AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3043
Study Code	D0510C00004
Edition Number	1
Date	10 December 2010

Phase I, Single Centre, Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous AZD3043 after A) a Single Ascending Bolus Dose and B) a Single Ascending Bolus Dose Followed by a Single Infusion Dose in Healthy Japanese Volunteers (age range 20-45 years)

Study dates: First subject enrolled: 01 December 2009
Last subject last visit: 05 August 2010

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 assess the safety and tolerability of AZD3043 following administration of single ascending bolus doses (Part A) and single ascending bolus doses followed by infusion (Part B) in Japanese healthy subjects.	Adverse events, vital signs, electrocardiograms (ECGs), laboratory variables, body temperature and other events as described in the Investigator's Brochure. Respiratory data (SpO2, EtCO2, arterial blood gases, respiratory frequency and pattern, occurrence of apnoea).	
Secondary(Part A and B)	**Secondary**	
To characterise the PK of AZD3043 and its main metabolite (THRX-108893), and provisionally assess the dose-proportionality of the PK following iv administration of single ascending doses of AZD3043.	PK parameters for AZD3043: C_{max} (in part B: bolus C_{max} and infusion C_{max}) and AUC_{last}, AUC, λ_z, $t_{½\lambda z}$, CL, V_{ss}, V_z, t_{max}, t_{last} and MRT in arterial and venous plasma. PK parameters for the metabolite (THRX-108893): C_{max}, AUC_{last}, AUC, t_{max}, t_{last}, λ_z and $t_{½\lambda z}$ in arterial and venous plasma.	
To evaluate the onset, level and recovery of/from sedation/anaesthesia.	BIS, clinical signs, quality of sedation or anaesthesia rated by the Principal Investigator and by the subject, MOAA/S score, level of alertness and recovery test and proprioception (Romberg's sign).	
Exploratory objectives (Part A and Part B)	**Exploratory**	
To investigate the relationship between AZD3043 exposure and different measures of clinical outcome including efficacy and safety. To collect and store an optional DNA sample for future exploratory research into genes/genetic variation that may influence response (i.e., PK, PD, safety, tolerability and efficacy) to AZD3043.	Identifying/exploring genetic variations that may affect PK, PD, safety, tolerability and efficacy related to AZD3043.	

The exploratory objectives are not reported in this CSR.

Study design

This was a Phase I, open, non-randomised, single ascending dose study in healthy male and female subjects conducted at a single centre. Only females of non-childbearing potential were allowed to participate in the study. The study consisted of two parts; in Part A single ascending bolus doses were given over 60 seconds in all cohorts, except Cohorts 8 and 9, where bolus doses were given over 30 and 15 seconds respectively. In Part B, a single bolus dose over 60 seconds was followed by an infusion dose for 30 minutes. The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure the safety of the subjects.

Target subject population and sample size

Up to 72 healthy subjects aged 20 to 45 years were to participate in a maximum of 5 cohorts within Part A and 4 cohorts within Part B. Subjects were enrolled into Part B of the study prior to completion of all cohorts in Part A. This design allowed assessment of the safety of the bolus and bolus plus infusion doses of AZD3043 likely to result in sedation prior to consideration of anaesthesia.

It was planned for eight subjects to participate in each cohort and receive AZD3043. Each subject only participated in one cohort.

Due to the exploratory nature of the study the sample size was not based on formal statistical considerations. The sample size was based on experience from previous similar Phase I studies with other compounds.

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

AZD3043 was provided as an emulsion (60 mg/mL)

Part A: Single intravenous bolus doses of AZD3043.

Part B: Single intravenous bolus doses of AZD3043 followed by infusion.

Table S1 Cohorts and doses given

Part A	Dose	Part B	Dose
Cohort 1	1.5 mg/kg/min	Cohort 4	0.8 mg/kg/min + 10 mg/kg/h
Cohort 2	2.0 mg/kg/min	Cohort 5	1.0 mg/kg/min + 15 mg/kg/h
Cohort 3	4.0 mg/kg/min	Cohort 6	3.0 mg/kg/min + 30 mg/kg/h
Cohort 8	2.0 mg/kg/30 sec[a]	Cohort 7	2.0 mg/kg/min + 20 mg/kg/h
Cohort 9	2.0 mg/kg/15 sec[b]		

a Equivalent to 4.0 mg/kg/min when given over 30 sec
b Equivalent to 8.0 mg/kg/min when given over 15 sec
Cohort numbering correlates to the order in which the dose levels were administered to subjects

Duration of treatment

Part A: Each subject received a single bolus dose of AZD3043 over 60 seconds. Subjects in two cohorts received a single bolus dose of AZD3043 over 30 and 15 seconds, respectively.

