AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D0475C00011
Edition Number	1
Date	29 January 2010

A Phase I, Open-label, Multi-Centre Study in Healthy Volunteers to Estimate the Effect of Multiple Doses of AZD2066 on the Activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 by Administering a Cocktail of Caffeine, Bupropion, Tolbutamide, Omeprazole, Metoprolol and Midazolam

Study dates: First healthy volunteer enrolled: 22 June 2009
Last healthy volunteer completed: 28 September 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

The primary objective of this study was to estimate the effect of repeated doses of AZD2066 on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 activity using single oral doses of caffeine, bupropion, tolbutamide, omeprazole, metoprolol and midazolam as probe drugs.

The secondary objective of this study was to evaluate safety and tolerability of single doses of the cocktail probes after repeated doses of AZD2066 by assessment of adverse events (AEs), physical examination, laboratory variables, vital signs and electrocardiograms (ECGs).

An exploratory objective of this study was to explore the exposure of AZD2066 in plasma following repeated dosing of AZD2066 when co-administered with caffeine, bupropion, tolbutamide, omeprazole, metoprolol and midazolam.

Study design

This was a multi-centre, open-label study to investigate the effect of AZD2066 on a cocktail of cytochrome P450 probe drugs.

Target subject population and sample size

Fifteen male Caucasian healthy volunteers, aged ≥18 to ≤60 years were recruited to ensure at least 12 evaluable healthy volunteers completed the study. All healthy volunteers were extensive metabolizers with respect to CYP2C9, CYP2C19 and CYP2D6, defined as having ≥1 and ≤2 functional alleles with at least one *1 allele for each enzyme.

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

AZD2066 capsules were administered orally on Days 1 to 4 (single 12 mg dose per day) and Days 5 to 12 (single 18 mg dose per day).

On Days –3 and 10 a single oral dose of caffeine (100 mg), tolbutamide (250 mg), omeprazole (20 mg) and midazolam (7.5 mg) was administered. On Days -2 and 11 a single oral dose of

metoprolol (100 mg) was administered and on Days -1 and 12 a single oral dose of bupropion (150 mg) was administered.

Duration of treatment

The treatment period lasted for 15 days; the cocktail probes were administered alone for 3 days (Days –3 to –1) and AZD2066 was administered for 12 days (Days 1 to 12). The maximum total expected duration of the study for each healthy volunteer was 67 days.

Criteria for evaluation - pharmacokinetics (main variables)

The primary PK variables were:

- CYP1A2: ratio of plasma concentrations of paraxanthine/caffeine at 4 hours post-dose of probe on Days -3 and 10
- CYP2C9: ratio of 4-hydroxytolbutamide amount excreted in urine (Ae)/tolbutamide Ae and carboxytolbutamide Ae/tolbutamide Ae on Days -3 and 10
- CYP2C19: ratio of plasma concentrations of omeprazole/ 5-hydroxyomeprazole at 3 hours post-dose of probe on Days -3 and 10
- CYP3A4: ratio of 1'-hydroxymidazolam AUC/midazolam AUC on Days -3 and 10
- CYP2D6: ratio of plasma concentrations of α-hydroxymetoprolol/metoprolol at 4 hours post-dose of probe on Days -2 and 11
- CYP2B6: ratio of hydroxybupropion $AUC_{(0-t)}$/ bupropion $AUC_{(0-t)}$ on Days -1 and 12

Criteria for evaluation - safety (main variables)

The safety variables were AEs, physical examination, laboratory assessments (chemistry, hematology, urinalysis), vital signs (supine blood pressure and pulse) and 12-lead electrocardiogram (ECG).

Statistical methods

Bioequivalence criteria were used to assess whether multiple doses of AZD2066 had an effect on the activity of any of the CYP450 isozymes (1A2, 2C9, 2C19, 2D6, 3A4, 2B6). A lack of effect of multiple doses of AZD2066 on the activity of the CYP450s investigated was concluded if the 90% confidence interval (CI) for the geometric mean ratio of the test to reference primary outcome variable was completely contained within the acceptance range of 0.80 – 1.25.

