Clinical Study Report Synopsis

Drug Substance AZD1981

Study Code D9830C00020

Edition Number 1

A Phase I, Open Label, Randomised, 4-way Cross-over Study to Investigate the Relative Bioavailability of Single Dose AZD1981 via 3 Different Tablets in Healthy Men and Healthy Women of Non-childbearing Potential

Study dates: First subject enrolled: 13 April 2011
Last subject last visit: 5 July 2011

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

One study centre in

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**	
To estimate the relative systemic bioavailability of AZD1981 after oral administration via a new small-particle tablet formulation versus the current small-particle tablet formulation in the fasting state by assessment of AUC and C_{max} after a single dose of AZD1981	AUC and C_{max}	Pharmacokinetic
Secondary	**Secondary**	
To estimate the relative systemic bioavailability of AZD1981 after oral administration via a new large-particle tablet formulation compared to a new small-particle tablet formulation by assessment of AUC and C_{max} after a single dose of AZD1981 in the fasted state	AUC and C_{max}	Pharmacokinetic
To estimate the relative systemic bioavailability of AZD1981 after oral administration via a new small-particle tablet formulation following a high-calorie and high-fat meal compared with the fasting state by assessment of AUC and C_{max} after a single dose of AZD1981	AUC and C_{max}	Pharmacokinetic
To evaluate basic systemic PK parameters after oral administration of a single dose of AZD1981	$AUC_{(0-t)}$, t_{max}, $t_{1/2\lambda z}$, CL/F, MRT, and V_z/F	Pharmacokinetic
To evaluate the safety and tolerability of AZD1981 in healthy subjects by assessment of AEs, laboratory safety parameters, vital signs, ECG, physical examination, and weight	AEs, laboratory safety parameters[a], vital signs, weight, physical examination, 12-lead ECG	Safety
Exploratory[b]	**Exploratory**	
To collect and store deoxyribonucleic acid for possible future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, and tolerability) to AZD1981	NA	Pharmacogenetic

[a] Laboratory variables are listed in Section 6.3.5 of the CSP.
[b] The results, if performed, will be reported separate from this Clinical Study Report.
AE: adverse event; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$: area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; CL/F: apparent plasma clearance; C_{max}: observed maximum plasma concentration; ECG: electrocardiogram; MRT: mean residence time; NA: not applicable; PK: pharmacokinetic(s); $t_{1/2\lambda z}$: terminal half-life; t_{max}: time to reach the observed maximum plasma concentration; V_z/F: apparent volume of distribution during terminal phase.

Study design

This was an open label, randomised, 4-way cross-over study investigating the relative bioavailability of AZD1981 after single dose administration via 3 different tablet formulations. Each subject was to receive 4 single oral doses of 300 mg AZD1981, 1 dose per treatment period. The treatments administered were:

- Treatment A: 3 x 100 mg of the current small-particle tablet formulation in a fasting state
- Treatment B: 3 x 100 mg of the new small-particle tablet formulation in a fasting state
- Treatment C: 3 x 100 mg of the new small-particle tablet formulation in a fed state, ie, after a high-calorie and high-fat breakfast
- Treatment D: 3 x 100 mg of the new large-particle tablet formulation in a fasting state

Target subject population and sample size

Healthy male and female (post-menopausal) subjects aged 18 to 55 years (inclusive) with a minimum weight of 50 kg and a body mass index of 19 to 30 kg/m^2 (inclusive) were to be enrolled.

Approximately 16 subjects were to be randomised to ensure evaluable data from 12 subjects.

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

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, route of administration, and strength	Manufacturer	Batch number
AZD1981 film-coated tablet 100 mg	Current small-particle formulation, film-coated oral tablet, 100 mg	AstraZeneca	11-000731AZ
AZD1981 film-coated tablet 100 mg, Phase 3 candidate formulation	New small-particle formulation, film-coated oral tablet, 100 mg	AstraZeneca	10-006528AZ
AZD1981 film-coated tablet 100 mg, Phase 3 candidate formulation, non-milled	New large-particle formulation, film-coated oral tablet, 100 mg	AstraZeneca	10-006529AZ

Duration of treatment

This study consisted of 4 treatment periods, each comprising Day -1 (admission), Day 1 (AZD1981 administration), Day 2 (pharmacokinetic [PK] sampling and discharge), and Day 3 (PK sampling).

Each treatment period was separated by a wash-out period of at least 4 days (ie, from Day 3 of the previous treatment period to Day -1 of the next treatment period).

