AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3190C00016
Edition Number	1
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A Phase I, Randomised, Open, Single-centre Study to Evaluate the Pharmacokinetics of Different Extended-release Formulations of AZD1305 When Given as Single and Repeated Oral Doses to Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 01 May 2009
Last healthy volunteer completed: 07 July 2009

Phase of development: Clinical pharmacology (I)

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

As the development of AZD1305 was terminated, the Sponsor decided to submit the report for this study as a synopsis-format clinical study report.

Study centre

The study was conducted at the Early Phase Clinical Unit at PAREXEL Northwick Park Hospital, Harrow, Middlesex, United Kingdom. The first healthy volunteer was enrolled 01 May 2009 and the last healthy volunteer was completed 07 July 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was

- to evaluate the pharmacokinetics (PK) of AZD1305 for 1 to 2 extended-release (ER) test formulations of AZD1305 after single oral dosing with and without food and relative to an ER reference formulation of AZD1305 after single oral dosing under fasting condition.

The secondary objectives of this study were:

- to evaluate the steady state performance with regard to PK and QTcF of ER test formulation 1
- to evaluate the safety and tolerability of AZD1305
- to collect and store DNA samples (from all randomised healthy volunteers who gave additional informed consent) for potential future exploratory research into genes which may influence drug response of AZD1305.

Study design

This was a phase I, single-centre, randomised, open-label study in healthy male volunteers, which consisted of two parts i.e. Part A and either Part B1 or B2. Part A had a three-period crossover design to evaluate single doses of 125 mg AZD1305 ER test formulation 1 (ER1) relative to 125 mg of the ER formulation of AZD1305 used in study D3190C00015 (JMAD study; H 1997-02-01, reference formulation, ER-R) both in the fasted state and to evaluate single doses of 125 mg AZD1305 ER1 under fed relative to fasted conditions. Depending on preliminary results of PK data from the crossover design with ER1 (Part A), either a repeated dosing (5 days) of 50 mg AZD1305 ER1 given twice daily (Part B1) or a three-period crossover design with single doses of 125 mg AZD1305 ER test formulation 2 (ER-2; H 1997-08-01; Part B2) was to be carried out. Actually, Part B1 was performed.

Target healthy volunteer population and sample size

A total of 24 healthy male volunteers, aged 18 to 45 years, both inclusive, were planned, enrolled, and randomised. One subject was not dosed due to premature ventricular contraction (PVC) developed on telemetry at pre-dose; he was replaced. Approximately 12 healthy male volunteers were planned in each part (Part A and either Part B1 or B2) in order to have at least 9 evaluable healthy volunteers completing per study part i.e. having PK data available from all treatment periods. In Part A, 13 subjects were randomised and 12 were analysed for safety, PK and PD. In Part B1, 11 subjects were randomised and analysed for safety, PK and PD.

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

In the crossover part (Part A), each healthy volunteer received 3 treatments, each as a single dose of AZD1305, in the morning of Day 1 of Visits 2, 3 and 4. The 3 treatments consisted of 125 mg AZD1305 ER1 without food (Treatment A), 125 mg AZD1305 ER1 with food (Treatment B) and 125 mg AZD1305 ER-R without food (Treatment C). In the repeat dose part (Part B1), 50 mg AZD1305 ER1 were given twice daily for 5 days (on Day 5 only in the morning; ER1 50 mg or Treatment D).

The following batch numbers were used:

Part A

ER1: Test formulation AZD1305 ER1, oral capsule, 125 mg, batch number H 1997-07-01-01

ER-R: Reference formulation AZD1305 ER-R, oral capsule, 125 mg, batch number H 1997-02-01-02

Part B1

ER1 50 mg: Test formulation AZD1305 ER1, oral capsule, 50 mg: batch number H 2076-02-01-01

Duration of treatment

Part A included 3 treatment periods, each with a single dose of 125 mg AZD1305 and a wash-out period between dosing of 6 to 21 days. Considering a Screening period of 21 days and a follow-up examination 10 to 14 days after receiving the last dose, the total duration of the study for each healthy volunteer was 25 days at minimum and 80 days at maximum.

