Clinical Study Report Synopsis

Drug Substance	AZD3043
Study Code	D0510C00001
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A Phase I, Single Centre, Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous AZD3043 after Single Ascending Doses in Healthy Male Volunteers

Study dates: First subject enrolled: 8 June 2009
Last subject last visit: 21 August 2009

Phase of development: Clinical Pharmacology (Phase 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 evaluate the safety and tolerability of AZD3043 following iv infusion of ascending doses and to estimate the MTD, if within the predefined exposure limits.	Adverse events Laboratory variables Vital signs: Blood pressure, Pulse, Body temperature ECG: 12-lead paper ECG and 3-lead telemetry SpO_2 and $EtCO_2$, respiratory pattern, respiratory frequency and occurrence of apnoea as measured by the Dräger monitor	Safety
Secondary	**Secondary**	
To characterise the PK of AZD3043 and its main metabolite (THRX-108893), and provisionally assess the dose-proportionality of the PK following iv infusion of single ascending doses of AZD3043.	For AZD3043: C_{max}, AUC_{last}, AUC, λ_z, t_{max}, $t_{½\lambda z}$, CL, f_e, V_{ss}, V_z, t_{last} and MRT. The fraction unbound (f_u) will be calculated for AZD3043 in venous plasma. For the metabolite THRX-108893 (where possible): C_{max}, AUC_{last}, AUC, t_{max}, t_{last}, λ_z, $t_{½\lambda z}$	PK
To assess the urinary excretion of AZD3043 and THRX-108893.	The cumulative amounts of AZD3043 and THRX-108893 in urine will be calculated	PK
To assess the onset of sedation/anaesthesia by means of MOAA/S score, Bispectral Index Score (BIS) (0-100) and clinical signs (time to: syringe drop, loss of response to oral command, loss of eye lash reflex).	MOAA/S score, BIS and clinical signs (time to: syringe drop, loss of response to oral command, loss of eye lash reflex)	PD
To assess the level of sedation/anaesthesia over time by means of MOAA/S score, BIS and by assessment of spontaneous movements.	MOAA/S score, BIS and spontaneous movements	PD
To assess the offset of sedation/anaesthesia by means of MOAA/S score, BIS and clinical signs (return of response to oral command and orientation to person, place and time).	MOAA/S score, BIS and clinical signs (time to: return of response to oral command, spontaneous eye opening), orientation	PD
To evaluate the time to recovery by an assessment of Romberg's Sign.	Proprioception (Romberg's sign)	PD

Objectives	Outcome variables	Type
To investigate the dose-response or PK/Pharmacodynamic (PD) relationships	Graphic presentation and/or modelling of variables, eg, BIS, MAP, MOAA/S, and investigators' assessment of quality of anaesthesia	PD
To evaluate the quality of sedation/anaesthesia by an overall assessment.	Quality of sedation (investigator and subject) Quality of anaesthesia (subject) Quality of anaesthesia (investigator)	Efficacy

PK pharmacokinetic; PD pharmacodynamic

Study design

AZD3043 is an investigational agent for sedation and anaesthesia. In this open label, uncontrolled single ascending dose study AZD3043 was administered as an intravenous infusion during 30 minutes. After each dose panel a Safety Review Committee evaluated all available safety, tolerability, pharmacokinetics and pharmacodynamics of AZD3043 and THRX-108893 and decided the next dose. Dose escalation continued until the maximum tolerated dose and/or the predefined maximum exposure level was reached

Target subject population and sample size

The target for this study was healthy men aged 18 to 45 years.

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

AZD3043 was administered as an intravenous infusion during 30 minutes.

Duration of treatment

Single dose, infusion over 30 minutes.

Statistical methods

The data were summarized using descriptive statistics. Dose proportionality was analysed by using the power model approach.

Subject population

In total, 53 Caucasian male healthy volunteers were included in the study at 1 study site, each received 1 administration of study drug during the planned treatment visit. One healthy volunteer did not complete the study (E0001005, missed follow up visit) and 52 healthy volunteers completed the study. There were 73 enrolled healthy volunteers withdrawn from the study before receiving treatment. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

The mean arterial C_{max} and AUC at the highest dose level (81 mg/kg/h given over 30 min) were 111 µM (highest individual 124 µM) and 4114 µM*min (highest individual 5139 µM*min), respectively. The mean venous C_{max} and AUC at the highest dose level were 79.3 µM (exceeded 100 µM in two individuals; 113 and 120 µM) and 3387 µM*min (highest individual 4928 µM*min), respectively. T_{max} (generally at the end of infusion) and concentration-time profiles indicated that steady-state was not reached within 30 min of infusion.

