AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9056
Study Code	D1520C00004
Edition Number	1
Date	27 October 2009

An Open-label, Randomized, 2-cohort, 2-period Crossover Study to Assess the Relative Bioavailability of the Phase III to the Phase IIb Formulation of AZD9056 in Healthy Male and Female Subjects

Study dates: First subject enrolled: 15 May 2009
Last subject completed: 3 July 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 15 May 2009.

The last subject completed on 3 July 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 2 formulations (Phase III [test] and Phase IIb [reference]) of AZD9056 across 2 dose levels (50 mg and 400 mg), by comparing the systemic AZD9056 exposure (maximum plasma [peak] drug concentration [C_{max}] and area under the plasma concentration-time curve from zero to infinity [AUC]).

The secondary objectives of the study were:

- To provide descriptive pharmacokinetic (PK) parameters for AZD9056 (time to peak or maximum concentrations following drug administration [t_{max}], AUC from zero to time to the last quantifiable plasma concentration [$AUC_{(0-t)}$], terminal elimination half-life [$t_{½}$], apparent oral clearance following extravascular dosing [CL/F] and apparent volume of distribution during terminal (λ_z) phase [V_z/F] following extravascular dosing).

- To further investigate the safety and tolerability of AZD9056 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 objective of the study was:

- To explore whether the variability in systemic AZD9056 exposures, and/or drug safety observations, could be explained by genetic variation.

The exploratory objective of the study does not form part of the Clinical Study Report (CSR) but will be described in supplementary reports if the analyses are performed.

Study design

A randomised, open-label, 2-cohort, 2-period crossover design was used to assess F_{rel} of AZD9056 Phase III tablet formulation (test formulation) relative to the Phase IIb tablet formulation (reference formulation).

Target healthy volunteer population and sample size

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

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

The test formulation in this study was the Phase III formulation of AZD9056 and the reference formulation was the Phase IIb formulation of AZD9056.

Cohort 1 received:

- Single dose of 50 mg AZD9056 oral tablet test formulation, batch number: P8006, manufacturer: AstraZeneca R&D Charnwood, UK
- Single dose of 50 mg AZD9056 oral tablet reference formulation, batch number: 07-011955AZ, manufacturer: AstraZeneca R&D Charnwood, UK.

Cohort 2 received:

- Single dose of 400 mg AZD9056 oral tablets test formulation , batch number: P8007, manufacturer: AstraZeneca R&D Charnwood, UK
- Single dose of 400 mg AZD9056 oral tablets reference formulation, batch number: 07-011979AZ, manufacturer: AstraZeneca R&D Charnwood, UK.

Duration of treatment

A pre-treatment screening visit was conducted up to 21 days before Day 1 of Period 1 for each cohort. For each cohort, the study consisted of 2 periods of 7 days each.

Subjects were admitted to the clinic in the morning of Day -1 of Period 1, and remained resident until the morning of Day 3, following the 48 hour post-dose blood sample; additional blood samples were then obtained over the following 4 days on an outpatient basis. There was a washout period of at least 14 days between Day 1 of Period 1 and Day 1 of Period 2.

Subjects returned to the clinic in the morning no earlier than 13 days after Day 1, Period 1, and remained resident until the morning of Day 3, following the 48 hour post-dose blood sample; additional blood samples were then obtained over the following 4 days on an outpatient basis. A follow-up visit occurred 5 to 10 days after the last assessment in Period 2.

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 AZD9056 C_{max} and AUC.

  The secondary PK variables were t_{max}, $AUC_{(0-t)}$, $t_{½}$, CL/F and V_z/F.

- Safety

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

Statistical methods

A separate analysis was performed for each cohort.

The primary outcome measure was the F_{rel} of the Phase III to Phase IIb formulation ie, ratio of the geometric means with associated 90% CI for the primary PK variables of AZD9056 C_{max} and AUC.

The PK parameters C_{max} and AUC of AZD9056 from the PK analysis set were compared between formulations using an analysis of variance (ANOVA) model.

A non-parametric analysis was used to compare the secondary PK parameter t_{max} between formulations. The individual pairwise differences between formulations were calculated and compared using the Wilcoxon Signed Rank test to obtain a non-parametric 90% CI for the difference in location between test and reference formulations based on the Hodges-Lehmann one sample estimator.

Bioequivalence limits of 0.8 to 1.25 for C_{max} and AUC were used to help with interpretation of the data. If the 90% CI of the ratio of the means lay within the 0.8 to 1.25 limits for C_{max} and AUC, it was stated that the Phase III formulation could be considered to be equivalent in terms of systemic exposure to the Phase IIb formulation.

Subject population

Twenty-four subjects were randomised and included in the study. Of the 12 subjects randomised within Cohort 1 (50 mg), all 12 subjects received the reference formulation, and all but one subject received the test formulation. Of the 12 subjects randomised within Cohort 2 (400 mg), all subjects received both the test and reference formulations. In Cohort 1, Subject E0001027 was withdrawn from the study on Day -1 of Period 2, due to out-of-range laboratory results (bilirubin >2 x the upper limit of normal [51.6 µmol/L]).

