AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3043
Study Code	D0510C00002
Edition Number	1
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Phase I, Single Centre, Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous AZD3043 after a Single Ascending Bolus Dose (Part A), and a Single Ascending Bolus Dose Followed by a Single Infusion Dose (Part B) in Volunteers Who are Healthy Males or Females of Non-Childbearing Potential (age range 18-65 years)

Study dates: First subject enrolled: 10 September 2009
Last subject last visit: 11 December 2009

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).	Adverse events Laboratory variables ECG: 12-lead paper ECG and 3-lead telemetry Vital signs: Blood pressure, Pulse, Body temperature SpO_2 and $EtCO_2$, respiratory pattern, respiratory frequency and occurrence of apnea 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 administration of single ascending doses of AZD3043	For AZD3043: C_{max} (in part B: bolus C_{max} and infusion C_{max}), AUC, AUC_{last}, t_{max}, t_{last}, $t_{½\lambda z}$, λ_z, CL, V_{ss}, V_z and MRT. For the metabolite THRX-108893 (where possible): C_{max}, AUC_{last}, AUC, t_{max}, $t_{last,}$ $t_{½\lambda z}$ and λ_z,	PK
To assess the onset of sedation/anaesthesia by means of Modified Observers Assessment of Alertness/Sedation (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	Clinical signs, orientation and proprioception (including Romberg's sign)	PD

Objectives	Outcome variables	Type
To evaluate the quality of sedation/anaesthesia by an overall assessment	Quality of sedation (investigator and subject) Quality of anaesthesia (investigator and subject)	Efficacy
Exploratory	.	
To investigate the relationship between AZD3043 exposure and different measures of clinical outcome including efficacy and safety (Not reported in this CSR.)	Not reported in the CSR	
To correlate BuChE phenotype and BuChE genotype. (Not reported in this CSR)	Not reported in the CSR	
To collect and store an optional DNA sample for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD3043 (see Appendix D of the Clinical Study Protocol). (Not reported in this CSR)	Not reported in the CSR	

Study design

AZD3043 is an investigational agent for sedation and anaesthesia. This was an open label, uncontrolled phase I study in two parts. In Part A, single bolus doses of AZD3043 were given as intravenous infusions over 60 seconds in 5 dose panels. In Part B, a single bolus dose over 60 seconds was followed by an infusion dose during 30 min in 4 dose panels. After each dose panel a Safety Review Committee evaluated all available safety, tolerability, pharmacokinetics and pharmacodynamics of AZD3043 and decided the next dose.

Target subject population and sample size

The target population for this study was healthy men and women of non-childbearing potential aged 18 to 65 years.

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

The investigational product was an emulsion of 60 mg/mL AZD3043 (batch no F13478) administered from 1 or 2 syringes of 50 mL. The study was performed as an open label study and no blinding procedures were used. In Part A, single bolus doses of AZD3043 were given as intravenous infusions over 60 seconds. In Part B, a single bolus dose over 60 seconds was followed by an infusion dose during 30 min.

Duration of treatment

Single dose

Statistical methods

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

Subject population

In total, 72 healthy volunteers (64 male and 8 female; 70 white and 2 black or African american) aged 20 to 65 years, were included in the study at 1 study site. Each received 1 single dose administration of study drug during the planned treatment visit. All included healthy volunteers completed the study. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

Part A – bolus dose

For AZD3043, the geometric mean arterial C_{max} and AUC at the highest bolus dose (6 mg/kg/min) were 134 µM (highest individual 200 µM) and 623 µM*min (highest individual 847 µM*min), respectively. Corresponding estimates obtained at the lowest dose level (1 mg/kg/min) were 26 µM (highest individual 41 µM) and 118 µM*min (highest individual 182 µM*min), respectively. The geometric mean venous C_{max} at 6 mg/kg/min was 42 µM (highest individual 120 µM; exceeding the pre-defined C_{max} exposure limit of 100 µM of AZD3043 in venous plasma). The interindividual variability (CV% in each dose panel) of arterial and venous C_{max} was 21 to 104%, respectively. Corresponding CV% for the arterial AUC was 18 to 39%.