Part B1 included one treatment period of 5 days twice daily dosing (on Day 5 only in the morning) of 50 mg AZD1305 (100 mg/day). Considering a Screening period of 21 days and a follow-up examination 10 to 14 days after receiving the last dose, the total duration of the study for each healthy volunteer was 15 days at minimum and 40 days at maximum.

Criteria for evaluation - pharmacokinetics and pharmacodynamics (main variables)

Pharmacokinetic

Primary variables (Part A): PK variables estimated for AZD1305: the area under the plasma concentration-time curve from time point zero extrapolated to infinity (AUC), the observed maximum plasma concentration (C_{max}), plasma drug concentration at time point 12 hours post-dose (C_{12h}), ratio between C_{max} and C_{12h} (C_{max}/C_{12h}), the area under the plasma concentration-time curve from time point zero to the last quantifiable concentration, C_{last}, ($AUC_{[0-t]}$), the time relative to administration to reach C_{max} (t_{max}) and the terminal half-life calculated as $\ln(2)/\lambda_z$ ($t_{1/2}$). The terminal rate constant, λ_z, was estimated using the last 3 observations in the terminal decline of the plasma concentration-versus time curve for all subjects.

Secondary variables (Part B1): PK variables estimated for AZD1305: C_{max}, the area under the plasma concentration-time curve from time point zero to C_{12h} ($AUC_{[0-12h]}$), C_{12h}, C_{max}/C_{12h}, t_{max}, the accumulation ratio (R_{ac}) based on $AUC_{(0-12h)}$, R_{ac} (AUC_{0-12h}) = $AUC_{(0-12h),d5}$/ $AUC_{(0-12h),\,d1}$ and the R_{ac} based on C_{max}, R_{ac} (C_{max}) = $C_{max,d5}$ / $C_{max,d1}$, and fluctuation index = $(C_{max} - C_{min})/(AUC_{(0-12h)}/12)$.

Pharmacodynamic

Secondary variables: QTcF levels (=$QT/RR^{(1/3)}$, where the RR interval is given in seconds) following single and repeat dosing.

The maximal observed QTcF level (and time point for it) on Day 1 ($QTcF_{max,d1}$) and, similarly, the maximal observed QTcF level (and time since last dose) on Day 5 ($QTcF_{max,d5}$) were registered for each individual. The subject's overall maximal QTcF level during the whole observation period since first dose (and time since first dose) was defined as $QTcF_{max,overall}$. Additionally, the following ratio of $QTcF_{max,d5}$ and $QTcF_{max,d1}$ (individually for each subject) was calculated: $QTcF_{max,ratio} = QTcF_{max,d5} / QTcF_{max,d1}$

Criteria for evaluation - safety (main variables)

Secondary variables: Adverse events occurring during the study, blood pressure, pulse, physical examination, safety laboratory variables, body weight and electrocardiogram variables (heart rate, RR, PQ [PR], QRS, QT, QTcF and overall evaluation).

Statistical methods

The log-transformed primary PK variables AUC, C_{max}, C_{max}/C_{12h} and C_{12h} were analysed using a mixed model ANOVA with fixed effects for sequence, period and treatment and a random effect for subject within sequence.

The effect of formulation on bioavailability (measured by AUC, C_{max}, C_{max}/C_{12h} and C_{12h}) was analysed for ER1 in Part A. A mixed effect analysis of variance model with the logarithm of the PK variable as dependent variable, formulation (ER test formulation or ER reference

formulation), period and sequence as fixed factors and subject within sequence as random factor was used.

The influence of food (fed or fasting) on bioavailability (measured by AUC, C_{max}, C_{max}/C_{12h} and C_{12h}) was analysed for ER1 in Part A. A mixed effect analysis of variance model with the logarithm of the PK variables as dependent variable and treatment (fed or fasting), period and sequence as fixed factors and subject within sequence as random factor was used.

The PK and the PD variables as well as safety and tolerability of AZD1305 in all study parts were evaluated using descriptive statistics.

Subject population

In total, 23 subjects were randomised, of whom 12 subjects were included in Part A, including one subject who was withdrawn after Period 2 due to incorrect enrolment, and 11 subjects were included in Part B1. The incorrect enrolment of one subject in Part A was considered to be an important protocol deviation.

