Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00008
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A Phase I Study to Investigate the Relative Bioavailability of Modified-Release Formulations of AZD1446 Compared to an Immediate-Release Capsule Under Fed and Fasting Conditions Following Single and Repeated Dose Administration to Young and Elderly Healthy Volunteers

Study dates: First subject enrolled: 22 February 2010
Last subject last visit: 5 July 2010

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)

The study was conducted at a single centre: Quintiles AB, Global Phase I Services, PO Box 1543, SE-751 45 Uppsala, Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables Part 1

Objectives	Outcome variables	Type
Primary	**Primary**	
To characterise the PK profile and to investigate the F_{rel} of AZD1446 following single, oral dose administrations of 4 MR formulations compared with an IR capsule in young healthy volunteers. In addition, the food effect on AZD1446 PK after single doses of MR formulations was investigated.	AUC, AUC_{0-t}, CL/F, C_{max}, F_{rel} , t_{max}, $t_{½\lambda z}$, V_z/F	PK
Secondary	**Secondary**	
To investigate the safety and tolerability of AZD1446 following single, oral dose administration of 4 MR formulations under fed and fasting conditions and an IR capsule under fasting conditions.	AEs, laboratory variables (clinical chemistry, haematology and urinalysis), vital signs (blood pressure and pulse), ECG, physical examination, C-SSRS	safety
Exploratory	**Exploratory**	
To collect and store DNA samples for possible future, exploratory genetic research. This was optional for all participants (is not included in the clinical study report).	Genotype	PGX

AEs adverse events; AUC total area under the plasma concentration versus time curve; AUC_{0-t} the area under the plasma concentration versus time curve from time zero to the time of the last measurable concentration; CL/F apparent plasma clearance; C_{max} the maximum plasma drug concentration; C-SSRS Columbia Suicide Severity Rating Scale; ECG electrocardiogram; F_{rel} relative bioavailability - ratio for MR formulation versus IR capsule and fed versus fasted, IR: immediate release; MR modified release, PK pharmacokinetic(s), PGx pharmacogenetic(s); t_{max} time to reach C_{max}; $t_{½\lambda z}$ terminal half-life; V_z/F apparent volume of distribution

Table S2 Primary and secondary objectives and outcome variables Part 2

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess safety and tolerability of the selected MR formulation(s) during once daily repeated administration in elderly healthy volunteers.	AEs, laboratory variables (clinical chemistry, haematology and urinalysis), vital signs (blood pressure and pulse), ECG, physical examination, C-SSRS	
Secondary	**Secondary**	
To characterise the PK of the selected MR formulation(s) during repeated dose administration in elderly healthy volunteers	AUC, AUC_{0-t}, AUC_{τ}, CL/F, C_{avg} (Day 9), C_{max}, C_{min} (Day 9), Fluctuation Ratio (Day 9), $RAUC_{\tau}$, RC_{max}, t_{max}, $t_{½\lambda z}$, t_{min} (Day 9), V_zF, AUC_{τ} Day9/AUC Day 1	PK
Exploratory	**Exploratory**	
To collect and store DNA samples for possible future, exploratory genetic research. This was optional for all participants (is not included in the clinical study report).	Genotype	

AEs adverse events; AUC total area under the plasma concentration versus time curve; AUC_{0-t} the area under the plasma concentration versus time curve from time zero to the time of the last measurable concentration; AUC_{τ} the area under the plasma concentration versus time curve over the dosing interval; C_{avg} calculated average drug concentration during a dosing interval; CL/F apparent plasma clearance; C_{min} observed minimum drug concentration; C-SSRS Columbia Suicide Severity Rating Scale; ECG electrocardiogram; MR modified release, PK pharmacokinetic(s), PGx pharmacogenetic(s); $RAUC_{\tau}$ accumulation ratio for AUC_{τ}; RC_{max} accumulation ratio for C_{max}; t_{max} time to reach C_{max}; t_{min} time of minimum plasma drug concentration; $t_{½\lambda z}$ terminal half-life; V_z/F apparent volume of distribution

Study design

The study consisted of 2 parts. Part 1 was a 3-period, single-dose, cross-over, partially randomised study. Young (aged ≥18 to ≤50) healthy volunteers were allocated to 1 of 4 cohorts in each of which single doses of an assigned MR formulation (360 mg; MR1 to MR4) and an IR formulation (90 mg) were administered under fasting conditions in the first 2 periods. In the third period, each MR formulation was administered under fed conditions (following a high fat breakfast).