The mean arterial C_{max} and AUC of THRX-108893 at the highest dose level were 192 µM and 18812 µM*min, respectively. Corresponding venous C_{max} and AUC were 169 µM and 19599 µM*min, respectively.

Negligible amounts of AZD3043 were excreted unchanged in urine. In most urine samples, no intact compound was quantifiable. AZD3043 was mainly excreted in urine as THRX-108893. Mean fraction excreted as THRX-108893 ranged from approximately 45 to 70% (with the highest estimate at the lowest dose).

The median arterial and venous $t_{½\lambda z}$ of AZD3043 were 13 and 15 min, respectively. Mean $t_{½\lambda z}$ estimates ranged from 10 to 17 min in arterial plasma and 11 to 35 min in venous plasma. The mean arterial $t_{½\lambda z}$, CL, V_{ss} and V_z at 12 mg/kg/h were 13 min, 2.2 L/min, 18 L and 42 L, respectively. Corresponding venous estimates were 15 min, 2.9 L/min, 45 L and 64 L, respectively. Mean $t_{½\lambda z}$ estimates of THRX-108893 ranged from 32 to 38 min in arterial plasma and 46 to 179 min in venous plasma. The mean arterial and venous $t_{½\lambda z}$ at 12 mg/kg/h was 34 min (t_{last} 2.5 h) and 72 min (t_{last} 9.6 h) respectively.

For AZD3043, AUC increased proportionally with increasing doses according to the power model, while C_{max} increased less than proportionally in relation to dose. For THRX-108893 C_{max} increased proportionally with increasing doses according to the power model while AUC increased more that proportionally in relation to dose.

Summary of pharmacodynamic results

The lowest dose level where an effect in MOAA/S was observed was 12 mg/kg/h where a MOAA/S <4 was seen in 1 healthy volunteer with a minimum MOAA/S of 2 at 20 to 30 min. In both the 18 to 27 mg/kg/h dose groups 5 out of 6 healthy volunteers recorded MOAA/S <4 at 20 min and all healthy volunteers showed a decrease in MOAA/S. In the 18 and 27 mg/kg/h dose groups 1 and 3 healthy volunteer reached MOAA/S=0 respectively. In the dose groups 36 and 81 mg/kg/h, all healthy volunteers had MOAA/S=0 at 10 to 30 minutes while in the 54 mg/kg/h dose group 1 healthy volunteer had a minimum MOAA/S of 1.

The lowest dose where an effect on BIS was observed as implied by a noticeable separation of the mean score from the mean of lower doses at 15 to 30 min was 12 mg/kg/h. At 18 mg/kg/h, there was a decrease in BIS seen between ca 5 to 35 minutes. At dose levels 36 and 54 mg/kg/h, mean BIS was around 40 to 50 at 10 to 30 minutes.

There was no loss of handgrip, loss of eye lash reflex or loss of response to oral command at doses of 1 to 6 mg/kg/h. At a dose of 12 mg/kg/h 2 healthy volunteers lost handgrip. In the dose panels of 36 mg/kg/h and higher, all healthy volunteers displayed clinical signs of anaesthesia. Clinical signs of onset of anaesthesia occurred earlier at 54 and 81 mg/kg/h than at lower doses.

In general, the time to return of response to oral command increased with dose. The return of response to oral command and spontaneous eye opening occurred at about 5 minutes after the end of infusion at a dose of 27 mg/kg/h, at about 10 minutes at a dose of 36 and 54 mg/kg/h and after more than 20 minutes at a dose of 81 mg/kg/h. The time to return of response to oral command ranged from 0.6 to 24.9 minutes.

The time to achieve all three correct answers in the orientation assessment increased with dose, ranging from 5 min at 12 mg/kg/h to 120 min at 81 mg/kg/h. Proprioception was assessed starting at 30 minutes after end of infusion (15 min in 1 case). At doses up to 36 mg/kg/h there was no dose dependency in the time to recovery of proprioception. At the highest doses 54 and 81 mg/kg/h all subjects had recovered proprioception at 45 minutes after end of infusion.

Summary of efficacy results

The overall quality of sedation was assessed 60 min after the end of administration of AZD3043 by asking the healthy volunteer and the investigator the question “How was the sedation?” (excellent, very good, good, fair or poor). The 5 healthy volunteers that had been sedated all rated the quality of sedation as excellent or very good. The investigator rated the quality of sedation as very good for 4 healthy volunteers and as poor for 1 healthy volunteer in the 27 mg/kg/h dose group due to disturbing movements.