Summary of pharmacokinetic results

Part A:

The exposure of AZD1305 after a single dose of 125 mg AZD1305 ER1 was similar to that of the reference formulation under fasting conditions as indicated by AUC, C_{max}, C_{max}/C_{12h} ratio and C_{12h} of AZD1305 ER1 (Table S 1), as the 95% CI for the formulation comparison included one. Similar t_{max} and $t_{1/2}$ were shown for ER1 and ER-R as indicated by median t_{max} values of approximately 8.0 and 9.0 hours, respectively, and geometric mean $t_{1/2}$ of approximately 10.6 and 10.3 hours, respectively.

The comparison of single dosing of 125 mg AZD1305 ER1 under fed versus fasting conditions revealed that AUC, C_{max}/C_{12h} and C_{12h} values of AZD1305 were not affected by intake of a high-fat, high-calorie breakfast, whereas AZD1305 C_{max} was slightly decreased following fed administration of AZD1305 ER1 (see Table S 2). Absorption of AZD1305 ER1 was slightly prolonged when given with food with median t_{max} of 10.9 hours compared to 8.0 hours under fasting conditions, whereas $t_{1/2}$ of AZD1305 remained almost unchanged under fed versus fasting conditions with geometric mean $t_{1/2}$ values of approximately 9.7 versus 10.6 hours, respectively.

Table S 1 Summary of effect of formulation (PK analysis set) - Part A

Formulation Comparison	Parameter	Geometric Means for ER1 (fasted)	Geometric Means for ER-R (fasted)	Ratio	
				Estimate	95% CI
ER1 (fasted) vs. ER-R (fasted)	AUC [µmol*h/L]	3.348	3.338	1.016	0.890, 1.160
	C_{max} [µmol/L]	0.2210	0.2106	1.044	0.890, 1.225

Formulation Comparison	Parameter	Geometric Means for ER1 (fasted)	Geometric Means for ER-R (fasted)	Ratio	
				Estimate	95% CI
	C_{max}/C_{12h} [µmol/L]	1.306	1.248	1.015	0.917, 1.123
	C_{12h} [µmol/L]	0.1692	0.1687	1.036	0.884, 1.213

CI = confidence interval

Table S 2 Summary of food effect analysis (PK analysis set) - Part A

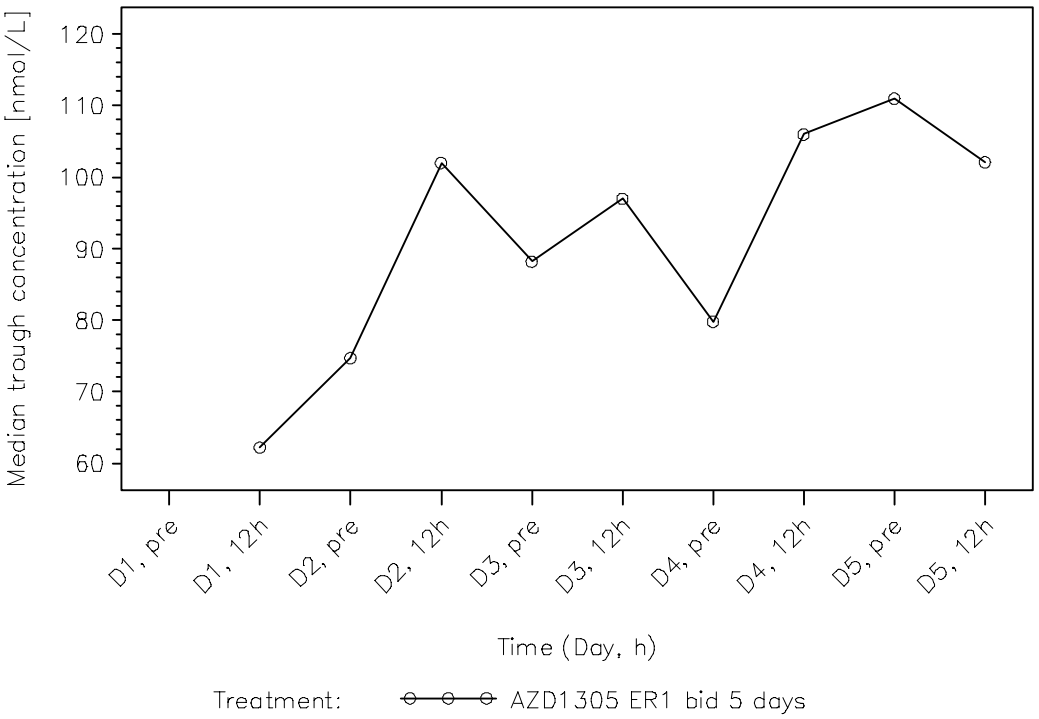
Comparison	Parameter	Geometric Means for Fed	Geometric Means for Fasted	Ratio	
				Estimate	95% CI
ER1 (fed) vs. ER1 (fasted)	AUC [µmol*h/L]	3.079	3.348	0.920	0.809, 1.045
	C_{max} [µmol/L]	0.186	0.221	0.842	0.722, 0.983
	C_{max}/C_{12h} [µmol/L]	1.222	1.306	0.936	0.848, 1.032
	C_{12h} [µmol/L]	0.152	0.169	0.900	0.773, 1.049

