AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8848
Study Code	D0540C00009
Edition Number	1
Date	29 November 2011

An Open, Non-controlled, Non-Randomised, Parallel-group Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Doses of AZD8848 Administered intranasally to Male and Female Butyrylcholinesterase Deficient Subjects and to Sex and Age Matched Control Subjects

Study dates:	First subject enrolled: 22 September 2010 Last subject completed Visit 6: 10 February 2011
Phase of development:	Clinical pharmacology (I)

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

Study centre(s)

The study was conducted at one centre in Denmark.

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 safety and tolerability of single ascending doses of AZD8848 following intranasal administration in butyrylcholinesterase (BChE) (homozygous silent [S/S]) deficient subjects in comparison with sex and age matched control subjects with normal BChE activity.	• Adverse events (AEs) (nature and incidence) • Laboratory variables (clinical chemistry, haematology, urinalysis) • Physical examination • Vital signs (blood pressure [BP], pulse and body temperature) • Electrocardiogram (ECG) • Spirometry (asthma patients only) • Autoantibodies • Clinical inspection of the nose	Safety
Secondary	**Secondary**	
1. To investigate the pharmacokinetics (PK) after single ascending doses of AZD8848 by determination of plasma and urine concentrations of AZD8848 and the acid metabolite (AZ12432045).	• Maximum plasma concentration (C_{max}) • Time to C_{max} (t_{max}) • Terminal rate constant (λ_z) • Terminal half-life ($t_{1/2\lambda z}$) • Area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC) • Apparent plasma clearance (CL/F) • Apparent volume of distribution during terminal phase (V_z/F) • Mean residence time (MRT) • Amount of drug excreted unchanged (Ae; nmol) • Fraction of drug excreted unchanged (Fe; % dose) • Renal clearance (CL_R)	Pharmaco kinetic

Objectives	Outcome variables	Type
2. To investigate the pharmacodynamic (PD) effect of AZD8848 by assessments of Interleukin-1-Receptor Antagonist (IL-1Ra) in plasma.	• Plasma concentration of IL-1Ra	Pharmaco dynamic

Study design

This was an open, non-controlled, non-randomised, parallel group study in subjects with no or very low BChE activity (defined as BChE deficient, S/S) and in sex and age matched subjects with normal BChE activity (defined as matched controls).

Target subject population and sample size

Men and women aged 18 to 52 years (inclusive) with a body mass index (BMI) between 19 and 32 kg/m^2 (inclusive) were included in the study. Women had to be of non-childbearing potential or use adequate contraceptive measures, as described in the Clinical Study Protocol (CSP). Pregnant women were not allowed to participate in the study.

BChE deficient subjects and matched controls had to show inability or ability to specifically hydrolyse AZD8848 in an *in vitro* screening assay in blood taken at Visit 1. Inability to hydrolyse AZD8848 was defined as a half-life >20 minutes, whereas ability to hydrolyse AZD8848 was defined as a half-life <2 minutes.

Since the number of subjects that fulfils the BChE deficiency criteria in a normal population is very small, the sample size was not based on formal statistical considerations but rather on safety data from previous clinical studies where data from three subjects was considered sufficient in order to gain adequate safety information to support further clinical studies in BChE deficient subjects.

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

The details of the investigational products and any study treatment are given in Table S2.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD8848	Concentrate for nasal spray, solution 60 mg/g	AstraZeneca	D0800394	10-000759AZ
Sodium chloride for injection	Solution for injection 9 mg/mL	N.A.	43 66 67	0263B10 and 0412B06

Duration of treatment

Single doses of AZD8848 were administered as nasal spray solutions. At each dose level, 1 spray (50 µL) was administered in each nostril.

The dose levels included were 1.4 µg, 7 µg and 30 µg AZD8848 and an optional dose of 60 µg AZD8848. Only BChE deficient subjects received the lower doses (1.4 µg and 7 µg AZD8848). A safety review committee (SRC) reviewed data from each dose level and made a decision regarding the next dose level. Data from the matched controls (at dose levels over 10 µg) were not part of the SRC evaluation.

There was a wash-out period of at least 7 days between each treatment visit to avoid interaction from the previous dose.

Statistical methods

No formal statistical hypothesis testing was performed in this study. Data were summarised using descriptive statistics and graphical presentations.