For THRX-108893, the geometric mean arterial C_{max} and AUC at 6 mg/kg/min were 21.8 µM and 1474 µM*min, respectively. The geometric mean venous C_{max} at 6 mg/kg/min was 20.7 µM. The interindividual variability (CV% in each dose panel) of arterial and venous C_{max} was 9 to 27%. Corresponding CV% for arterial AUC was 13 to 28%.

The arterial mean $t_{½\lambda z}$ and median t_{max} of AZD3043 ranged between 9 and 14 min and 0.92 and 1.9 min, respectively. Corresponding mean CL, V_{ss} and V_z were 1.9 to 2.3 L/min, 13 to 20 L and 25 to 41 L, respectively. The arterial mean $t_{½\lambda z}$ and median t_{max} of THRX-108893 ranged between 34 and 39 min and 15 min, respectively.

According to the power model, the exposure of AZD3043 and THRX-108893 in arterial and venous plasma increased proportionally with increasing doses. These results were in agreement with dose *vs* CL, $t_{½\lambda z}$, V_{ss} and V_z.

Part B – bolus dose + infusion dose:

For AZD3043, the geometric mean arterial C_{max} after bolus (C_{maxB}), after infusion (C_{maxI}) and AUC, at 4 mg/kg/min + 40 mg/kg/h were 95 µM (highest individual 141 µM), 64 µM (highest individual 73 µM) and 2594 µM*min (highest individual 3014 µM*min), respectively. The geometric mean venous C_{max} at 4 mg/kg/min + 40 mg/kg/h was 52 µM (highest individual 77 µM).

For THRX-108893, the geometric mean arterial C_{max} and AUC at 4 mg/kg/min + 40 mg/kg/h were 109 µM and 9220 µM*min, respectively. The geometric mean venous C_{max} at 4 mg/kg/min + 40 mg/kg/h was 109 µM (highest individual 180 µM). The interindividual variability (CV% in each dose panel) of arterial C_{max} and AUC were 16 to 29%, and 10 to 29%, respectively. The corresponding interindividual variability of venous C_{max} was 22 to 30%.

The arterial mean $t_{½\lambda z}$ and median t_{max} of AZD3043 ranged between 12 and 17 min and 0.86 and 1.9 min, respectively. The arterial mean $t_{½\lambda z}$ and median t_{max} of THRX-108893 ranged between 34 and 38 min and 32 and 37 min, respectively.

According to the power model, the bolus and infusion C_{max} of AZD3043 and C_{max} and AUC of THRX-108893 in arterial plasma increased proportionally with increasing doses. This was also the case for venous C_{max} of AZD3043. The arterial AUC of AZD3043, venous Cmax of THRX-108893 and venous AUC of THRX-108893 increased slightly more than proportionally in relation to dose.

Summary of pharmacodynamic results

Part A – bolus dose

MOAA/S < 4 was observed in 3, 5 and 8 healthy volunteers in the 1.5, 4 and 6 mg/kg/min dose groups respectively. In the 4 and 6 mg/kg/min dose groups, 5 and 8 healthy volunteers respectively reached MOAA/S 0 or 1.

A dose related decrease was seen in BIS with a minimum at 2 to 3 min after the start of administration. At 1 mg/kg/min the BIS decreased to a minimum of around 80 while for the 4 and 6 mg/kg/min dose groups the minimum BIS was around 45.

At a dose of 1, 1.5 and 2 mg/kg/min 1, 3 and 4 healthy volunteers respectively showed clinical signs indicating onset of sedation/anaesthesia (either loss of handgrip, loss of eye lash reflex or loss of response to oral command). In the dose panels of 4 and 6 mg/kg/min, all healthy volunteers displayed all clinical signs of anaesthesia. The time to clinical signs of onset of anaesthesia decreased with dose. At a dose of 4 and 6 mg/kg/min all clinical signs of onset of anaesthesia occurred at around 1 to 2 min after the start of administration. In general, the time to return of response to oral command increased with dose. The median time to return of response to oral command and spontaneous eye opening was 3 min after the end of administration at a dose of 2 mg/kg/min, between 3.5 and 8 min at a dose of 4 mg/kg/min and 6 to 8 min at a dose of 6 mg/kg/min.

