AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00019
Edition Number	1
Date	2 October 2009

An Open-label, Randomized, 4-Period Crossover, Replicate Study to Assess the Relative Bioavailability of the Phase III and Phase IIb Formulations of AZD5672 in Healthy Male and Female Subjects

Study dates:	First subject enrolled: 9 March 2009 Last subject completed: 20 May 2009
Phase of development:	Clinical pharmacology (I)

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

Study centre

The study was conducted at one study centre at ICON Development Solutions, Skelton House, Manchester Science Park, UK.

The first subject was enrolled on 9 March 2009.

The last subject completed on 20 May 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was:

- To assess the relative oral bioavailability (F_{rel}) of AZD5672 Phase III formulation (test) to AZD5672 Phase IIb formulation (reference) using AZD5672 area under the plasma concentration time curve during a dosing interval at steady-state (AUC_{ss}) and maximum plasma concentration at steady-state ($C_{max,ss}$) at 2 dose levels (40 mg and 100 mg).

The secondary objectives of the study were:

- To provide descriptive pharmacokinetic (PK) parameters for AZD5672 (AUC_{ss}, $C_{max,ss}$, time to $C_{max,ss}$ [$t_{max,ss}$] and apparent oral clearance following extravascular dosing at steady-state [CL/F_{ss}]).

- To further investigate the safety and tolerability of AZD5672 by assessment of adverse events (AEs), laboratory variables (clinical chemistry, haematology, urinalysis), physical examination, 12-lead electrocardiogram (ECG) and vital signs (blood pressure [BP] and pulse).

The exploratory objectives of the study were:

- To provide deoxyribonucleic acid (DNA) samples to allow investigation of genetic factors that may help explain some of the variability observed in the PK, tolerability and safety of AZD5672.

- Possible pharmacokinetic (PK) analysis for AZD5672 metabolite(s).

The results of the data addressing the exploratory objectives do not form part of the Clinical Study Report (CSR) for this study but are to be described in supplementary reports if performed.

Study design

A randomised, open-label, 2-cohort, 4-period crossover, replicate design was used to assess the relative bioavailability of AZD5672 Phase III tablet formulation (test formulation, T) relative to the Phase IIb tablet formulation (reference formulation, R).

Target healthy volunteer population and sample size

Healthy male and female (non-childbearing potential) subjects, aged ≥18 to ≤55 years were recruited for this study, to ensure 24 evaluable, randomised subjects, 12 per cohort.

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

The test formulation in this study was the Phase III formulation of AZD5672 and the reference formulation was the Phase IIb formulation of AZD5672.

Cohort 1 received:

- 40 mg AZD5672 oral tablet test formulation (T) once daily, batch number: 09-001299AZ (P7983), manufacturer: AstraZeneca R&D Charnwood, UK.
- 40 mg (2 x 20 mg) AZD5672 oral tablets reference formulation (R) once daily, batch number: 08-012856AZ, manufacturer: AstraZeneca R&D Charnwood, UK.

Cohort 2 received:

- 100 mg AZD5672 oral tablet test formulation (T) once daily, batch number: 09-001301AZ (P7984), manufacturer: AstraZeneca R&D Charnwood, UK.
- 100 mg (2 x 50 mg) AZD5672 oral tablets reference formulation (R) once daily, batch number: 08-001769AZ, manufacturer: AstraZeneca R&D Charnwood, UK.

Duration of treatment

A pre-treatment screening visit was conducted up to 28 days before the first dose of AZD5672. The study consisted of 4 consecutive 7-day treatment periods with no washout period between: ie, 28 days of treatment in total. A follow-up visit occurred 7 to 10 days after the last assessment in the last treatment period.

Criteria for evaluation - main variables

- Pharmacokinetics

  F_{rel} of the Phase III to Phase IIb formulation was calculated ie, ratio of the geometric means with associated 90% confidence interval (CI) for the primary PK variables of AZD5672 AUC_{ss} and $C_{max,ss}$.

  The secondary PK variables were $t_{max,ss}$ and CL_{ss}/F.

- Safety

  The safety variables were AEs, laboratory assessments (chemistry, haematology, urinalysis), physical examination, 12-lead ECG, vital signs (BP and pulse).

Statistical methods

To assess F_{rel}, the primary PK variables AUC_{ss} and $C_{max,ss}$ of AZD5672 from the PK analysis set were compared between formulations using a mixed effects analysis of variance (ANOVA) model (SAS PROC MIXED). AUC_{ss} and $C_{max,ss}$ were log-transformed prior to analysis.

Subject population

Twenty-four subjects were randomised and included in the study. Of the 12 subjects randomised within Cohort 1, all received treatment in Periods 1, 2, 3 and 4. Of the 12 subjects randomised within Cohort 2, all received treatment in Periods 1, 2 and 3. 11 subjects received treatment in Period 4. One subject was withdrawn from the study after receiving IP in Period 3, due to an AE (urinary tract infection), and was not replaced. Thus 23 subjects completed the study according to the clinical study protocol.