Part 2 was a multiple dose, double-blind, randomised, placebo-controlled, parallel-group study in which a selected MR formulation (MR2) from Part 1 was evaluated. Elderly (aged ≥65 to ≤80) healthy volunteers were randomised to AZD1446 (180 mg) or placebo in a ratio of 6:3 in 2 cohorts.

AZD1446 is intended for treatment of Alzheimer's disease and Attention deficit and hyperactivity disorder.

Target subject population and sample size

The main inclusion criteria were male and/or non-fertile female young and elderly healthy volunteers with a body mass index (BMI) between 19 and 30 kg/m^2, clinically normal findings on physical examination in relation to age and a normal ECG.

In Part 1, up to 40 evaluable young healthy volunteers were to participate in 4 cohorts. Part 1 of the study was open. The sample size for Part 1 was not based on any formal power calculations. A sample size of 8 evaluable healthy volunteers per cohort was considered adequate, based on experience from the interaction part in the preceding single ascending dose study.

In Part 2, up to 18 elderly healthy volunteers were to be randomised 6:3 to active treatment or placebo in up to 2 cohorts. In order to evaluate safety in Part 2, a double-blind placebo design was chosen. A sample size of 9 or 18 in Part 2 was considered adequate to evaluate safety.

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

Table S3 Details of investigational product

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Material ID	Batch number
AZD1446 MR Fast	MR1 capsule 90 mg, white size 0, oral administration	AstraZeneca R&D Sweden	D0900542	10-000354AZ
AZD1446 MR Moderate	MR2 capsule 90 mg, white size 0, oral administration	AstraZeneca R&D Sweden	D0900544	10-000384AZ
AZD1446 MR Slow	MR3 capsule 90 mg, white size 0, oral administration	AstraZeneca R&D Sweden	D0900575	10-000385AZ
AZD1446 MR Slow + IR	MR4 combination of MR3 capsule 90 mg, white size 0 and IR capsule 80 mg, brown size 1 + IR capsule 10 mg, brown size 1	AstraZeneca R&D Sweden	MR3: D0900575 IR 80 mg capsule: D0900394 IR 10 mg capsule: D0900391	MR3: 10-000385AZ IR 80 mg capsule: 09-005446AZ IR 10 mg capsule: 09-005442AZ
AZD1446 IR	IR capsule 80 mg, brown size 1 + IR capsule 10 mg, brown size 1	AstraZeneca R&D Sweden	80 mg capsule: D0900394 10 mg capsule: D0900391	80 mg capsule: 09-005446AZ 10 mg capsule: 09-005442AZ
Placebo MR	capsule white size 0	AstraZeneca R&D Sweden	D0900541	10-000340AZ

Duration of treatment

Part 1: single doses of AZD1446 were administered in 3 treatment periods. Each treatment period lasted for 4 days (Day-1 to Day 3). Each dose was separated by a washout period of at least 4 days (96 hours).

Part 2: multiple doses of AZD1446 or matching placebo were administered on Day 1 and on Day 3 to Day 9 (ie, 1 single dose and 7 multiple doses of AZD1446).

Statistical methods

All analyses were performed by Quintiles AB, Global Phase I Services, Uppsala Sweden. All statistical calculations were performed using the SAS® software, version 9.2. Pharmacokinetic parameters were derived using standard non-compartmental methods in WinNonlin® Professional Edition, version 5.2.

The data were summarized using descriptive statistics. For the assessment of F_{rel}, the values for the MR formulation were compared with the corresponding values for the IR formulation using a mixed-effect analysis of variance model. A non-parametric analysis was used to assess the effect of formulation on t_{max}.

For the determination of food effect, the values for the MR formulations obtained under fed conditions were compared to corresponding values for the MR formulation under fasting conditions using a mixed-effect analysis of variance model. A non-parametric analysis was used to assess the effect of food on t_{max}.

Subject population

Part 1: 44 male young healthy volunteers aged 18 to 50, of which 43 were white and 1 was black, were randomised into the study at 1 study site. All but 5 healthy volunteers completed Part 1 of the study and received 3 administrations of AZD1446. There was one discontinuation of IP due to AEs (DAE: myalgia and pyrexia 3 days post treatment with the IR formulation). One healthy volunteer discontinued IP due to personal reasons and 3 healthy volunteers were discontinued from IP due to protocol violations (use of drugs of abuse). The safety analysis set included all randomised healthy volunteers who received at least one dose of AZD1446, ie, 44 healthy volunteers. The PK analysis set included all randomised healthy volunteers for whom PK data were available and for whom no important protocol deviations were noted, ie, 43 healthy volunteers of which 41 received the IR formulation and 41 received any of the MR formulations. One healthy volunteer was excluded from the PK analysis set due to vomiting in all 3 treatment periods. Overall, the treatment groups were comparable with respect to demographic characteristics