The overall quality of anaesthesia as judged by the healthy volunteer was assessed 60 minutes after the end of administration of AZD3043 by answering the question “How was the anaesthesia?” (excellent, very good, good, fair or poor). Of 24 anaesthetized healthy volunteers 23 rated the quality of anaesthesia as good to excellent. The remaining healthy volunteer rated the quality of anaesthesia as poor.

The overall quality of anaesthesia was assessed by the investigator 60 minute after end of administration for the 24 healthy volunteers that were anaesthetized. The overall score was a composite score based on 4 subtests (Body movement, Respiration, Wakefulness/Awareness and Vital signs). The overall quality of anaesthesia was based on the sum of the subtest results but if any subtest had a score of 3 (worst), the overall quality of anaesthesia was considered to be Poor. The quality of anaesthesia was rated by the investigator as good to excellent at doses of 12 mg/kg/h and 18 mg/kg/h. At doses of 27 mg/kg/h and above, the overall quality of anaesthesia was judged by the investigator to be either fair or poor, based on one or more of the following: an increase in heart rate of more than 40%, presence of disturbing movements and/or the need for respiratory support.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of IP due to adverse events (DAEs), or any other significant adverse event (OAEs) in the study. A total of 26 adverse events occurred in 16 of the 53 subjects. For 20 out of the 26 adverse events, the investigator considered that there was a reasonable possibility that the event may have been caused by AZD3043. Adverse events occurring in more than one subject were headache, chest discomfort, nausea, erythema and dyspnoea. All of the AEs were of mild or moderate intensity. No spontaneous reports of pain on injection were reported. The frequency of AEs did not increase and the character of the AEs did not change with increased doses. From the three subjects who experienced erythema after the start of the infusion, two experienced simultaneous dyspnoea and chest pressure but without ECG, vital signs or laboratory changes. Erythema was not accompanied by any other clinical relevant abnormal signs. Nausea occurred in two subjects after the stop of the infusion.

There were no clear or clinically relevant trends or treatment related changes in laboratory values, systolic blood pressure, diastolic blood pressure or mean arterial blood pressure in subjects exposed to AZD3043 during the study.

Increases in the heart rate due to sinus tachycardia were clearly observed during administration of AZD3043 at infusion rates of 27 mg/kg/h and higher. The increase in heart rate began shortly after the start of the infusion and returned to near baseline at about 15 minutes after the end of infusion. The increase in heart rate appeared to be dose-related. At the highest dose panel (81 mg/kg/h), the mean heart rate was approximately 130 beats per minute around 20 minutes after the start of infusion. Changes in heart rate were not associated with changes in the blood pressure. Both the supine systolic and diastolic blood pressures were maintained.

A number of moderate QTc shortenings were observed in the high dose groups (up to 40 ms in the highest dose panel, 81 mg/kg/h). The QTc shortenings seemed related to the increase in heart rate. No QTc prolongation of more than 30 ms was observed.

There were no clinically relevant treatment-related changes or trends in peripheral oxygen saturation or respiratory frequency in subjects exposed to AZD3043 during the study.

Occasional low $EtCO_2$ values were the result of apnoeas or pauses of breath of <30 seconds. A trend of decreased $EtCO_2$ was observed in the 27 mg/kg/h dose panel while with the higher dosages (36 to 81 mg/kg/h), a trend of increased $EtCO_2$ was seen during the AZD3043 infusion. Noted, however, was that the arterial plasma CO_2 concentration in all dose panels (including 27 mg/kg/h, either remained the same or showed a mild increase. Dose levels lower than 27 mg/kg/h did not show any consistent pattern for the changes in $EtCO_2$.

There were 3 episodes of apnoea (≥30 s) in subjects exposed to AZD3043 during the study (3, 12 and 27 mg/kg/h. In none of the subjects the SpO_2 fell below 94%. None of the subjects needed assisted breathing during the study. In the 12 mg/kg/h dose panel subjects were snoring but resisted chin lift. In the 18 to 54 mg/kg/h dose panels some subjects received chin

lift or oral airway because of snoring. In the 81 mg/kg/h dose panel all subjects needed chin lift. Except for snoring there were no clinically relevant treatment-related changes or trends in respiratory pattern in subjects exposed to AZD3043 during the study.

Involuntary movements were observed in the majority of anaesthetized healthy volunteers in the dose groups 27 to 81 mg/kg/h. The movements began shortly after the start of infusion and ceased shortly after stopping. The movements consisted of shivering and to a varying extent slow but strong internal rotation of the limbs. These were accompanied by an increase in muscle tone. The vast majority of the healthy volunteers displayed a calm demeanor.