Table S1 Summary of demographic data

Parameter	Statistic	40 mg (N = 12)	100 mg (N = 12)
Age (years)	Mean (SD)	30.1 (7.4)	31.3 (11.2)
	Minimum	22	18
	Maximum	43	47
Weight (kg)	Mean (SD)	78.4 (9.9)	70.4 (8.2)
	Minimum	61	56
	Maximum	91	81
Height (cm)	Mean (SD)	177.1 (9.4)	177.0 (7.7)
	Minimum	154	165
	Maximum	192	188
Sex			
Female	n (%)	1 (8.3)	3 (25.0)
Male	n (%)	11 (91.7)	9 (75.0)
Race			
White	n (%)	12 (100)	12 (100)

SD - standard deviation

Summary of pharmacokinetic results

Table S2 presents the results of the statistical analysis of steady-state PK parameters following 40 mg AZD5672 administered as either a Phase III tablet formulation and the Phase IIb tablet formulation.

Table S2 AZD5672 Phase III tablet formulation (Test) versus AZD5672 Phase IIb tablet formulation (Reference) – 40 mg AZD5672

Parameter	Test		Ref		Geometric mean Ratio (Test/Ref)	90% CI
	n	GLS mean	n	GLS mean		
AUC_{ss} (nM·h)	12	318.26	12	311.11	1.023	(0.939, 1.115)
$C_{max,ss}$ (nM)	12	47.35	12	40.07	1.182	(0.975, 1.433)

Parameter	Test		Ref		Hodges-Lehmann Estimator (Test-Ref)	90% CI
	n	Median	n	Median		
$t_{max,ss}$	12	1.875	12	1.875	0.048	(-0.391, 0.434)

GLS - geometric least squares mean

For AUC_{ss} following 40 mg AZD5672 point estimate of the geomean ratio for the comparison of test/reference formulation was very close to 1.00 and the associated 90% CI was wholly contained within the predefined 0.8 to 1.25 limits for equivalence. The point estimate of the geomean ratio for $C_{max,ss}$ was 1.18 and the associated 90% CI included 1.0 but was outside the predefined 0.8 to 1.25 limits for equivalence at the upper end (0.98 to 1.43).

For $t_{max,ss}$ the 90% CI for the median difference of test formulation – reference formulation for 40 mg AZD5672 contained 0. Consequently, $t_{max,ss}$ from the Phase IIb and Phase III tablets was concluded to be not statistically significantly different.

Table S3 presents the results of the statistical analysis of steady-state PK parameters following 100 mg AZD5672 administered as either a Phase III tablet formulation and the Phase IIb tablet formulation.

Table S3 AZD5672 Phase III tablet formulation (Test) versus AZD5672 Phase IIb tablet formulation (Reference) – 100 mg AZD5672

Parameter	Test		Ref		Geometric mean Ratio (Test/Ref)	90% CI
	n	GLS mean	n	GLS mean		
AUC_{ss} (nM·h)	12	1099.91	12	1072.62	1.025	(0.949, 1.108)
$C_{max,ss}$ (nM)	12	181.77	12	178.59	1.018	(0.879, 1.179)

Parameter	Test		Ref		Hodges-Lehmann Estimator (Test-Ref)	90% CI
	n	Median	n	Median		
$t_{max,ss}$	12	0.750	12	1.250	-0.275	(-0.729, 0.104)

GLS - geometric least squares mean

For AUC_{ss} and $C_{max,ss}$ following 100 mg AZD5672 point estimate of the geomean ratio for the comparison of test/reference formulation were very close to 1.00 and the associated 90% CI was wholly contained within the pre-defined 0.8 to 1.25 limits for equivalence.

For $t_{max,ss}$ the 90% CI for the median difference of test formulation – reference formulation for 100 mg AZD5672 contained 0. Consequently, $t_{max,ss}$ from the Phase IIb and Phase III tablets was concluded to be not statistically significantly different.

Summary of safety results

Once daily dosing with AZD5672 40 mg and 100 mg from both test and reference formulations appeared to be generally well tolerated in this study.

A total of 105 AEs were reported throughout the study, with more than triple the number of AEs reported by subjects receiving 100 mg than by subjects receiving 40 mg.

In subjects receiving 40 mg, all 12 subjects reported at least 1 AE; 8 (66.7%) subjects reported 16 AEs following the test formulation (Phase III tablet formulation) and 8 (66.7%) subjects reported 10 AEs following the reference formulation (Phase IIb tablet formulation).

In subjects receiving 100 mg, 11 subjects reported at least 1 AE; 8 (66.7%) subjects reported 27 AEs following the test formulation (Phase III tablet formulation) and 10 (83.3%) subjects reported 52 AEs following the reference formulation (Phase IIb tablet formulation).

There were no severe AEs reported in this study in either cohort. There were no deaths, SAEs or other significant AEs in either cohort. One subject in Cohort 2 was discontinued following Period 3 due to an AE (urinary tract infection).

The only AEs that were reported by more than one subject receiving 40 mg were: fatigue, nasopharyngitis and dizziness. All other AEs were restricted to single subjects.

The following AEs were reported by more than one subject receiving 100 mg: headache, nasopharyngitis, nausea, dizziness and back pain, panic attack, dizziness postural, abdominal discomfort and pain in extremity.

There were no clinically relevant changes in laboratory parameters, vital signs and ECGs.