Part B: Each subject received a single bolus dose of AZD3043 over 60 seconds followed by an infusion of AZD3043 over 30 minutes.

Statistical methods

The analysis of the primary objective safety and tolerability as well as the secondary objectives PK, PD and PK/PD relationship mainly consisted of descriptive statistics, including listings, summary statistics, and graphs as appropriate. Dose proportionality was analysed using a confidence interval approach through a linear (power) regression model. The model was applied to the following pharmacokinetic parameters: C_{max}, AUC, and $AUC_{(0-t)}$.

Subject population

Of the planned 72 healthy Japanese subjects, 70 subjects aged between 20 and 38 years (mean age of 27 years), were included into the study at 1 study site. 7 subjects were included in the 0.8 mg/kg/min + 10 mg/kg/h and 2.0 mg/kg/min + 20 mg/kg/h dose levels. Each subject received 1 administration of study drug during the planned treatment visit (see Appendix 12.2.5.1). The first healthy volunteer entered the study on 01 December 2009 and the last healthy volunteer finished the study on 05 August 2010. All subjects included and receiving treatment completed the study.

Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of safety results

No major safety concerns were identified in this study in doses up to the highest dose given in Part A (4.0 mg/kg/min) and Part B (3.0 mg/kg/min + 30 mg/kg/h). A total of 2 subjects in Part A and 4 subjects in Part B reported adverse events during the study. None of the observed AEs occurred in a dose dependent manner. Nausea was reported by 1 subject in Part B and was not observed at any of the doses given in Part A or the higher doses in Part B (Table S2).

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Table S2 **Number (%) of healthy volunteers who had at least 1 AE by preferred term, arranged by system organ class (Safety analysis set)**

System Organ Class Preferred Term	1.5 mg/kg/min (N=8)	2.0 mg/kg/min (N=8)	2.0 mg/kg/30 sec (N=8)	2.0 mg/kg/15 sec (N=8)	4.0 mg/kg/min (N=8)	0.8 mg/kg/min + 10 mg/kg/h (N=7)	1.0 mg/kg/min + 15 mg/kg/h (N=8)	2.0 mg/kg/min + 20 mg/kg/h (N=7)	3.0 mg/kg/min + 30 mg/kg/h (N=8)	Total (N=70)
CARDIAC DISORDERS	0	0	0	0	0	0	0	1	0	1
BRADYCARDIA	0	0	0	0	0	0	0	1(14.3%)	0	1(1.4%)
EYE DISORDERS	1	0	0	0	0	0	0	0	0	1
EYE IRRITATION	1(12.5%)	0	0	0	0	0	0	0	0	1(1.4%)
GASTROINTESTINAL DISORDERS	0	0	0	0	0	1	0	0	0	1
NAUSEA	0	0	0	0	0	1(14.3%)	0	0	0	1(1.4%)
NERVOUS SYSTEM DISORDERS	0	0	0	0	0	0	0	0	1	1
HEADACHE	0	0	0	0	0	0	0	0	1(12.5%)	1(1.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0	0	1	0	0	0	1
RHINITIS ALLERGIC	0	0	0	0	0	1(14.3%)	0	0	0	1(1.4%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	0	0	0	0	0	0	0	0	1
CONTUSION	1(12.5%)	0	0	0	0	0	0	0	0	1(1.4%)

There were episodes of apnoea in 13 healthy subjects exposed to AZD3043 during the study. The frequency and duration of apnoea increased with the dose. All healthy subjects breathed spontaneously. None of the healthy subjects had a persistent decline in SpO_2. None of the healthy subjects needed assisted breathing during the study. However, in the two highest dose groups in Part A (1 out of 16 subjects) and in the two highest dose groups in Part B (4 out of 15 subjects) the use of chin lift and/or oral-pharyngeal/naso-pharyngeal airway was necessary to maintain a clear airway.