Subject population

Fifteen healthy volunteers were randomized onto the study and received at least 1 dose of AZD2066. Fourteen healthy volunteers successfully completed the study and 1 was withdrawn due to AEs.

Table S1 Demographic characteristics

Demographic and baseline characteristic		Overall (N=15)
Sex n (%)	Male	15 (100)
	Female	0
Age (years)	Mean	28.9
	Min	19
	Median	24.0
	Max	54
Race n (%)	White	15 (100)

Summary of pharmacokinetic results

The primary PK variables are described above in the section Criteria for evaluation - pharmacokinetics (main variables).

A summary of the statistical analysis of the effect of steady state AZD2066 on the paraxanthine/caffeine plasma concentrations ratio at 4 hours is given in Table S2. A negligible effect (inhibition) of AZD2066 on CYP1A2 was indicated that is unlikely to be of clinical relevance.

Table S2 Summary of statistical analysis of plasma paraxanthine/caffeine (CYP1A2) C_{4h} ratio: PK analysis set

n		Geometric LSmean		Geometric LSmean Ratio	90% CI for Geometric LSmean Ratio
Test	Reference	Test	Reference	(Test/ Reference)	[Lower - Upper]
15	15	0.322	0.378	0.854	[0.777, 0.937]

LSmean: least squares mean
Test = AZD2066 + cocktail probes (Day 10)
Reference = Cocktail probes alone (Day -3)

A summary of the statistical analysis of the effect of steady state AZD2066 on the omeprazole/5-hydroxyomeprazole plasma concentration ratio at 3 hours is given in Table S3. AZD2066 had no effect on CYP2C19 activity.

Table S3 Summary of statistical analysis of plasma omeprazole/ 5-hydroxyomeprazole (CYP2C19) C_{3h} ratio: PK analysis set

n		Geometric LSmean		Geometric LSmean Ratio	90% CI for Geometric LSmean Ratio
Test	Reference	Test	Reference	(Test/ Reference)	[Lower - Upper]
15	15	0.924	0.888	1.040	[0.884, 1.223]

Test = AZD2066 + cocktail probes (Day 10)
Reference = Cocktail probes alone (Day -3)

A summary of the statistical analysis of the effect of steady state AZD2066 on the 1'-hydroxymidazolam/midazolam PK parameter ratios is given in Table S4. A negligible effect (inhibition) of AZD2066 on CYP3A4 was indicated that is unlikely to be of clinical relevance.

Table S4 Summary of statistical analysis of the 1'-hydroxymidazolam/ midazolam (CYP3A4) PK parameter ratios: PK analysis set

Parameter ratio	n		Geometric LSmean		Geometric LSmean Ratio	90% CI for Geometric LSmean Ratio
	Test	Reference	Test	Reference	(Test/Reference)	[Lower - Upper]
AUC	15	15	0.271	0.303	0.892	[0.777, 1.024]
$AUC_{(0-t)}$	15	15	0.265	0.296	0.897	[0.782, 1.028]
C_{max}	15	15	0.292	0.319	0.914	[0.772, 1.081]

Test = AZD2066 + cocktail probes (Day 10)
Reference = Cocktail probes alone (Day -3)

A summary of the statistical analysis of the effect of steady state AZD2066 on the 4-hydroxytolbutamide/tolbutamide PK parameter ratios is given in Table S5. A negligible effect (inhibition) of AZD2066 on CYP2C9 was indicated for Ae which is not likely to be clinically relevant. A lack of effect on CYP2C9 for AUC, $AUC_{(0-t)}$ and C_{max} can be concluded.