Subject population

A total of 22 subjects were enrolled in the study, whereof 17 subjects (with a mean age of 31 years) were dosed and evaluable for safety. In total, 3 subjects were exposed to 1.4 µg, 3 subjects to 7 µg, 15 subjects to 30 µg and 7 subjects to 60 µg of AZD8848, given as single doses. The disposition of the subjects in this study is summarised by treatment group in Table S3.

Table S3 Subject disposition

	BChE deficient subjects	Matched controls	All
Enrolled subjects			22
Not dosed			5
-Eligibility criteria not fulfilled			5
Dosed	6	11	17
Completers	6	11	17

Sufficient matching was achieved between BChE deficient subjects and control subjects for comparative purposes.

Summary of pharmacokinetic results

Plasma concentrations of AZD8848 and its metabolite were measurable after administration of 30 µg and 60 µg AZD8848 in BChE deficient and matched control subjects with normal enzyme activity. The concentration of AZD8848 in plasma tended to be higher in BChE deficient subjects compared with the controls.

The fraction of dose excreted as unchanged parent and metabolite in urine was low in both BChE deficient subjects and controls. The results indicate that the amount of AZD8848 excreted unchanged was lower in controls compared with BChE deficient subjects, whereas the fraction of dose excreted as acid metabolite tended to be higher in the control subjects than in BChE deficient subjects.

Summary of pharmacodynamic results

The pharmacodynamic response, measured as IL-1Ra concentration in plasma, did not differ substantially between the BChE deficient subjects and the control subjects with normal enzyme activity. Ranges for IL-1Ra concentration in plasma are shown by dose and treatment group in Table S4.

Table S4 P-IL-1Ra concentration ranges by dose and treatment group

Treatment	Group	n	Range
AZD8848 1.4 µg	BChE deficient	3	99-1050
AZD8848 7 µg	BChE deficient	3	68-178
AZD8848 30 µg	BChE deficient	5	93-1320
	Controls	10	25-460
AZD8848 60 µg	BChE deficient	2	188-2820
	Controls	5	456-1140

Summary of pharmacogenetic results

At screening (Visit 1), DNA samples for analysis of BChE genotype and exploratory genetic research on genes or genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD8848, were collected from subjects who had signed a separate genetic informed consent form (ICF). The results from sequencing of the coding region of the BCHE gene in the BChE deficient subjects showed that all six subjects carried two mutations with putative functional consequences, likely to cause ablation of BChE activity. The combination of BCHE mutations identified is likely to cause complete ablation of BChE activity in all six subjects, however due to the nature of the mutations this could not be stated with complete certainty. The results from the gene sequencing are presented in detail in a separate report, which is included in Appendix 12.1.13 to the CSR.

Summary of safety results

There was no difference in the safety and tolerability profiles between the BChE deficient subjects and the control subjects with normal enzyme activity.

The most commonly reported AEs on the preferred term level were epistaxis, headache and nasopharyngitis. All reported AEs were of mild intensity. The most commonly reported AEs judged by the Investigator to be causally related to the investigational product were epistaxis,

nasopharyngitis and rhinorrhoea. The AE profile seen in this study is similar to what has been observed in the previous SAD studies.

One BChE deficient subject in the study developed laboratory signs of hypothyreosis, but without clinical signs or symptoms. The event was reported as a serious adverse event (SAE) (thyroid function test abnormal, mild in intensity) after administration of the 30 µg dose of AZD8848 and the subject discontinued investigational product but fulfilled the follow-up visit (Visit 6). AstraZeneca considers that the findings of positive titres of anti-thyroglobulin (TG) antibodies (Abs) and Thyroid Stimulating Hormone (TSH) above upper limit of normal (ULN) already prior to first dose strongly implies that the subject had a pre-existing disorder.

In some treatment groups (30 µg BChE deficient, 60 µg BChE deficient and 60 µg control), a transient slight decrease in lymphocyte concentration was observed after dosing, but values were back to normal at 48 hours post-dose. There were no individual clinically important abnormalities in laboratory variables during Visits 1 to 6, except for the SAE.

An increased body temperature of 38.0°C and 38.3°C was noted 24 hours post-dose for the two BChE deficient subjects receiving 60 µg AZD8848. The body temperature was back to normal 48 hours post-dose. No clinically relevant changes were observed on vital signs or ECG.