AstraZeneca

**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | AZD6765 |
| Study Code | D6702C00008 |
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# A Phase I Open-label, Fixed Sequence Study to Determine the Effect of Multiple Intravenous Doses of AZD6765 on the Pharmacokinetics of Oral Midazolam (*CYP3A4* Substrate) in Healthy Subjects

**Study dates:** First subject enrolled: 10 February 2010
Last subject last visit: 11 May 2010

**Phase of development:** Clinical pharmacology (I)

**Co-ordinating Investigator:**

**Sponsor's Responsible Medical Officer:**

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

## Study center(s)

The study was conducted at a single center:

## 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** | |
| The primary objective of this study was to determine the effects of repeated intravenous doses of AZD6765 on the pharmacokinetic profile of a *CYP3A4* substrate (midazolam). | $C_{max}$, $t_{max}$, AUC, $AUC_{(0-t)}$, $\lambda_z$, $t_{1/2}$, CL/F, $V_z$/F of midazolam alone and AZD6765 plus midazolam | Pharmacokinetic |
| **Secondary** | **Secondary** | |
| The secondary objectives were to:<br>Evaluate the safety and tolerability of repeated intravenous doses of AZD6765 in combination with oral midazolam. | Adverse events, supine and standing blood pressure and pulse rate, oral temperature, electrocardiogram variables, physical examination, clinical laboratory variables, Clinician Administered Dissociative States Scale, Columbia Suicide Severity Rating Scale, neurological examination | Safety |
| Evaluate the pharmacokinetics of AZD6765 at steady state. | $AUC_\tau$, $C_{max}$, $t_{max}$, $C_{min}$, $t_{min}$, $C_{avg}$, $\lambda_z$, $t_{1/2}$, CL, $V_{ss}$, $V_z$ of AZD6765 | Pharmacokinetic |
| **Exploratory** | **Exploratory** | |
| The exploratory objectives were to:<br>Evaluate the pharmacodynamic effects of AZD6765 in combination with midazolam on selected psychometric assessments using a Bond-Lader Visual Analog Scale, and compare to treatment with midazolam alone. | Bond-Lader Visual Analog Scale scores | Pharmacodynamic |
| Evaluate changes in renal function by assessing for quantitative analytes and electrolytes in urine, or by exploratory analysis for proximal tubular injury; additionally, urine aliquots for exploratory renal biomarker analysis were collected. | Renal biomarkers, including α-glutathione-S-transferase and Kidney Injury Molecule-1 | Other |
| Collect and store a blood sample for possible future genotyping. | DNA exploratory research | Pharmacogenetics |

## Study design

This was a single-center, open-label, fixed-sequence, nonrandomized study in healthy male and female volunteers.

The study consisted of a screening period within 3 to 30 days of dosing, an in-house treatment period (Day -2 to Day 7), and a follow-up visit 7 to 10 days after discharge from the treatment period.

On Day -1, all volunteers received a single dose of 5 mg midazolam oral solution (midazolam alone treatment). On Days 1 to 6, volunteers received a 60-minute infusion of AZD6765 (150 mg) once daily. On Day 6, volunteers received a single dose of 5 mg midazolam oral solution at the completion of the 60-minute infusion of AZD6765 (AZD6765 plus midazolam). The volunteers were discharged on Day 7, following the completion of all scheduled procedures and assessments and returned to the Clinical Research Unit 7 to 10 days after discharge for the follow-up visit.

**Target subject population and sample size**

Forty-six healthy male and female (women of nonchildbearing potential or on an accepted method of contraception) volunteers within an age range of 18 to 55 years, inclusive, were enrolled.

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

AZD6765 150 mg (15 mg/mL, intravenous infusion), administered as a 60-minute infusion, Batch number 09-008862AZ

Midazolam 5 mg (2 mg/mL oral solution), administered via an oral syringe, Batch number 957S1 7A

**Duration of treatment**

The duration of each volunteer's participation was approximately 49 days, including a screening period within 3 to 30 days of dosing, a treatment period of 9 days and 8 nights, and a follow-up visit 7 to 10 days after discharge from the treatment period.

All volunteers received a single, oral dose of midazolam (5 mg) on Day -1 and Day 6. Volunteers received a single, daily intravenous infusion of AZD6765 (150 mg) on Days 1 to 6.

**Statistical methods**

Safety data were summarized using descriptive statistics.

Pharmacodynamic variables (Bond-Lader Visual Analog Scale) were summarized using descriptive statistics and plotted. There was no formal statistical analysis of the pharmacodynamic variables.