Table S5 Summary of statistical analysis of the 4-hydroxytolbutamide/ tolbutamide (CYP2C9) PK parameter ratios: PK analysis set

	n		Geometric LSmean		Geometric LSmean Ratio	90% CI for Geometric LSmean Ratio
Parameter	Test	Reference	Test	Reference	(Test/ Reference)	[Lower - Upper]
Ae	15	15	111.91	126.17	0.887	[0.777, 1.012]
AUC	15	15	0.0115	0.0125	0.922	[0.885, 0.960]
$AUC_{(0-t)}$	15	15	0.0110	0.0119	0.926	[0.890, 0.965]
C_{max}	15	15	0.0105	0.0107	0.982	[0.917, 1.051]

Test = AZD2066 + cocktail probes (Day 10)
Reference = Cocktail probes alone (Day -3)

A summary of the statistical analysis of the effect of steady state AZD2066 on the carboxytolbutamide/tolbutamide PK parameter ratios is given in Table S6. A negligible effect (inhibition) on CYP2C9 was indicated for Ae which is not likely to be clinically relevant. A lack of effect on CYP2C9 for AUC, $AUC_{(0-t)}$ and C_{max} can be concluded.

Table S6 Summary of statistical analysis of the carboxytolbutamide/tolbutamide (CYP2C9) PK parameter ratios: PK analysis set

	n		Geometric LSmean		Geometric LSmean Ratio	90% CI for Geometric LSmean Ratio
Parameter	Test	Reference	Test	Reference	(Test/ Reference)	[Lower - Upper]
Ae	15	15	771.30	882.23	0.874	[0.773, 0.989]
AUC	15	15	0.0414	0.0436	0.951	[0.905, 1.000]
$AUC_{(0-t)}$	15	15	0.0406	0.0428	0.950	[0.908, 0.994]
C_{max}	15	15	0.0382	0.0383	0.996	[0.934, 1.061]

Test = AZD2066 + cocktail probes (Day 10)
Reference = Cocktail probes alone (Day -3)

A summary of the statistical analysis of the effect of steady state AZD2066 on the α-hydroxymetoprolol/metoprolol plasma concentration ratio at 4 hours is given in Table S7. A weak effect (inhibition) on CYP2D6 was indicated that is unlikely to have clinical relevance.

Table S7 Summary of statistical analysis of plasma α-hydroxymetoprolol/metoprolol (CYP2D6) C_{4h} ratio: PK analysis set

n		Geometric LSmean		Geometric LSmean Ratio	90% CI for Geometric LSmean Ratio
Test	Reference	Test	Reference	(Test/ Reference)	[Lower - Upper]
14	14	0.395	0.555	0.712	[0.650, 0.780]

Test = AZD2066 + cocktail probes (Day 11)
Reference = Cocktail probes alone (Day -2)

A summary of the statistical analysis of the effect of steady state AZD2066 on the hydroxybupropion/bupropion PK parameter ratios is given in Table S8. AZD2066 had no effect on CYP2B6 activity.

Table S8 Summary of statistical analysis of the hydroxybupropion/bupropion (CYP2B6) PK parameter ratios: PK analysis set

	n		Geometric LSmean		Geometric LSmean Ratio	90% CI for Geometric LSmean Ratio
Parameter	Test	Reference	Test	Reference	(Test/ Reference)	[Lower - Upper]
$AUC_{(0-t)}$	14	14	6.8478	7.3008	0.938	[0.867, 1.015]
C_{max}	14	14	3.0380	3.0207	1.006	[0.890, 1.136]

Test = AZD2066 + cocktail probes (Day 12)
Reference = Cocktail probes alone (Day -1)

Due to failure to meet quality control criteria in the bioanalytical assay for AZD2066 concentration data were not available. Consequently, no PK analysis was performed for AZD2066.

Summary of safety results

There were no deaths or SAEs during the study. The majority of AEs were mild in intensity. The most common (number of healthy volunteers) AEs were dizziness, somnolence and insomnia. One healthy volunteer was discontinued from treatment on Day 10 and withdrawn from the study following AEs of hypomania and polydipsia. A psychiatric assessment concluded that the healthy volunteer had suffered a transient hypomanic episode probably secondary to the cocktail of medications and possibly compounded by the change in routine. Both AEs leading to the discontinuation of the healthy volunteer were considered by the Investigator to be related to the study drug.

There were no clinically relevant changes in safety laboratory variables, vital signs, ECG and physical examination.