CI = confidence interval

Part B1:

Steady state levels of AZD1305 were attained after 5 days of administration of 50 mg of the ER1 formulation twice daily as can be seen from median trough concentrations of AZD1305 in plasma depicted in Figure S 1. AZD1305 concentrations and exposure accumulated moderately by 2.9-fold for R_{ac} (AUC_{0-12}) and 1.7-fold for R_{ac} (C_{max}) after multiple dosing of the ER1 formulation. The geometric mean fluctuation index of AZD1305 was low (0.51) during dosing of the ER1 formulation every 12 hours at steady state.

Figure S 1 Plot of median trough concentrations (C_{trough} in nmol/L) of AZD1305 after dosing 50 mg AZD1305 ER-1 twice daily on linear scale versus time (Day 1 to Day 5) (PK analysis set) - Part B1



Summary of pharmacodynamic results

Part A:

After single dosing of 125 mg AZD1305, there were almost no differences in the mean maximum change from baseline in QTcF between the ER1 formulation in the fasted state (29.3 ms; range: 14.3 – 40.7 ms), ER1 in the fed state (29.0 ms; range: 7.3 – 51.3 ms) and ER-R in the fasted state (32.1 ms; 12.3 – 53.7 ms). The maximum individual QTcF observed was 461 ms in Part A.

Part B1:

The mean maximum change from baseline in QTcF increased by approximately 2-fold from 9.9 ms (range: 1.7 – 22.0 ms) after single dosing on Day 1 to 19.2 ms (range: 2.3 – 41.3 ms) at steady state on Day 5. There was low fluctuation of the mean of the maximum change of QTcF from baseline between Day 2 and Day 5. Also, fluctuation of QTcF on Day 5 at steady-state was low. The maximum individual QTcF observed was 455 ms in Part B1.

There was an apparent (and thus predictable) correlation between QTcF and C_{max} after single dosing (Day 1) and at steady state (Day 5). There was also an apparent correlation between

maximum QTcF after single dosing (Day 1) and maximum QTcF at steady-state (Day 5). QTcF prolongation observed at steady-state was reversible.

Summary of safety results

No safety or tolerability concerns were identified in Part A or Part B1 of this study. There was no serious adverse event and no subject discontinued study treatment due to adverse events. In total, 10 (43%) of all 23 subjects reported 15 AEs after single dosing of 125 mg AZD1305 in Part A or repeated dosing of 50 mg AZD1305 twice-daily in Part B1.

Constipation and nasopharyngitis were the most commonly reported adverse events overall, which occurred each in 2 subjects in Part A or Part B1, while all other AEs in Parts A and B1 occurred in single subjects (see Table S 3 and Table S 4).

The only AE that was considered by the Investigator to be causally related to any treatment with AZD1305 was headache, which was reported in one subject after single dosing of ER-R (fasted).

Most AEs were mild in intensity except for 2 AEs (toothache and constipation) in 2 subjects, which were considered to be moderate.

There were no clinically significant findings in any safety laboratory variables, vital signs or physical examination.

