Drug Product	N/A	**SYNOPSIS**	
Drug Substance	AZD3778		
Edition Number	1		
Study Code	D2530C00011		
Date	12 June 2006		

A randomised, double-blind, placebo controlled, three-way crossover study exploring the efficacy of AZD3778 compared with placebo and an oral antihistamine (loratadine) in a model of seasonal allergic rhinitis

International co-ordinating investigator

[redacted]

Study centre

The study was conducted at one single centre and aimed to include 40 randomised subjects.

Publications

None at the time of this CSR.

Study dates		**Phase of development**
First subject enrolled	18 October 2005	Therapeutic exploratory (II)
Last subject completed	27 February 2006	

Objectives

The primary objective of this study was to explore the efficacy of AZD3778 compared with placebo and an oral antihistamine, loratadine, in relieving the symptoms of allergic rhinitis in a model of seasonal allergic rhinitis by assessment of subjects' subjective nasal symptom scores and nasal peak inspiratory flow.

The secondary objectives of this study were to:

- assess the safety and tolerability of AZD3778 by assessment of the incidence and nature of adverse events, effects on ECG, vital signs and laboratory assessments
- evaluate drug exposure by measurement of plasma concentrations of AZD3778

- perform exploratory analysis on effects of AZD3778 on inflammatory mediators/markers in nasal tissue and nasal lavages (collected before and after provocation with bradykinin)

- collect pharmacogenetic samples for possible retrospective exploratory analysis, to investigate the influence of genotype on pharmacokinetics, pharmacodymanic response and safety associated with AZD3778 and its target receptors (optional part of this study).

Study design

This was a randomised, double-blind, double-dummy, three-way crossover, single centre study to explore the efficacy of AZD3778 in relieving symptoms of allergic rhinitis compared with placebo and an oral antihistamine (loratadine). A model of allergic rhinitis consisting of repeated nasal allergen challenges outside the natural pollen season was used.

Target subject population and sample size

Forty men and post menopausal or surgically sterile women aged 18-60 years with seasonal allergic rhinitis due to birch and/or timothy grass pollen. From previous studies with Rhinocort in allergic rhinitis and using the same provocation model, it was estimated that the standard deviation for the total nasal symptom score (TNSS) (morning or evening) was about 0.8 units. Using a two-sided test at a 5% significance level, 40 subjects gave an 80% power to detect a pairwise difference of 0.5 units between any two treatments.

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

AZD3778 300 mg twice daily (bid) as an oral suspension making a total daily dose of 600mg. Batch numbers: [redacted]. Placebo suspension to match AZD3778. Batch numbers: [redacted].

Loratadine administered as a 10 mg tablet once daily. Batch numbers: [redacted]. Placebo to match loratadine. Batch numbers: [redacted].

Duration of treatment

Each treatment period lasted 10 days with allergen challenges on the last 7 days, and followed by a washout period of at least 2 weeks.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

Primary variables: Total Nasal Symptom Score (TNSS), morning and evening recordings

Secondary variables: TNSS, assessed immediately post-allergen challenge; Nasal Peak Inspiratory Flow (nasal PIF) assessed immediately post-allergen challenge; nasal PIF,

morning and evening recordings; individual nasal symptom scores (runny nose, blocked nose, nasal itching and sneezing); nasal lavage and biopsy for inflammatory mediators; plasma concentrations of AZD3778.

Safety

The incidence and nature of adverse events, clinical laboratory (haematology, clinical chemistry and urinalysis) data, vital signs, ECG, nasal examination and physical examination.

Pharmacogenetics

Genetic samples were collected and stored for potential future research into genes which may influence the safety, PK and/or PD effects related to AZD3778 and its target receptors. This research was to form part of possible future pooled analysis and is not therefore reported as part of this study.

Statistical methods

Morning and evening variables were analysed using an analysis of variance model with fixed factors subject, period and treatment and using baseline as a covariate. Post-challenge variables and variables from nasal lavages were analysed using similar models but without baseline as covariate. Variables from nasal biopsies were analysed using an analysis of variance model with only fixed factor treatment. The full analysis set, consisting of all randomised patients with evaluable data from at least 2 treatment periods, was used for all efficacy analyses.

Subject population

A total of 46 subjects at 1 centre were enrolled into the study. Of these, 38 subjects were randomised and received at least one dose of study drug. Of those randomised, 38 were analysed for safety and 37 were analysed for efficacy using the full analysis set. In total there were 6 withdrawals from the study; 1 due to an AE. For disposition data see Table S1.

Of the 38 subjects allocated to treatment, all were Caucasian men. The average age was 24.9 years (range: 20 to 51) and average BMI was 23.8 kg/m^2 (range: 20 to 29). The median time since diagnosis of rhinitis was 13.5 (range: 2 to 33) years. The subjects recruited were considered to be representative of the target population for the study.

Table S1 Subject population and disposition

Treatment	Treated	Discontinued	Evaluable Efficacy	Safety
AZD3778	35	2	35	35
Loratadine	36	3	35	36
Placebo	36	1	35	36
All randomised	38	6	37	38

Efficacy and pharmacokinetic results

The primary efficacy variables were the total nasal symptom score (TNSS) night-time and daytime from the diary cards, recorded in the morning and evening, summarised using 3-day treatment means. Mean change from the baseline period to the treatment period in TNSS data were numerically lowest in the AZD3778 group, but treatment comparisons indicated no statistically significant differences for AZD3778 or loratadine versus placebo (Table S2).