The time required to answer correctly to all 3 questions in the orientation assessment increased with dose and ranged from 5 min (1, 1.5 and 4 mg/kg/min) to 15 min (6 mg/kg/min) after end of administration.

Proprioception was assessed starting at 30 min after the end of infusion. All healthy volunteers had recovered proprioception at 30 min after the end of infusion except for one healthy

volunteer in the 2 mg/kg/min group who had recovered proprioception at 45 min after the end of infusion.

Part B – bolus dose + infusion dose

MOAA/S<4 was seen in 1 and 4 healthy volunteers in dose groups 0.8 mg/kg/min + 10 mg/kg/h and 1 mg/kg/min + 15 mg/kg/h respectively, with a minimum MOAA/S of 3 and 1 respectively, after 21 min. In dose groups 3 mg/kg/min + 30 mg/kg/h and 4 mg/kg/min + 40 mg/kg/h all volunteers reached a MOAA/S 0 at 21 and 3 minutes after the start of the administration respectively

The mean BIS decreased with increasing doses of AZD3043. A decrease in BIS was seen for all doses of AZD3043. The minimum mean BIS was between 70 and 80 for the two lowest dose groups and below 50 for the two highest dose groups. The decline in BIS levelled off between 20 and 30 minutes after the start of administration in the two lowest dose groups.

In the lowest dose group (0.8 mg/kg/min + 10 mg/kg/h) 5 volunteers lost handgrip but there was no loss of eye lash reflex or loss of response to oral command. In the 1 mg/kg/min + 15 mg/kg/h dose group 6 healthy volunteers lost handgrip while loss of eyelash reflex and loss of oral command was reported for 2 healthy volunteers each. In the two highest dose groups, all volunteers displayed all clinical signs of anaesthesia. Clinical signs of onset of anaesthesia occurred significantly earlier in the two highest dose groups when compared to the lower dose groups. In the two highest dose groups the median time to all clinical signs of onset of anaesthesia ranged from 0.9 to 1.9 min after the start of administration.

In general, the time to return of response to oral command increased with dose. The median time to return of response to oral command and spontaneous eye opening was between 3 and 8 min after the end of administration at a dose of 1 mg/kg/min + 15 mg/kg/h and 3 mg/kg/min + 30 mg/kg/h and 14 min at a dose of 4 mg/kg/min + 40 mg/kg/h.

The time required to answer correctly to all 3 questions in the orientation assessment increased with dose and ranged from 15 min (0.8 mg/kg/min + 10 mg/kg/h) to 25 min (3 mg/kg/min + 30 mg/kg/h) after the end of administration

Proprioception was assessed starting at 30 minutes after end of infusion. All healthy volunteers had recovered proprioception at 30 minutes after end of infusion except for one volunteer in the 4 mg/kg/min + 40 mg/kg/h who had recovered proprioception at 45 minutes after the end of infusion.

Summary of efficacy results

The quality of sedation was rated as fair, good, very good or excellent by volunteers and investigator except as poor in 1 healthy volunteer at a dose of 2 mg/kg/min, due to headache and nausea and vomiting. The quality of anaesthesia was rated as fair, good, very good or excellent by volunteers but generally as poor by the investigator in the two highest dose groups in both Part A and Part B, due to increases in heart rate and disturbing movements.

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 35 non-serious adverse events occurred in 21 of the 72 healthy volunteers. All of the AEs were of mild or moderate intensity except for 1 period of vomiting of severe intensity in one healthy volunteer in the 2 mg/kg/min group. For 26 out of the 35 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 1 healthy volunteer were headache, nausea, vomiting and fatigue. Nausea was not observed in the 2 lowest dose groups of both parts A and B, which is suggestive of a possible dose relationship. Nausea was accompanied by vomiting in 3 healthy volunteers. The frequency of AEs did not increase and the character of the AEs did not change with increased doses. No spontaneous reports of pain on injection were reported.

One healthy volunteer in the 1 mg/kg/min + 15 mg/kg/h group experienced chest discomfort of moderate intensity that started shortly after the bolus infusion of AZD3043, but after the first sedative effects, and lasted for only approximately 15 s. In the 12-lead ECGs, vital signs and laboratory of this 24 year old healthy volunteer, no significant abnormalities were observed. This healthy volunteer showed minimal flushing.