Part 2: 18 white elderly healthy volunteers aged 66 to 76 years, of which 11 were females and 7 were males, were randomised into the study at 1 study site. All elderly healthy volunteers randomised to treatment completed the study and received 8 administrations of AZD1446 or placebo during the planned treatment visit. The safety analysis set included all randomised elderly healthy volunteers who received at least one dose of AZD1446 or placebo, ie, 18 healthy volunteers, whereas the PK analysis set included all randomised elderly healthy volunteers who received at least one dose of AZD1446, ie, 12 healthy volunteers. Overall, the treatment groups were comparable with respect to demographic characteristics except for a higher frequency of females in the placebo group.

Summary of pharmacokinetic results

Part 1: The absorption of the IR formulation was fast with a median t_{max} of 1.5 hours. The release rate of the MR formulations followed the predicted pattern: MR1 (fast release rate)

was absorbed with the fastest rate (median t_{max} 2.0 hours), MR2 (moderate release rate) was absorbed less rapidly (median t_{max} 3.0 hours), and MR3 was most slowly absorbed (median t_{max} 4.0 hours), whereas MR4 (MR3 portion + IR portion) followed the pattern of MR2.

The bioavailability of the MR formulations relative to the IR formulation (F_{rel}) was 88 to 106% in terms of AUC and 31 to 48% in terms of C_{max}. Time to reach C_{max} was significantly delayed following administration of all MR formulations as compared to the t_{max} following administration of the IR formulation. There was no significant food effect on AUC for any of the MR formulations. For MR2 and MR4, C_{max} was slightly higher under fed conditions than under fasting conditions. The median t_{max} was significantly delayed under fed conditions for all MR formulations but MR3.

Part 2: Median t_{max} after a single 180 mg dose of AZD1446 (MR2) was 3 hours in elderly healthy volunteers. Geometric mean C_{max} was 1610 nmol/L and geometric mean AUC was 17500 h*nmol/L. Geometric mean $t_{½\,\lambda z}$ was 10.3 hours and CL/F was 42.7 L/h. The variability in the PK parameters was low. On Day 9, after repeated once daily dosing for 7 days, steady state conditions could be assumed. In line with a $t_{½\,\lambda z}$ of approximately 10 hours, the exposure following repeated dose administration was slightly higher on Day 9 compared to Day 1 (mean accumulation was 22% for C_{max} and 28% for AUC_{τ}). Time to reach C_{max} (t_{max}), $t_{½\,\lambda z}$, CL/F and V_z/F were comparable following single and multiple dose administration and AUC_{τ} (Day 9)/AUC (Day 1) was close to 1 and thus there was no indication of time-dependent PK.

Summary of safety results

Part 1: There was 1 DAE but no deaths, other serious AEs (SAEs), or any other significant adverse event (OAEs). Most of the AEs were mild or moderate in intensity. All post treatment AEs of severe intensity (n=12) were associated with vomiting (MR1 [n=7], MR3 [n=2], MR4 [n=1] and IR [n=2]). None of the healthy volunteers receiving MR2 vomited.

The frequency of healthy volunteers reporting AEs, as well as the number of AEs, was higher under fasting conditions than under fed conditions following administration of MR2, MR3 and MR4. The most common AEs following administration of the MR formulations (360 mg) were associated with gastrointestinal disorders (nausea) and nervous system disorders (headache and dizziness). Nausea was more common during fasting conditions than during fed conditions both with respect to the frequency of healthy volunteers reporting nausea as well as the number of events. For headache and dizziness, there was no clear difference in incidence between fasting and fed conditions. A majority of the events of nausea started in association with high plasma levels of AZD1446 both under fed and fasting conditions. Similar AEs were observed following administration of the IR formulation (90 mg). The most common AEs following administration of the IR formulation were nausea and headache.

Part 2: There were no deaths, other SAEs, DAEs or OAEs. All of the AEs were mild to moderate in intensity. The most common AEs following administration of the MR2 formulation (180 mg) were associated with gastrointestinal disorders (nausea and diarrhoea), nervous system disorders (headache and postural dizziness) and general disorder and

administration site conditions (fatigue). All of these AEs were more commonly reported by elderly healthy volunteers in the placebo group except diarrhoea and postural dizziness, which was only reported by elderly healthy volunteers receiving active treatment.

There were no clinically relevant changes or trends in any laboratory variables, vital signs, ECG physical findings or other safety variables (including physical examination and C-SSRS) in the study.