Statistical methods

Relative bioavailability between the new and current small-particle tablet formulations (Treatment B versus A); the new large-particle and new small-particle tablet formulations (Treatment D versus B); and the new small-particle tablet formulation in the fed versus fasted state (Treatment C versus B), respectively, was estimated using an analysis of variance model with the logarithm of AUC and C_{max} for AZD1981 as the response variable, treatment, and period as fixed factors, and subject as random factor. The 90% confidence interval (CI) approach was used for testing bioequivalence and bioequivalence was accepted if the 90% CI for the ratio of the geometric least squares (LS) mean point estimates for AUC and C_{max} was contained within the range 80.00% to 125.00%.

Subject population

Enrolled: 16 subjects

Randomised: 16 subjects

Completed: 15 subjects

All subjects enrolled were eligible to be included in this study.

Summary of pharmacokinetic results

Except for a slightly lower peak following the new large-particle tablet formulation (Treatment D) there was a high similarity in the shape of the geometric mean plasma concentration-time profile of AZD1981 amongst the current small-particle tablet formulation (Treatment A), the new small-particle tablet formulation (Treatment B), and the new large-particle tablet formulation (Treatment D). Peak median AZD1981 concentrations occurred in plasma between 2 to 3 hours post-dose. From C_{max}, the disposition appeared to be biphasic with a relatively rapid decline and slow terminal elimination with the terminal phase having mean $t_{1/2\lambda z}$ of 14.5 to 15.2 hours. The shape of the geometric mean plasma concentration-time profile of AZD1981 was similar when the new small-particle tablet formulation was administered in the fasting state (Treatment B) and fed state (Treatment C).

Table S3 Statistical comparison of primary PK parameters

Var	Tablet formulation	n	Geo LS mean	95% CI	Comp	Ratio (%)	90% CI
AUC	A-current small-particle	13	33520	(29030, 38720)			
(h*nmol/L)	B-new small-particle	13	34610	(29990, 39940)	B/A	103.23	(95.61, 111.45)
	C- new small-particle (fed)	12	32470	(28090, 37530)	C/B	93.83	(86.61, 101.65)
	D-new large-particle	13	30100	(26080, 34730)	D/B	86.97	(80.38, 94.11)
C_{max}	A-current small-particle	15	7147	(5957, 8573)			
(nmol/L)	B-new small-particle	15	6920	(5768, 8310)	B/A	96.82	(79.68, 117.65)
	C- new small-particle (fed)	15	6996	(5832, 8993)	C/B	101.10	(83.20, 122.85)
	D-new large-particle	16	5828	(4887, 6951)	D/B	84.23	(69.51, 102.07)

CI confidence interval; Comp comparison; Geo geometric; LS least squares; Var variable.

In the comparison between the new and current small-particle tablet formulations (Treatment B/A), the point estimates of geometric LS mean ratios for AUC and C_{max} were close to 100%. The 90% CI was entirely contained within the 80.00% to125.00% range for AUC while the lower limit was slightly below 80.00% for C_{max}.

In the comparison between new large-particle and new small-particle tablet formulations (Treatment D/B), the 90% CI was entirely contained within the 80.00% to 125.00% range for AUC, while the lower limit was below 80% for C_{max}. The point estimates of geometric LS mean ratios for AUC and C_{max} indicated 13% and 16% lower plasma exposure, respectively, following administration of the new large-particle tablet formulation compared to new small-particle tablet formulation.

There seemed to be no effect of food on the bioavailability of AZD1981 for the new small-particle tablet formulation (Treatment C/B). The point estimates of plasma exposure

parameter ratios (AUC and C_{max}) were close to 100% and the 90% CIs were entirely contained within the 80.00% to 125.00% range for the new small-particle tablet formulation in the fed state compared to the fasted state.

Summary of safety results

No deaths, serious adverse events (SAEs), discontinuations due to adverse events (DAEs), other significant adverse events (OAEs), or severe adverse events (AEs) were reported. Overall, 21 AEs were reported for 9 subjects (56.3%), of which 13 events were considered to be causally related to AZD1981 by the Investigator. Two AEs were reported after Treatment A; 4 AEs after Treatment B; 8 AEs after Treatment C; and 7 AEs after Treatment D. Causally related AEs, as judged by the Investigator, included headache (after Treatments A, B, and C), fatigue (after all treatments), abdominal pain (after Treatment C), decreased appetite (after Treatments B, C, and D), and pain in extremity (after Treatment D).

Based on the reported AEs, laboratory measurements, vital signs, weight, ECG evaluations, and physical examination findings, AZD1981 can be considered well tolerated in the population studied.