Twenty-three subjects completed the study according to the clinical study protocol.

Table S1 Summary of demographic data

Parameter	Statistic	50 mg (N = 12)	400 mg (N = 12)
Age (years)	Mean (SD)	29.7 (9.2)	27.1 (7.8)
	Minimum	21	19
	Maximum	47	43
Weight (kg)	Mean (SD)	78.6 (14.1)	80.1 (8.8)
	Minimum	60	65
	Maximum	100	91
Height (cm)	Mean (SD)	176.7 (8.9)	178.4 (6.3)
	Minimum	162	168
	Maximum	193	187
Sex			
Male	n (%)	12 (100)	12 (100)
Race			
Asian	n (%)	1 (8.3)	0
Black or African American	n (%)	1 (8.3)	1 (8.3)
Other	n (%)	1 (8.3)	0
White	n (%)	9 (75.0)	11 (91.7)

Summary of pharmacokinetic results

Table S2 presents the results of the statistical analysis of the PK parameters following 50 mg AZD9056 administered as either a Phase III tablet formulation or the Phase IIb tablet formulation.

Table S2 AZD9056 Phase III tablet formulation (test) versus AZD9056 Phase IIb tablet formulation (reference) – 50 mg

Parameter	Test		Reference		Geometric mean Ratio (Test/Ref)	90% CI
	n	GLS Mean	n	GLS Mean		
AUC (nM·h)	11	1962.78	11	1989.94	0.986	(0.913, 1.066)
C_{max} (nM)	11	128.91	11	127.97	1.007	(0.933, 1.088)

Parameter	Test		Reference		Hodges-Lehmann Estimator (Test-Ref)	90% CI
	n	Median	n	Median		
t_{max}	11	2.500	11	2.500	0.120	(-0.750, 1.500)[a]

[a] Includes zero therefore not statistically significantly different

For both AUC and C_{max} following 50 mg AZD9056, the point estimate of the geomean ratios for the treatment 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.

For t_{max} the 90% CI for the median difference of test formulation – reference formulation for 50 mg AZD9056 contained 0. Consequently, t_{max} 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 the PK parameters following 400 mg AZD9056 administered as either a Phase III tablet formulation or the Phase IIb tablet formulation.

Table S3 AZD9056 Phase III tablet formulation (test) versus AZD9056 Phase IIb tablet formulation (reference) – 400 mg AZD9056

Parameter	Test		Reference		Geometric mean Ratio (Test/Ref)	90% CI
	n	GLS Mean	n	GLS Mean		
AUC (nM·h)	12	22844.3	12	22266.0	1.026	(0.925, 1.138)
C_{max} (nM)	12	1515.93	12	1378.33	1.100	(0.919, 1.317)

Parameter	Test		Reference		Hodges-Lehmann Estimator (Test-Ref)	90% CI
	n	Median	n	Median		
t_{max}	12	3.500	12	3.250	-0.298	(-1.165, 0.490)[a]

[a] Includes zero therefore not statistically significantly different

Following 400 mg AZD9056, the point estimate of the AUC geomean ratios for the treatment comparison of test/reference formulation was 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. The point estimate of the geomean ratio for C_{max} was 1.100 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 (0.919 to 1.317).

For t_{max} the 90% CI for the median difference of test formulation – reference formulation for 400 mg AZD9056 contained 0. Consequently, t_{max} from the Phase IIb and Phase III tablets was concluded to be not statistically significantly different.

Summary of safety results

AZD9056 50 mg and 400 mg from both test and reference formulations appeared to be generally well tolerated in this study.

A total of 26 AEs were reported throughout the study, with many more AEs reported by subjects in Cohort 2 (22 AEs) than by subjects in Cohort 1 (4 AEs).

In Cohort 1 (50 mg), 3 (25.0%) subjects reported at least 1 AE; 2 (16.7%) subjects reported 2 AEs following the test formulation (Phase III tablet formulation) and 1 (8.3%) subject reported 2 AEs following the reference formulation (Phase IIb tablet formulation).

In Cohort 2 (400 mg), 6 (50.0%) subjects reported at least 1 AE; 3 (25.0%) subjects reported 5 AEs following the test formulation (Phase III tablet formulation) and 5 (41.7%) subjects reported 17 AEs following the reference formulation (Phase IIb tablet formulation).

The following AEs were reported by more than one subject in Cohort 2: diarrhoea (4 subjects reported 4 AEs), abdominal discomfort (2 subjects reported 3 AEs), headache (2 subjects reported 3 AEs), seasonal allergy (2 subjects reported 3 AEs) and fatigue (2 subjects reported 2 AEs).

There were no severe AEs reported in this study in either cohort. There were no deaths, SAEs, other significant AEs or discontinuations due to an AE in either cohort.

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