Dose related increases in heart rate were observed during the study. The highest mean change from baseline was 34 bpm observed in the 4.0 mg/kg/min dose level (Part A) with a maximum change of 63 bpm. The HR changes observed in Part B were not that prominent and were maintained at a steady level until the end of infusion. HR increases began shortly after the start of administration and returned to baseline after the end of dosing. These changes were not associated with changes in blood pressure.

At the highest dose of 4.0 mg/kg/min in Part A and the highest two doses of 2.0 mg/kg/min + 20 mg/kg/h and 3.0 mg/kg/min + 30 mg/kg/h in Part B, subjects showed involuntary movements which included spontaneous and disturbing movements. None of the involuntary movements were reported as adverse events.

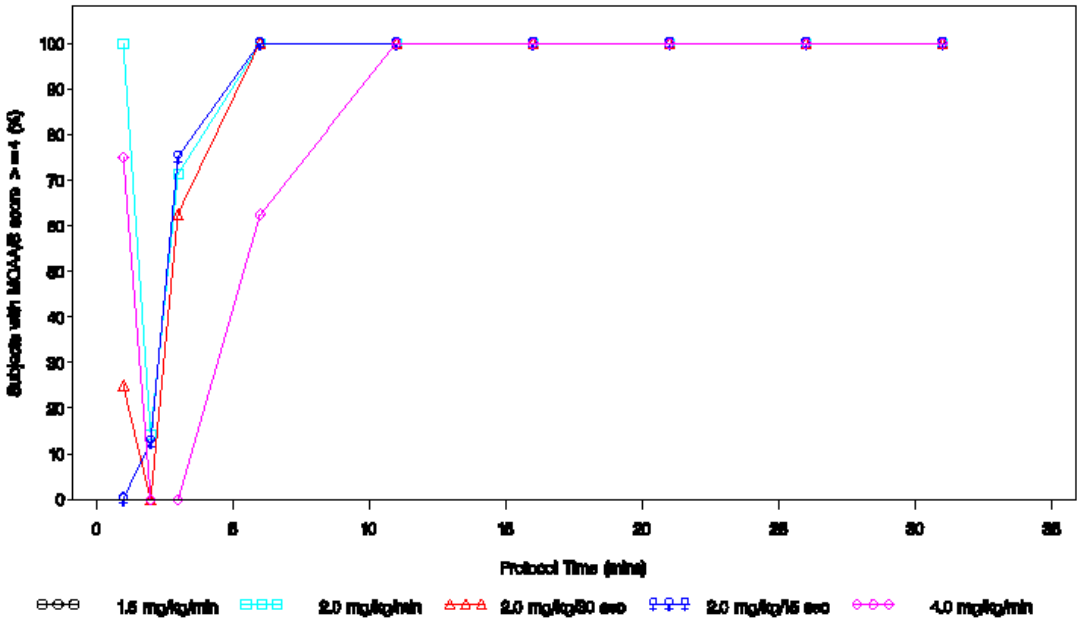
Summary of pharmacokinetic results

The chosen bolus+infusion dosing strategies resulted in a rapidly achieved drug concentration plateau. AZD3043 was rapidly eliminated from plasma once bolus and infusion had been completed. Dose-proportional PK was generally demonstrated for both AZD3043 and THRX-108893 (venous AUC for AZD3043 was shown to be slightly less than dose proportional) when AZD3043 was administered as a bolus followed by an infusion. The $t_{½\lambda z}$ of AZD3043 averaged approximately 13 to 21 min in arterial and venous plasma. After a bolus dose of AZD3043, exposure of AZD3043 in terms of C_{max} and AUC were higher in arterial (C_{max}: 2.6 to 5.1 times higher; AUC: 0.9 to 1.7 times higher) compared to venous samples. After a bolus followed by an infusion, the C_{max} and AUC were higher in arterial (C_{max}: 0.8 to 1.5 times higher; AUC: 1.1 to 1.3 times higher) compared to venous plasma.

