24.1**
	19-30	20-25	21-34	**19-34**
Race				
White	8	7	8	**23**
BMI (kg/m^2)	22.9	22.8	23.6	**23.1**
	21-28	21-26	20-27	**20-28**
Rhinitis (yrs)[a]	17.3	13.3	14.8	**13.9**
	8-23	9-15	10-18	**8-23**
FEV_1 (L)	4.2	5.0	4.5	**4.5**
	3-5	4-5	4-5	**3-5**
FEV_1 (% p.n.)	96.1	103.2	95.9	**98.2**
	83-108	90-117	84-112	**83-117**

a Median

Summary of pharmacokinetic results

Due to the rapid turnover of AZD8848 to the acid metabolite in human plasma the parent drug could not be measured. Plasma exposure of the acid metabolite (representing the sum of AZD8848 and metabolite) was increased with dose and no obvious differences in plasma concentration of acid metabolite between healthy subjects and patients with allergic rhinitis were observed. A high degree of variability in exposure was observed. An overall t_{max} was observed after 24 minutes. The overall geometric mean $t_{½}$ based on Part A, B and C was 36 minutes.

Summary of pharmacodynamic results

In plasma, AZD8848 increased the levels of neopterin and IL-1Ra, compared to placebo. In Part A statistically significant effects were seen at 100 µg and above, and in Part B and C at 30 µg and above.

Summary of pharmacogenetic results

Pharmacogenetic samples will be reported separately.

Summary of safety results

Doses of AZD8848 between 0.3 and 600 µg appeared safe and doses of 60 µg and below were well tolerated. At 100 µg AZD8848 and above, transient influenza-like symptoms (headache, pyrexia, myalgia, malaise and chills), accompanied by variable rises in body temperature and C-Reactive Protein and decreases in lymphocyte counts, were observed. Doses of 100 µg and above were also associated with an increase in mild AEs related to local nasal symptoms, such as nasal epistaxis and nasal mucosal ulcerations. There was no difference in tolerability to AZD8848 between healthy volunteers and allergic rhinitis patients and AZD8848 did not increase sensitivity to allergen.