The comparison of the baseline laboratory data with the data from Day 2 revealed non-significant changes in some of the plasma parameters (increase in e.g. CK, albumin, glucose, leucocytes; decrease in e.g. potassium). The observed apparent shifts mostly remained within the normal reference laboratory ranges and were not recognized as being dose-dependent. Therefore the data did not describe a consistent trend that would suggest a clear treatment effect of AZD3043. In addition, these observations were not associated with any of the reported AEs.

Increases in the heart rate (HR) due to sinus tachycardia were observed during administration of AZD3043. The increase in HR began shortly after the start of the infusion and returned to near baseline within 10 in after the end of infusion. The increase in HR appeared to be dose-related. The maximum mean increase in HR was about 10 to 15 bpm in the two lowest dose groups of parts A and B. In the highest dose in part A (6 mg/kg/min) an increase in mean HR to around 100 bpm (40 bpm increase from baseline) was observed 2 minutes after start of administration. In the highest dose groups in part B the mean HR increased to around 100 bpm (20 to 30 bpm increase from baseline) at the end of the infusion. Changes in HR were not associated with significant changes in the blood pressure and the observed apparent changes in the HR were not causally associated with any of the reported AEs.

A dose dependent increase in blood pressure was observed. Increases of up to 10 to 17 mmHg were observed in mean arterial, systolic and diastolic blood pressure at 5 to 15 min after the start of administration in the 4 mg/kg/h, 6 mg/kg/h and 4 mg/kg/h + 40 mg/kg/min dose groups in part A and B. A decrease of 5 to 9 mmHg in mean arterial blood pressure and systolic blood pressure was observed in the 3 mg/kg/min + 30 mg/kg/h group in Part B at between 5 and 15 min after the start of administration. There were no clear trends in changes in blood pressure in other dose groups.

A number of moderate QTcF shortenings of up to 24 ms (mean change from baseline) were observed in the high dose groups, at 3 min after the start of infusion in the 6 mg/kg/min and at the end of infusion in the 4 mg/kg/min + 40 mg/kg/h dose group. The QTcF shortenings seemed related to the increase in heart rate described above. No individual QTcF shortening of more than 41 ms and no QTcF prolongation of more than 29 ms were observed.

SpO_2 did not fall below 94% except for an incidental value of 93% in 1 healthy volunteer in the 4 mg/kg/min dose group 3 min after start of administration, and for an isolated value of 80% that was considered an artefact.

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 6 mg/kg/min and 4 mg/kg/min + 40 mg/kg/h dose panel. Volunteers in lower dose levels showed minimal changes in $EtCO_2$.

Apnoea was defined as a pause of breath of ≥30 seconds or if the pause resulted in SpO_2 falling to 93% or less. The number of apnoeas increased with dose. There were episodes of apnoea of up to 97 seconds in 13 healthy volunteers exposed to AZD3043 during the study. All healthy volunteers breathed spontaneously. None of the healthy volunteers had a persistent decline in SpO_2. None of the healthy volunteers needed assisted breathing or artificial/ mechanical ventilation during the study. However in the two highest dose groups in part A (5 out of 16 volunteers) and in the two highest dose groups in part B (15 out of 16 volunteers) the use of chin lift and/or oral-pharyngeal/naso-pharyngeal airway was necessary to maintain a clear airway. Forced, irregular, shallow and deep breathing occurred more frequently in the high dose groups than at lower doses.

There were no clinically relevant treatment-related changes or trends in body temperature in healthy volunteers exposed to AZD3043 during the study.

Involuntary movements were not observed in the 3 lowest dose groups of Part A. Minor involuntary movements were observed in some healthy volunteers in the 2 lowest dose groups of Part B. Disturbing movements were observed in 1 volunteer in each of the 2 highest dose groups of Part A, and in 3 and 6 volunteers in the two highest dose groups of Part B, respectively. The movements began shortly after the start of infusion and ceased shortly after end of administration. The movements consisted of twitching, chewing, and to a varying extent slow but strong internal rotation of the limbs and torso. These were accompanied by an increase in muscle tone. The vast majority of the healthy volunteers displayed a calm demeanor and none of the involuntary movements were reported as adverse events.