Summary of pharmacodynamic results

Part A: At dose levels of 1.5 mg/kg/min healthy subjects were minimally sedated, the lowest MOAA/S score was 5 and one subject lost response to oral command. At dose level of 2.0 mg/kg/min clinical effects varied between sedation and anaesthesia. All subjects were anaesthetised at a dose level of 4.0 mg/kg/min. For the dose levels 2.0 mg/kg/30 sec and 2.0 mg/kg/15 sec a MOAA/S score of 0 was reached quicker than the other doses levels (within 1 min). Generally, there was no difference in PD outcomes following the change in bolus injection duration from 60 to 30 and 15 seconds for the 2.0 mg/kg dose level. Approximately 50% of the subjects administered both dose levels were anaesthetised.

Figure S1 **Percentage of healthy subjects reporting MOAA/S ≥ 4 over time after start of administration – Part A, bolus (PD analysis)**



The denominator for the percentage is the number of subjects for which MOAA/S assessment performed = yes

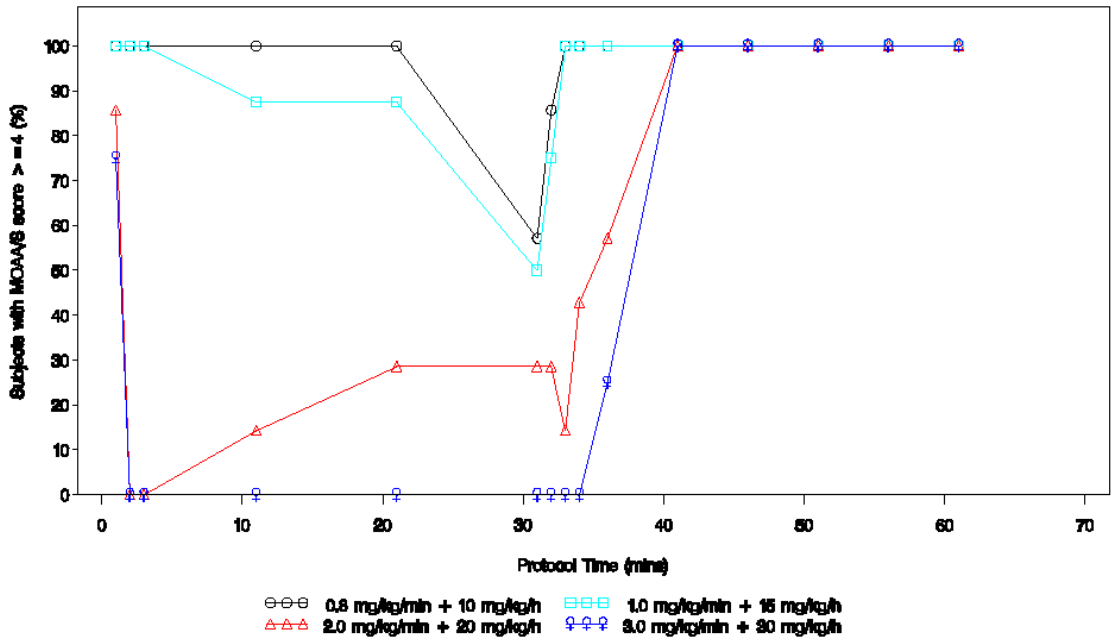
The depth of sedation/anaesthesia as judged by the Investigator was assessed at discrete time points (same as for MOAA/S) and the quality of sedation/anaesthesia assessment based on the Investigator's overall judgement. The onset and offset of sedation/anaesthesia was rapid and dose dependent. At a dose of 4.0 mg/kg/min clinical signs of onset of anaesthesia occurred at about 1 min from the start of administration (Table S3). Mean time to recovery as assessed by clinical signs was 5 min from the start of administration.

