AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8931
Study Code	D0102C00005
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A Phase I, Randomised, Open-label, Cross-over, Single-centre Study in Healthy Male and Non-fertile Female Volunteers to Determine the Relative Bioavailability of the Phase II Wet Granulation Tablet Formulation Compared to the Phase II/III Roller Compacted Tablet Formulation of AZD8931

Study dates: First subject enrolled: 13 April 2011
Last subject last visit: 08 June 2011

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

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

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

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**	**Primary**
To determine the relative bioavailability of 40 mg AZD8931 Phase II wet granulation tablet formulation (Treatment A) in relation to the 40 mg AZD8931 Phase II/III roller compacted tablet formulation (Treatment B)[a].	AUC, $AUC_{(0-t)}$, and C_{max} of AZD8931 for relative bioavailability	Pharmacokinetic
	AUC, $AUC_{(0-t)}$, C_{max}, $t_{1/2, \lambda z}$, t_{max}, t_{last}, CL/F and V_z/F, V_{ss}/F, RC_{max}, and $RAUC_{(0-t)}$ of AZD8931 (and where applicable o-desmethyl AZD8931)	
Secondary	**Secondary**	**Secondary**
To further investigate the safety and tolerability of AZD8931	Adverse events, vital signs, physical examinations, visual acuity examination, electrocardiograms and clinical laboratory evaluations	Safety

λz:Terminal elimination rate constant; AUC:Area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$: Area under the plasma concentration-time curve from zero to time t; CL/F: Apparent systemic clearance after extravascular dosing; C_{max}: Maximum plasma (peak) drug concentration after single dose administration; DNA deoxyribonucleic acid; t_{max}: Time to reach C_{max} following drug administration; t_{last}: Time at which last quantifiable plasma concentration was observed; $t_{½,\lambda z}$: Terminal plasma half-life; V_{ss}/F: Apparent oral volume of distribution at steady state, and V_z/F: Apparent oral volume of distribution during terminal phase.

[a] Instead of as stated in the primary objective above and in the Clinical Study Protocol (CSP), since the AZD8931 Phase II/III roller compacted tablet formulation is to be used in ongoing and future clinical studies, for statistical comparisons this was treated as the test formulation and the Phase II wet granulation tablet formulation was treated as the reference formulation.

Note: Results from any genetic research (exploratory objective), if performed, will be reported separately from this CSR.

Study design

This was a randomised, open-label, cross-over, single-centre study planned to enrol 26 healthy volunteers to receive single doses of both the Phase II wet granulation (Treatment A) and the Phase II/III roller compacted tablet formulation (Treatment B).

The duration of the study was 40 to 45 days. This included a 28-day screening period; 2 treatment periods of 5 days each with a minimum of 5-day washout between doses; and a final follow-up visit between 5 to 10 days after the last dose of AZD8931.

Target subject population and sample size

The planned target population was healthy male and female (non-childbearing potential) volunteers aged 18 to 55 years with a body mass index between 18 and 30 kg/m^2, and weight ≥50 kg and ≤100 kg.

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

- AZD8931, wet granulation tablet, formulation 40 mg (white film coated), single dose, oral, manufactured by AstraZeneca Batch number 11-000590AZ

- AZD8931, roller compacted tablet, formulation 40 mg (beige film coated), single dose, oral, manufactured by AstraZeneca Batch number 11-000591AZ.

Duration of treatment

Each volunteer received a single dose of AZD8931 40 mg wet granulation tablet formulation and a single dose of AZD8931 40 mg roller compacted tablet formulation in a randomised order. Dosing occurred on the morning of Day 1 of each treatment period. The duration of each treatment period was 5 days and there was a wash-out period of at least 5 days between doses.

Statistical methods

Plasma concentrations of AZD8931, and the metabolite o-desmethyl AZD8931 and their derived pharmacokinetic parameters were summarised by treatment using descriptive statistics.

The relative bioavailability of the wet granulation tablet (Treatment A) and the roller compacted tablet (Treatment B) was assessed using the primary pharmacokinetic variables AUC, $AUC_{(0-t)}$, and C_{max} of plasma AZD8931 (and o-desmethyl AZD8931 where possible). These endpoints were natural log-transformed and subjected to a linear mixed effects model with sequence, period and treatment as fixed effects, and volunteer nested within sequence as a random effect. The difference in treatment (formulation) means was determined along with its associated 90% confidence interval and back-transformed to give an estimate of the relative bioavailability. The results of this analysis were presented in terms of adjusted geometric least-squares means for both treatments, the relative bioavailability (ie, the ratio of the treatment formulation geometric least-squares means and its 90% confidence interval).

The above treatment comparisons were also performed for t_{max} as secondary analyses. Nonparametric methods were used to compute median t_{max} for each treatment, median t_{max} differences, and associated 90% confidence interval for median differences. The data were analysed by a Wilcoxon Signed-Rank Test. The 90% confidence interval were calculated using the method of Hahn and Meeker.

All safety variables were presented descriptively.

Subject population

This study was conducted at one centre in London. The first volunteer was enrolled on 13 April 2011 and received his first dose of study drug on 10 May 2011. The last volunteer received the last dose of study drug on 20 May 2011.

The study planned to enrol and randomise 26 healthy male and female volunteers. However, only male volunteers were enrolled. Thus, the population consisted of 26 healthy male volunteers with a mean age of 35 (±9.7) years.