The pharmacokinetic concentrations and parameters for midazolam and AZD6765 were summarized using descriptive statistics and plotted as appropriate.

Pharmacokinetics of Midazolam:

The natural log-transformed variables AUC, $AUC_{(0-t)}$, and $C_{max}$ were compared between treatments. Estimates of the mean difference between treatments ([AZD6765 + midazolam] – midazolam alone) and corresponding 90% confidence intervals were calculated. The mean differences and the confidence limits were transformed back to the original scale in order to give estimates of the true ratios ([AZD6765 + midazolam] / midazolam alone) and 90% confidence intervals for these ratios.

No clinically relevant effect on the pharmacokinetics of midazolam after coadministration of AZD6765 was concluded if the two-sided 90% confidence intervals for the ratios were within the range of 80.00% to 125.00%.

Pharmacokinetics of AZD6765:

Steady state was assessed by comparing the log trough concentrations on Days 4, 5, 6, and 7 by comparing each day with the remaining later days, using a mixed-effect model with day as fixed effect and volunteer as random effect. The mean differences and the confidence limits were transformed back to the original scale in order to give an estimate of the true ratios and 90% confidence intervals for these ratios.

**Subject population**

The first volunteer was enrolled on 10 February 2010 and the last volunteer completed the study on 11 May 2010. Forty-six volunteers were enrolled and received investigational product. Of the 46 volunteers enrolled in the study, 39 completed the study. Four volunteers discontinued due to loss to follow-up (E0001027, E0001034, E0001056, and E0001070); 1 volunteer discontinued due to volunteer decision (E0001057); 1 volunteer discontinued due to an adverse event of mild infusion site pain (E0001051); and 1 volunteer was discontinued due to Sponsor decision (the volunteer experienced more frequent premature ventricular contractions upon dosing of AZD6765 [E0001064]).

All 46 volunteers enrolled in the study were included in the PK analyses, summaries, and statistical comparisons of midazolam and/or AZD6765 until their time of discontinuation, except for subject E0001078 who was excluded from AZD6765 PK analyses and summarization on Day 6 (due to a discontinuity/prolongation of AZD6765 dosing) but was included in the midazolam PK analyses, summarization, and statistical comparisons on this day.

All 46 volunteers who were enrolled in the study were included in the safety and pharmacodynamic analyses.

The volunteer population consisted of 28 healthy males and 18 healthy females with a mean age of 28 years and a mean body mass index of 25.4 $kg/m^2$.

## Summary of efficacy results

Not applicable.

## Summary of pharmacokinetic results

The results of statistical comparisons of the primary midazolam pharmacokinetic parameters are presented below:

**Table S2 Statistical comparison of key midazolam pharmacokinetic parameters**

| Parameter | Treatment | N | Geo. LS Mean | 95% CI | Comparison (AZD6765 + Midazolam vs. Midazolam Alone) | |
|---|---|---|---|---|---|---|
| | | | | | Ratio (%) | 90% CI (%) |
| AUC (ng*h/mL) | Midazolam Alone | 46 | 54.94 | 47.99, 62.89 | 95.22 | 89.30, 101.54 |
| | Midazolam + AZD6765 | 43 | 52.31 | 45.64, 59.95 | | |
| $AUC_{(0-t)}$ (ng*h/mL) | Midazolam Alone | 46 | 51.86 | 45.32, 59.35 | 95.15 | 89.17, 101.53 |
| | Midazolam + AZD6765 | 43 | 49.35 | 43.07, 56.54 | | |
| $C_{max}$ (ng/mL) | Midazolam Alone | 46 | 25.49 | 22.44, 28.96 | 91.63 | 84.40, 99.47 |
| | Midazolam + AZD6765 | 43 | 23.36 | 20.52, 26.58 | | |

Note: Results are based on a linear mixed-effects model with terms for treatment as a fixed effect and volunteer as a random effect.
CI confidence interval; Geo.geometric; LS least-squares; N number of volunteers/observations.

In *in vitro* studies, AZD6765 was found to be a weak inhibitor of cytochrome P450 3A4 (*CYP3A4*) (Ki value of 5.35 µg/mL [27.0 µM]). This study determined that when administered as multiple doses of 150 mg daily, AZD6765 does not affect the pharmacokinetic profile of midazolam, a *CYP3A4* substrate. The geometric least-squares mean ratios and 90% confidence intervals for midazolam AUC, $AUC_{(0-t)}$, and $C_{max}$ were within the 80% to 125% limits when AZD6765 plus midazolam treatment was compared to midazolam alone, demonstrating that the 2 treatments were equivalent. Midazolam mean CL/F (91.0 and 95.2 L/h for midazolam alone and AZD6765 plus midazolam, respectively) and mean $t_{1/2}$ (3.26 and 3.18 hours for midazolam alone and AZD6765 plus midazolam, respectively) were also similar between treatments. Thus, this study demonstrates that AZD6765 does not inhibit *CYP3A4* activity at clinically relevant concentrations.

