AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00010
Edition Number	1
Date	19 March 2009

A Randomised, Open-label, Crossover, Phase I Study to Assess the Effect of Multiple Oral Doses of ZD4054 on the Pharmacokinetics of a CYP450 3A Probe (midazolam) in Healthy Male Subjects

Study dates: First healthy volunteer enrolled: 11 July 2008
Last healthy volunteer completed: 28 August 2008

Phase of development: Clinical pharmacology (I)

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

Study period		Phase of development
First healthy volunteer enrolled	11 July 2008	Clinical pharmacology (I)
Last healthy volunteer completed	28 August 2008	

Publications

None at the time of writing this report.

Objectives

Primary objective of this study was to evaluate the effect of ZD4054 on the pharmacokinetics of midazolam.

The secondary objectives of this study were:

- To demonstrate exposure to ZD4054.
- To assure the safety of the healthy volunteers dosed.

The exploratory objective of this study was to evaluate the effect of ZD4054 on the pharmacokinetics of 1-hydroxy and 4-hydroxy midazolam.

Study design

The clinical study was an open-label, randomised crossover study to investigate the effect of ZD4054 on the pharmacokinetics of midazolam.

Target healthy volunteer population and sample size

Healthy male volunteers aged between 18 and 65 years (inclusive) with a Body Mass Index (BMI) of 18 to 30 kg/m^2 (inclusive).

Investigational products: dosage, mode of administration and batch numbers´

Drug: ZD4054
Formulation: Tablet
Strength: 10 mg
Dose: 10 mg as single dose on 7 consecutive days in Treatment B
Batch number: 6710.1/1

Drug: midazolam
Formulation: Tablet
Strength: 7.5 mg
Dose: one single dose in the morning of Day 1 in Treatment A,
one single dose in the morning of Day 6 in Treatment B
Batch number: B1594G02

On Day 6 of Treatment B, ZD4054 was administered first, immediately followed by midazolam, together with 200 mL of water.

Duration of treatment

The study consisted of 2 treatment periods:

- Treatment A: single oral 7.5 mg-dose of midazolam.
- Treatment B: ZD4054 (10 mg) given once daily for 7 consecutive days. Single oral 7.5 mg-dose of midazolam given on Day 6 of daily dosing of ZD4054.

The wash-out period between both treatment periods was at least 1 week after the last pharmacokinetic (PK) sample of the previous treatment period. Considering a Screening period of 2 to 21 days before the first administration of the investigational product and a Follow-up visit between 7 to 14 days after final administration of the investigational product the total duration of this study for a healthy volunteer was between 18 and 44 days.

Criteria for evaluation - pharmacokinetics (main variables)

Primary endpoints: C_{max}, AUC_{0-t} and AUC for midazolam following the 2 treatments.

In addition: t_{max}, $t_{1/2}$, k_{el}, CL/F, V_{ss}/F and MRT were also to be reported.

Secondary endpoints: Exposure to ZD4054 (Treatment B only) confirmed by collection of a pre-dose and a 2-hours post-dose sample on Days 1, 3, 5, 6 and 7 of ZD4054 dosing.

Criteria for evaluation - safety (main variables)

Vital signs, ECG, clinical chemistry, haematology, urinalysis and adverse events.

Statistical methods

AUC and C_{max} were logarithmically transformed using natural logarithms (back-transformed results were to be reported). These parameters were analysed using an analysis of variance (ANOVA) model, fitting effects for sequence, subject within sequence, period and treatment (midazolam with ZD4054 in steady state and midazolam alone).

The results of these analyses were presented in terms of geometric least square means (GLSmean) for each treatment, the treatment effect (the ratio of midazolam + ZD4054 GLSmean/ midazolam alone GLSmean) and its 90% confidence interval. An interaction between midazolam and ZD4054 was considered to have occurred if the upper limit of the confidence interval for the ratio was above 1.5.

All pharmacokinetic data were listed, and summarised by treatment using standard summary statistics.

Demography and baseline data were summarised and listed using appropriate summary statistics.

All safety data including adverse events were summarised by means of descriptive statistics. The safety data addressed the secondary objective to assure the safety of all healthy volunteers by assessment of pulse and BP, ECG, clinical chemistry, haematology and adverse events.

Subject population

In total, 12 healthy male volunteers between the age of 32 and 59 were enrolled into the study and randomised, all of them received treatment and completed the study as per protocol. All volunteers were healthy based on the screening examination, complied with the inclusion criteria and none met any exclusion criteria. The 12 subjects were all included in the safety and in the PK analysis set. No major protocol deviations were recorded.

Summary of pharmacokinetic results

The main PK parameters of midazolam derived after treatment alone and after combined treatment with ZD4054 are shown in Table S1. The results of the statistical analysis of the primary endpoints of the study are summarised in Table S2.