Table S3 **Clinical signs indicating onset of sedation / anaesthesia – Part A, bolus (PD Analysis set)**

Cohort	N	Number (%) of subjects, Loss of Handgrip	Median time (min,max) to Loss of Handgrip (min)	Number (%) of subjects, Loss of Eyelash Reflex	Median time (min,max) to Loss of Eyelash Reflex (min)	Number (%) of subjects, Loss of Response to Oral Command	Median time (min,max) to Loss of Response to Oral Command (min)
1.5 mg/kg/min	8	0	0	0	0	1 (12.5)	3.00 (3.00 , 3.00)
2.0 mg/kg/min	7	1 (14.3)	2.37 (2.37 , 2.37)	2 (28.6)	2.00 (2.00 , 2.00)	4 (57.1)	2.00 (1.00 , 2.00)
2.0 mg/kg/30 sec	8	1 (12.5)	2.00 (2.00 , 2.00)	5 (62.5)	1.25 (1.00 , 1.67)	7 (87.5)	1.00 (1.00 , 1.50)
2.0 mg/kg/15 sec	8	0	0	3 (37.5)	1.17 (1.00 , 1.25)	5 (62.5)	1.00 (1.00 , 1.00)
4.0 mg/kg/min	8	5 (62.5)	1.83 (1.18 , 2.75)	8 (100.0)	1.21 (1.00 , 1.50)	8 (100.0)	1.17 (1.00 , 2.00)

Part B: At dose levels of 0.8 mg/kg/min + 10 mg/kg/h healthy subjects were minimally sedated, the lowest MOAA/S score was 2 and none of the subjects showed any clinical signs of onset of anaesthesia (Figure S2). At a dose level of 1.0 mg/kg/min + 15 mg/kg/h the clinical effects varied between sedation and anaesthesia. At dose levels of 2.0 mg/kg/min + 20 mg/kg/h and 3.0 mg/kg/min + 30 mg/kg/h all healthy subjects were anesthetised.

Figure S2 **Percentage of healthy subjects reporting MOAA/S ≥ 4 over time after start of administration – Part B, bolus (PD analysis)**



The denominator for the percentage is the number of subjects for which MOAA/S assessment performed = yes

The time of onset and recovery of sedation/anaesthesia were dose dependent. Clinical signs of onset of anaesthesia occurred within 25 minutes after the start of infusion at a dose of 1.0 mg/kg/min + 35 mg/kg/h and within 2 minutes after the start of infusion at a dose of 2.0 mg/kg/min + 20 mg/kg/h and 3.0 mg/kg/min + 30 mg/kg/h (Table S4). Mean time to recovery as assessed by clinical signs was between 35 to 38 minutes from the start of infusion at the two highest dose levels.

Table S4 Clinical signs indicating onset of sedation/anaesthesia - Part B, bolus + infusion (PD Analysis set)

Cohort	N	Number (%) of subjects, Loss of Handgrip	Median time (min,max) to Loss of Handgrip (min)	Number (%) of subjects, Loss of Eyelash Reflex	Median time (min,max) to Loss of Eyelash Reflex (min)	Number (%) of subjects, Loss of Response to Oral Command	Median time (min,max) to Loss of Response to Oral Command (min)
0.8 mg/kg/min + 10 mg/kg/h	7	0	0	0	0	0	0
1.0 mg/kg/min + 15 mg/kg/h	8	2 (25.0)	25.71 (21.58, 29.83)	0	0	0	0
2.0 mg/kg/min + 20 mg/kg/h	7	1 (14.3)	2.00 (2.00 , 2.00)	6 (85.7)	1.75 (1.33 , 20.00)	7 (100.0)	2.00 (1.00 , 2.00)
3.0 mg/kg/min + 30 mg/kg/h	8	6 (75.0)	2.13 (1.25 , 15.33)	8 (100.0)	2.00 (1.00 , 10.00)	8 (100.0)	1.50 (1.00 , 2.00)

Summary of anaesthesia results

The quality of sedation was rated as fair, good, very good by subjects and Investigator except as poor in 1 healthy subject in Part A (at a dose of 1.0 mg/kg/min, due to eye irritation) and as poor in 2 healthy subjects in Part B (at a dose level of 2.0 mg/kg/min + 20 mg/kg/h, due to restless leg/arm movements and body movement).

The quality of anaesthesia was rated as fair to good by subjects but generally as poor by the Investigator in the highest dose groups in both Part A (6 out of 18 subjects) and Part B. (10 out of 12 subjects), due to disturbing movements, requirement of respiratory support and increases in heart rate.