Table S 3 Summary of number (%) of volunteers who had at least 1 AE by preferred term, arranged by system organ class (Safety analysis set) – Part A

	Number (%) of Volunteers*			
System Organ Class Preferred term	**ER1 (fasted) N= 12**	**ER1 (fed) N= 12**	**ER-R (fasted) N= 11**	**Total**
Volunteers with any AE:	**4 (33.3)**	**1 (8.3)**	**3 (27.3)**	**5 (41.7)**
Gastrointestinal disorders	**1 (8.3)**	**0**	**2 (18.2)**	**2 (16.7)**
Constipation	0	0	2 (18.2)	2 (16.7)
Toothache	1 (8.3)	0	0	1 (8.3)
Nervous system disorders	**1 (8.3)**	**0**	**1 (9.1)**	**2 (16.7)**
Dizziness postural	1 (8.3)	0	0	1 (8.3)
Headache	0	0	1 (9.1)	1 (8.3)
General disorders and administration site conditions	**1 (8.3)**	**0**	**0**	**1 (8.3)**
Catheter site related reaction	1 (8.3)	0	0	1 (8.3)
Infections and infestations	**0**	**1 (8.3)**	**0**	**1 (8.3)**

Table S 3 Summary of number (%) of volunteers who had at least 1 AE by preferred term, arranged by system organ class (Safety analysis set) – Part A

	Number (%) of Volunteers*			
System Organ Class Preferred term	**ER1 (fasted) N= 12**	**ER1 (fed) N= 12**	**ER-R (fasted) N= 11**	**Total**
Nasopharyngitis	0	1 (8.3)	0	1 (8.3)
Respiratory, thoracic and mediastinal disorders	**1 (8.3)**	**0**	**0**	**1 (8.3)**
Oropharyngeal pain	1 (8.3)	0	0	1 (8.3)

Each AE in Part A was assigned to the period of the study in which the AE started as follows: the first treatment period was the time between receipt of the first treatment dose of study drug and the second treatment period. The second treatment period was the time between receipt of the second treatment dose of study drug and the third treatment period. The third treatment period was the time between receipt of third treatment dose of study drug and the follow-up assessment at the end of the study. The treatment period was subdivided according to which food condition and/or which test / reference treatment was received in.

*Number (%) of volunteers with AEs sorted by System Organ Class and preferred term, in decreasing order of frequency.

A volunteer can have one or more preferred terms reported under a given SOC.

ER1 (fasted) 125 mg: Single dose of 125 mg AZD1305 ER test formulation 1 without food

ER1 (fed) 125 mg: Single dose of 125 mg AZD1305 ER test formulation 1 with food

ER-R (fasted) 125 mg: Single dose of 125 mg AZD1305 ER reference formulation without food

Table S 4 Summary of number (%) of volunteers who had at least 1 AE by preferred term, arranged by system organ class (Safety analysis set) – Part B1

	Number (%) of Volunteers*
System Organ Class Preferred term	**ER1 50 mg N= 11**
Volunteers with any AE	**5 (45.5)**
General disorders and administration site conditions	**2 (18.2)**
Fatigue	1 (9.1)
Feeling hot	1 (9.1)
Musculoskeletal and connective tissue disorders	**2 (18.2)**
Musculoskeletal chest pain	1 (9.1)
Musculoskeletal pain	1 (9.1)
Infections and infestations	**1 (9.1)**
Nasopharyngitis	1 (9.1)
Injury, poisoning and procedural complications	**1 (9.1)**

Table S 4 Summary of number (%) of volunteers who had at least 1 AE by preferred term, arranged by system organ class (Safety analysis set) – Part B1

	Number (%) of Volunteers*
System Organ Class **Preferred term**	**ER1 50 mg** **N= 11**
Chest injury	1 (9.1)
Skin and subcutaneous tissue disorders	**1 (9.1)**
Skin irritation	1 (9.1)

For Part B1, the adverse events were assigned to the last date and time of dosing.
*Number (%) of volunteers with AEs sorted by System Organ Class and preferred term, in decreasing order of frequency.
A volunteer can have one or more preferred terms reported under a given SOC.
ER1 50 mg: Multiple dose (5 days) of 50 mg AZD1305 ER test formulation 1 twice daily (on Day 5 only in the morning)