Table S1 Summary of pharmacokinetic parameters of midazolam (PK analysis set)

Parameter	Summary statistics	Midazolam N=12	Midazolam + ZD4054 N=12
C_{max}	Geometric mean (CV%)	37.527 (50.5)	39.424 (38.9)
[ng/mL]	n	12	12
AUC	Geometric mean (CV%)	91.458 (50.9)	109.527 (47.1)
[ng.h/mL]	n	12	12
AUC_{0-t}	Geometric mean (CV%)	89.803 (51.2)	107.901 (47.5)
[ng.h/mL]	n	12	12
t_{max}	Median (range)	0.500 (0.50 – 1.00)	0.500 (0.50 – 2.00)
[h]	n	12	12
$t_{1/2}$	Arithmetic mean (SD)	5.366 (1.059)	4.717 (1.498)
[h]	n	12	12
k_{el}	Geometric mean (CV%)	0.13224 (24.5)	0.15666 (42.5)
[1/h]	n	12	12
CL/F	Arithmetic mean (SD)	1518.20 (748.88)	1259.83 (652.03)
[mL/min]	n	12	12
MRT	Arithmetic mean (SD)	4.411 (0.932)	4.400 (1.235)
[h]	n	12	12
V_{ss}/F	Arithmetic mean (SD)	379.79 (137.79)	301.88 (89.67)
[L]	n	12	12

AUC= area under the plasma concentration-time curve; AUC_{0-t}= area under the plasma concentration-time curve from time point 0 to the time of the last quantifiable concentration; CL/F= total apparent clearance; C_{max}= maximum plasma concentration; CV= coefficient of variation; MRT= mean residence time; N= number of subjects; n = number of observation; SD= standard deviation; $t_{1/2}$= terminal half-life; t_{max}= time to reach $C_{max;}$ V_{ss}/F= volume of distribution at steady-state.

Table S2 Summary of GLSmean, geometric mean and 90% CIs for ratio of midazolam+ZD4054 versus midazolam (PK analysis set)

Pharmacokinetic parameter	Midazolam +ZD4054		Midazolam		Point estimate of GLSmean ratio of midazolam +ZD4054 to midazolam	90%CI of GLSmean ratio of midazolam +ZD4054 to midazolam
	N	GLSmean	N	GLSmean		
AUC [ng.h/mL]	12	109.5	12	91.5	1.1976	1.0469; 1.3699
AUC_{0-t} [ng.h/mL]	12	107.9	12	89.8	1.2015	1.0462; 1.3799
C_{max} [ng/mL]	12	39.4	12	37.5	1.0506	0.8378; 1.3174

AUC= area under the plasma concentration-time curve; AUC_{0-t}= area under the plasma concentration-time curve from time point 0 to the time of the last quantifiable concentration; CI= confidence interval; C_{max}= maximum plasma concentration; GLSmean= geometric least square mean; N= number of subjects.

The plasma concentration-time profile of midazolam at steady-state levels of ZD4054 was characterised on average by slightly higher plasma concentrations compared with midazolam alone. C_{max} did not markedly change at steady-state levels of ZD4054 (39.4 ng/mL) compared with midazolam alone (37.5 ng/mL) and t_{max} was achieved both at median 0.5 hours. Overall exposure (AUC) to midazolam increased at steady-state levels of ZD4054 (109.5 ng.h/mL) by about 1.2-fold versus midazolam given alone (91.5 ng.h/mL). Mean terminal half-live ($t_{1/2}$) of midazolam was 5.4 hours versus 4.7 hours upon treatment with midazolam alone and combined treatment with ZD4054.

According to the pre-defined criteria, an interaction between midazolam and ZD4054 is not indicated by the margin of the 90% CIs of the GLSmean ratios for AUC, AUC_{0-t} and C_{max}. The upper limits of the corresponding 90% CIs did not exceed a value of 1.5, indicating no clinically relevant effect of steady-state levels of ZD4054 on the primary PK parameters of midazolam.

The evaluation of ZD4054 trough and 2 hours post-dose plasma concentrations indicated achievement of steady state prior to combined dosing with midazolam.

The evaluation of the mean plasma concentration profiles and derived PK parameters of 1-hydroxy and 4-hydroxy midazolam did not indicate any marked effect on the PK of these metabolites by steady-state levels of ZD4054.

Summary of safety results

A total of 68 AEs were reported by 12 (100.0%) subjects under ZD4054 alone, while under midazolam, alone or combined with ZD4054, 10 (83.3%) and 11 (91.7%) subjects reported 14 and 13 AEs, respectively. The AEs most commonly reported under ZD4054 alone were headache and nasal congestion, while fatigue was the leading AE upon treatment with midazolam, alone or in combination with ZD4054, at comparable frequencies. Most AEs were of CTC grade 1 or 2. One fatigue (midazolam alone) was judged to be CTC grade 3 and was

classified as other significant AE. There were no discontinuations due to an AE, deaths or serious AEs during the study.

No clinically important changes in laboratory safety variables, 12-lead ECG, vital signs and physical examination. Small reductions in systolic and diastolic blood pressure were noted during treatment with ZD4054 which were not considered as of clinical relevance.

Overall, the safety profile of ZD4054 seen in this study corresponded to the known safety profile for ZD4054.