Table S2 Treatment comparisons for TNSS from the diary cards

Variable	Treatment	Mean difference	95% CI	P-value
Total nasal symptom score				
-morning (0-9)	AZD3778 vs. Placebo	-0.378	(-0.85, 0.093)	0.114
	Loratadine vs. Placebo	-0.016	(-0.49, 0.458)	0.946
	AZD3778 vs. Loratadine	-0.362	(-0.842, 0.118)	0.137
-evening (0-9)	AZD3778 vs. Placebo	-0.33	(-0.903, 0.244)	0.255
	Loratadine vs. Placebo	-0.002	(-0.572, 0.569)	0.995
	AZD3778 vs. Loratadine	-0.328	(-0.9, 0.244)	0.256

CI = confidence interval

Analysis of TNSS using 5-days treatment period means showed statistically significant differences between AZD3778 and placebo in the morning and evening (p=0.023 and 0.022), but no differences for loratadine.

The nasal PIF revealed no statistically significant differences between any treatments in the morning or evening. The individual symptom scores (blocked nose, runny nose, nasal itching and sneezing) revealed that both AZD3778 and loratadine statistically significantly reduced itchy nose compared to placebo, but with no difference between the active compounds. There were no statistically significant differences between AZD3778 and placebo on blocked nose, runny nose or sneezing.

Both AZD3778 and loratadine statistically significantly reduced post-challenge TNSS and runny nose, itchy nose and sneezing, compared to placebo. AZD3778, but not loratadine, also statistically significantly reduced blocked nose and increased nasal PIF compared to placebo. Loratadine gave statistically significantly lower symptoms than AZD3778 on runny nose, but no differences between AZD3778 and loratadine on the other variables.

Nasal lavages were analysed for α_2-macroglobulin, tryptase and ECP. No statistically significant differences were found on α_2-macroglobulin. On ECP, AZD3778 gave statistically significantly lower values than both placebo and loratadine, as measured by the post-bradykinin values. On tryptase no difference between AZD3778 and placebo was found. Using the pre-bradykinin values loratadine statistically significantly increased tryptase versus both placebo and AZD3778. In the biopsy analyses no statistically significant differences

were found on EPO, PMDi and CCR3+ in nasal biopsy samples collected once on Day 10 of the last period.

The mean plasma AZD3778 steady state levels were as expected from the preceding multiple ascending dose study performed with AZD3778. The minimum recorded plasma concentration was approximately 300 nmol/L, with a total of 6 pre-dose samples being below the 3 x A_2 level of 600 nM for CCR3, fulfilling the requirements of a sufficient exposure around the clock.

Safety results

All 38 subjects randomised in the study were evaluable for safety. There were no deaths, SAEs or OAEs in the study. Four subjects discontinued study drug due to AEs; one of these also withdrew from the study as a result of the AE. The occurrence of AEs is presented in Table S3. One AE was judged by the investigator as possibly being causally related to AZD3778; allergic dermatitis in a subject who used daivonex for psoriasis during the study. The most frequently reported AEs were nasopharyngitis, headache and pharyngolaryngeal pain (Table S4). These AEs were reported on all treatments. Nasopharyngitis was reported more frequently on the placebo arm than the other two arms.

There were no findings of clinical concern in laboratory parameters between active treatments and placebo for the mean change from baseline (Day 1) to treatment (Day 10). A small but statistically significant increase in creatinine was seen on AZD3778 (4.3 µmol/L [range -20 to 12]); however these changes were judged to be of no clinical importance. One subject had a decrease in platelet count (from 130 x 10^9/L at Day 1 to 50 x 10^9/L at Day 10), and a high CRP value (130 mg/L at Day 10), after treatment with AZD3778. The platelet count was found to be normal when reassessed a few days later. This is the first observation of decreased platelet counts in the clinical programme so far, and thrombocytopenia or decreased platelet counts have not been associated with exposure to AZD3778 pre-clinically across several animal species.

There were no findings of clinical concern in vital signs, ECG or physical examination.

Table S3 Number (%) of subjects who had at least 1 AE in any category, and total numbers of AEs

	AZD3778 (n=35)	Loratadine (n=36)	Placebo (n=36)	All randomised (n=38)
Number of deaths	0	0	0	0
Number of SAEs[a] other than death	0	0	0	0
Number of other significant AEs	0	0	0	0
Number of DAEs[b]	1	1	2	4
Number (%) subjects with DAEs[b]	1 (3%)	1 (3%)	2 (6%)	4 (11%)
Number of AEs	8	10	16	34
- Mild	7	8	11	26
- Moderate	1	2	4	7
- Severe	0	0	1	1
Number (%) subjects with AEs	6 (17%)	7 (19%)	10 (28%)	19 (50%)
Max number of AEs per subject	2	2	3	3

[a] Serious adverse events
[b] Discontinuations from study drug due to AEs

Table S4 Number (%) of subjects with most commonly reported AEs, sorted by decreasing order of frequency as summarised over all treatment arms

Preferred term	AZD3778 n=35	Loratadine n=36	Placebo n=36	All n=38
Nasopharyngitis	2 (6%)	1 (3%)	6 (17%)	9 (24%)
Headache	2 (6%)	3 (8%)	1 (3%)	6 (16%)
Pharyngolaryngeal pain	1 (3%)	1 (3%)	1 (3%)	3 (8%)
Aspartate aminotransferase increased	0	1 (3%)	1 (3%)	2 (5%)
Alanine aminotransferase increased	0	1 (3%)	1 (3%)	2 (5%)
Infectious mononucleosis	0	1 (3%)	1 (3%)	2 (5%)

This table shows AEs reported on more than one occasion

Conclusions

Date of the report

12 June 2006