Of the 26 healthy volunteers randomised, 25 (96%) volunteers completed the study. One volunteer discontinued the study since he was positive for cotinine at Visit 3, which was considered an important protocol deviation.

Summary of pharmacokinetic results

These results indicate that the bioavailability of the roller compacted formulation relative to the wet granulation is approximately 100% and furthermore, since the treatment ratio for all parameters tested [AUC, $AUC_{(0-t)}$, and C_{max}] and the associated 90% CI of the geometric LS mean ratios fell entirely within the 80 to 125% range, it can be concluded that there is no difference in in vivo performance between the 2 formulations (Table S2).

Table S2 Statistical comparison of key PK parameters for Treatments A and B

						Comparison of B to A	
Analyte	**Parameter (unit)**	**Tmt [a]**	**N**	**Geometric LS Mean**	**Geometric LS Mean 95% CI**	**Ratio (%)**	**90% CI**
AZD8931	AUC (ng·h/mL)	A	26	743.5	(652.6, 847.0)		
		B	25	747.5	(655.7, 852.1)	100.54	(94.91, 106.50)
	$AUC_{(0-t)}$ (ng·h/mL)	A	26	739.9	(649.1, 843.4)		
		B	25	743.6	(652.0, 848.1)	100.50	(94.84, 106.50)
	C_{max} (ng/mL)	A	26	90.63	(79.73, 103.0)		
		B	25	90.79	(79.72, 103.4)	100.18	(90.25, 111.20)
o-desmethyl AZD8931	$AUC_{(0-t)}$ (ng·h/mL)	A	23	176.5	(136.6, 227.9)		
		B	23	169.5	(131.2, 218.9)	96.02	(85.51, 107.83)
	C_{max} (ng/mL)	A	23	3.490	(2.862, 4.255)		
		B	23	3.228	(2.647, 3.936)	92.50	(83.16, 102.88)

CI: confidence interval; LS: least-squares; Tmt: treatment.

a Treatment A: 40 mg AZD8931 wet granulation tablet formulation
Treatment B: 40 mg AZD8931 roller compacted tablet formulation.
Results based on linear mixed effects model with fixed effects for sequence, period, and treatment and a random effect for volunteer nested within sequence.

For o-desmethyl AZD8931, the total and maximum exposures [$AUC_{(0-t)}$ and C_{max}] were slightly lower for roller compacted tablet formulation (Treatment B) compared to wet granulation tablet formulation (Treatment A). The geometric least-squares mean for C_{max} for roller compacted tablet formulation (Treatment B) was lower on average by about 8% relative to wet granulation tablet formulation (Treatment B); however, the 90% confidence interval of the geometric mean ratios were fully contained within the 80% to 125% boundaries. While AUC could not be determined reliably for this metabolite, the geometric least-squares mean for $AUC_{(0-t)}$ for roller compacted tablet formulation (Treatment B) was lower on average by about 4% relative to wet granulation tablet formulation (Treatment B); however, the 90% confidence interval of the geometric least-squares mean ratios were fully contained within the 80% to 125% boundaries.

The table below shows the statistical comparison of t_{max} for AZD8931 and o-desmethyl AZD8931 between the two formulations.

Table S3 Comparison of t_{max}

				Comparison of B to A			
Analyte	**Tmt[a]**	**N**	**Median (95% CI for Median)[b] (h)**	**N for Difference**	**Median Difference**	**90% CI for Median Difference[b]**	**p-value[c]**
AZD8931	A	25	1.50 (1.02, 2.00)				
	B	25	1.50 (1.00, 2.00)	25	-0.18	(-0.50, 0.50)	0.8367
o-desmethyl AZD8931	A	21	12.00 (8.00, 12.00)				
	B	21	12.00 (12.00, 24.00)	21	0	(0.00, 3.97)	0.3232

h: hours; CI: confidence interval.
Analyses are restricted to volunteers with t_{max} estimates for both treatments. Treatment differences in median t_{max} are assessed using the Wilcoxon signed rank test.
a Treatment A: 40 mg AZD8931 wet granulation tablet formulation;
Treatment B: 40 mg AZD8931 roller compacted tablet formulation.
b Confidence interval calculated using the method of Hahn and Meeker.
c p-value for treatment difference in median t_{max} calculated using the Wilcoxon signed rank test.

The time to reach maximum concentration was the same for both formulations for both the parent and the o-desmethyl metabolite.

Summary of safety results

All 26 randomised volunteers were included in the Safety Analysis Set.

Overall, 7 (27%) volunteers experienced adverse events during the study: 5 [19%]) volunteers during Treatment A (wet granulation tablet formulation) versus 4 [16%]) volunteers during Treatment B (roller compacted tablet formulation).

With the exception of the serious adverse event of severe intensity, all other adverse events were of mild (6 [86%]) intensity. Five (19%) volunteers experienced adverse events that were judged by the Investigator as causally related to the study drug.

There were no deaths, other adverse events or discontinuation due to adverse events. One volunteer experienced an SAE of severe ulcerative keratitis with abnormal Snellen visual acuity examination result at onset of the event (ie, 7 days after his second single dose of AZD8931). This event was considered to be related to study drug and was resolved with residual scarring which was not clinically manifest (ie, the patient reported no continuing ocular symptoms). An Independent expert ophthalmologist reviewed the data for this volunteer and concluded that this event is likely to be the result of a minor previous ocular injury that caused a delayed effect in the volunteer.

There were no clinically significant changes in clinical laboratory, ECG, vital signs, physical examination findings, and no apparent difference in findings between the 2 treatment groups.