Statistical and graphical assessment of AZD6765 trough concentrations on Days 4 to 7 indicated that steady state was achieved by Day 6. AZD6765 mean $AUC_{\tau}$ and $C_{max}$ were 18500 ng*h/mL and 1510 ng/mL, respectively. AZD6765 mean $t_{1/2}$, CL, and $V_{ss}$ were 10.4 hours, 8.09 L/h, and 122 L, respectively, which are generally similar to estimates of these

parameters obtained from previous multiple-dose studies with AZD6765 in healthy adult volunteers.

**Summary of pharmacodynamic results**

Based on Bond-Lader Visual Analog Scale scores evaluating alertness, volunteers tended to be less alert and more sedated immediately after midazolam and AZD6765 dosing, though the effect tended to wear off with time after dosing as well as following multiple dosing with AZD6765 (ie, effect on Day 6 was less than Day 1). No synergistic effect of midazolam and AZD6765 coadministration was observed (on Day 6). No changes or treatment-related trends were observed in most of the mood-related visual analog scale scores.

**Summary of pharmacokinetic/pharmacodynamic relationships**

Not applicable.

**Summary of pharmacogenetic results**

A summary of pharmacogenetic results will be provided in a separate report.

**Summary of safety results**

In this population of healthy male and female volunteers, 150-mg AZD6765 was generally well tolerated when administered intravenously for 6 days and in combination with a single dose of 5 mg midazolam. There were no deaths or SAEs reported during study conduct. One volunteer (E0001051) was discontinued from the study due to an AE of infusion site pain 11 minutes following the start of the 150-mg AZD6765 infusion. The AE was considered to be mild in intensity and nonserious, and the AE resolved spontaneously approximately 1 day later. The Investigator considered the AE to be related to IP; however, the Investigator indicated that the volunteer was discontinued primarily due to the inability to administer IP and not due to side effects of the IP. Another volunteer (E0001064) was noted to have an isolated occurrence of premature ventricular contractions on the Day 1 ECG. As a special precaution in this volunteer, the volunteer was placed on continuous ECG monitoring via telemetry. Upon dosing of AZD6765, the volunteer began to have more frequent premature ventricular contractions. Dosing was discontinued and the volunteer was discontinued from the study due to Sponsor decision.

A significant other adverse event of interest occurred in 1 volunteer (E0001085) receiving AZD6765 alone. The volunteer experienced symptomatic postural hypotension with an onset on Day 1 (approximately 1 hour following the stop of the AZD6765 infusion). The postural hypotension was considered mild in severity and related to study treatment. The AE lasted 7 minutes and the volunteer recovered from the event.

Dizziness was the most frequently reported AE in volunteers receiving AZD6765 alone. A greater number of volunteers in the AZD6765 alone treatment group reported euphoric mood compared to the midazolam alone group and the AZD6765 plus midazolam group (no volunteers in either treatment group reported euphoric mood).

Anemia was the most frequently reported AE in volunteers receiving AZD6765 plus midazolam. Seven volunteers receiving AZD6765 plus midazolam experienced decreases in hemoglobin, hematocrit, and/or RBCs at the follow-up visit (Day 14 of the study) which were reported as AEs of mild anemia. Decreases in hematocrit, hemoglobin, and RBCs are not unusual in studies during which multiple blood draws are collected from each volunteer. Due to the sequential study design, the AZD6765 plus midazolam was the last treatment to be received by volunteers and the last of the 3 serial PK blood sample collections. All but one of the occurrences of anemia were assessed as not related to study treatment (anemia in Volunteer E0001037 was assessed as asymptomatic but related to study treatment). There were no associated symptoms with the decreases in hemoglobin, hematocrit, or RBCs, and hematocrit and hemoglobin values returned to baseline values by the end of the study.

In general, there were no significant changes in vital signs, ECG findings, physical examination findings, neurological examination findings, or CADSS during study conduct.

Pregnancy was not considered to be an adverse event in this study. Volunteer E0001005 tested positive for pregnancy via urine and serum hCG at the follow-up visit. The volunteer elected to continue the pregnancy. The volunteer is currently in her second trimester and appears to have a normal pregnancy. No fetal abnormalities have been reported as of the time of the writing of this clinical study report. The outcome of the pregnancy is being followed.