AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8848
Study Code	D0540C00016
Edition Number	1
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A Single-blind, Randomized, Placebo Controlled, Parallel-group, Adaptive-design Study to Investigate the Impact of Dose and Dosing Frequency of AZD8848 Administered Intranasally for up to 7 days, on the Biomarker Response in Healthy Female and Male Volunteers

Study dates: First subject enrolled: 9 November 2010
Last subject last visit (Visit 12): 10 March 2011

Phase of development: Clinical pharmacology (I)

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

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 investigate the effect of dose and dosing frequency of intranasal dosing of AZD8848 on the systemic and local biomarker response in healthy volunteers	CXCL10/IP-10 protein levels and mRNA expression of IFNα regulated genes in blood and nasal lavage	PD
Secondary	**Secondary**	
To investigate the safety and tolerability of intranasal dosing of AZD8848 at different doses and dosing frequencies in healthy volunteers	AEs, laboratory variables, ECG, vital signs, physical and nasal examinations, PNIF	Safety
Exploratory[a]	**Exploratory**	
To investigate the effect of dose and dosing frequency of AZD8848 on the systemic and local mRNA expression of genes including but not limited to genes related to T-helper cell phenotypes and inflammatory and immune functions, in healthy volunteers	mRNA expression of genes including but not limited to genes related to T-helper cell phenotypes and inflammatory and immune functions in blood and nasal lavage	PD
To collect and store DNA samples for possible future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to AZD8848, and associated biomarkers, where appropriate	DNA/genotype (optional)	PGx

AEs Adverse events, CXCL10 Chemokine (C-X-C motif) ligand 10, ECG Electrocardiogram, IFNα interferon α, IP-10 10 kDa interferon-gamma-induced protein, PD Pharmacodynamics, PGx Pharmacogenetics, PNIF Peak nasal inspiratory flow

[a] Results from the exploratory objectives will be reported separately from this clinical study report.

Study design

This was a single-blind, randomized, placebo-controlled, parallel group, adaptive-design clinical pharmacology study conducted to assess the effect of dose and dosing frequency of intranasal dosing of AZD8848, a toll like receptor 7 (TLR7) agonist, on the systemic and local biomarker response in healthy male and female volunteers. The study comprised 3 successive 7-day treatment periods, each involving 4 treatment groups with 4 to 5 healthy volunteers in

each group. Doses between 2 and 60 µg AZD8848 were administered with a dosing frequency of 0, 2, 4 or 7 doses over 7 days. A data monitoring committee evaluated available PD and safety data after each treatment period and decided on the dose and dosing frequency for the next period.

Target subject population and sample size

The main inclusion criteria were male or female healthy volunteers aged 18 to 55 (inclusive) with a body mass index (BMI) between 19 and 32 kg/m^2 (inclusive) and with the ability to metabolize AZD8848, as assessed by an *in vitro* butyrylcholinesterase (BChE) activity above a pre-defined limit. Females had to be of non-childbearing potential or had to have been stable on a highly effective contraceptive method for at least 3 months prior to Visit 1 and had to be willing to continue on the chosen contraceptive method, with additional use of a condom by male partners, until 3 months after last dose.

No formal sample size calculation was performed. For each of the 3 treatment periods, 4 or 5 healthy volunteers were to be included in each of 4 treatment groups, ie 48 to 60 healthy volunteers.

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

Table S2 Details of investigational product

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Material ID	Batch number
AZD8848	Concentrate for nasal spray solution, 60 mg/g	AstraZeneca	D0800394	10-004748AZ
Sodium chloride	Solution, 9 mg/mL	Not applicable	VNR477786	10-005120AZ

Duration of treatment

Doses of 2 µg to 60 µg AZD8848 were administered at a frequency of 2, 4 or 7 doses over a 7-day period. The maximum single dose did not exceed 60 µg and the highest total dose that was administered over the 7-day treatment period was 140 µg (20 µg daily).

Statistical methods

The statistical analysis was performed at Quintiles AB, Global Phase I Services, Uppsala, Sweden using SAS®, Version 9.2. Quintiles standard operating procedures and working instructions were used.

Quantitative continuous variables were summarized using descriptive statistics including n, mean, standard deviation (SD), median, minimum and maximum values. Additionally, for PD

variables, geometric means and geometric coefficient of variation in percent (CV%) were reported. All individual data were listed.

Subject population

A total of 55 healthy volunteers were randomized to treatment in the study. Forty-seven healthy volunteers received IP and completed all visits up to and including Visit 12 according to the clinical study protocol (CSP). Five healthy volunteers were discontinued from investigational product (IP) due to AEs (DAEs) and 3 healthy volunteers interrupted treatment with IP for 1 to 2 days due to AEs. The PD and safety analysis sets included all randomized healthy volunteers.

Summary of pharmacodynamic results

The mRNA expression of 5 IFNα-regulated genes, as well as the protein levels of CXCL10 protein, was analyzed in blood and nasal lavage following administration of AZD8848. In general the CXCL10 protein levels as well as the expression of the IFNα-regulated genes peaked either 24 hours after first dose (Visit 3) or 24 hours after last dose (Visit 9) and then declined towards baseline levels or below during the following days, independent of dose or dosing frequency. The response was similar locally and systemically but the levels of the CXCL10 protein and of the IFNα-regulated genes were in general higher in nasal lavage than in plasma. The CXCL10 protein and most IFNα-regulated genes appeared to reach plateau levels of expression already at low doses of AZD8848. Overall, the most determinant factor for expression levels appeared to be the last dose given. In general there was no consistent effect of dosing frequency on expression levels of the IFNα-regulated genes or on CXCL10 protein levels.

Summary of safety results

AZD8848 was tolerated and no safety concerns were identified. The most frequently reported AEs, nasal congestion and epistaxis, were more common in treatment groups where AZD8848 was administered with a high dosing frequency independent of dose. Major reductions in PNIF were associated with high dosing frequency.

In agreement with what has been described in the literature regarding systemic effects of drug induced TLR7 activation in man, a number of influenza-like symptoms were reported by a number of healthy volunteers in the study. All symptoms were of non-serious nature and all, but 1, were of mild to moderate intensity. There was no indication of a dose or dosing frequency dependent effect on the prevalence of influenza-like symptoms.