AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3839
Study Code	D4080C00001
Edition Number	1
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EudraCT Number	2011-001337-16

A Phase I, Randomised, Double-blind, Placebo-controlled, Parallel-group Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effect on Biomarkers of AZD3839 Including an Open-label Food Effect Group in Healthy Male and Female Volunteers of Non-childbearing Potential

Study dates: First subject enrolled: 15 June 2011
Last subject last visit: 25 November 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.

Study centre(s)

One study centre in the United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of single ascending oral doses of AZD3839 and to estimate the maximum tolerated dose, if within the pre-defined exposure, in healthy male and female volunteers of non-childbearing potential (Part 1)	Adverse events, laboratory assessments[a], vital signs, physical examination, 12-lead ECG, telemetry, and C-SSRS
Secondary	Pharmacokinetic	To investigate single dose pharmacokinetics and provisionally assess the dose proportionality of the pharmacokinetics following oral administration of AZD3839 in healthy male and female volunteers of non-childbearing potential (Part 1)	AZD3839 $AUC_{(0\text{-}t)}$, AUC, $AUC_{(0\text{-}24)}$, C_{max}, t_{max}, λ_z, $t_{1/2\lambda z}$, CL/F, V_z/F, A_e, f_e, and CL_R %unbound AZD3839 in plasma
	Pharmacokinetic[b]	To investigate the potential influence of food on the pharmacokinetics and/or tolerability following administration of AZD3839 as an oral solution in healthy male and female volunteers of non-childbearing potential (Part 2)	AZD3839 $AUC_{(0\text{-}t)}$, AUC, $AUC_{(0\text{-}24)}$, C_{max}, t_{max}, λ_z, $t_{1/2\lambda z}$, CL/F, V_z/F, A_e, f_e, relative bioavailability, and CL_R
	Pharmacokinetic/ Pharmacodynamic	To investigate the pharmacokinetic/ pharmacodynamic relationship of the effect of AZD3839 on safety, tolerability, and/or biomarkers relevant for Alzheimer's disease in plasma in healthy male and female volunteers of non-childbearing potential (Part 1), as applicable	CFB and %CFB amyloid-beta 1-40 and amyloid-beta 1-42 plasma concentrations, $AUC_{(0\text{-}t),}$ $AUC_{(0\text{-}24)}$, $\%C_{min}$, t_{min}, $t_{BBL(0\text{-}24)}$, and Av%CFB

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory[a]	Pharmacogenetic	To collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may affect the pharmacokinetics, pharmacodynamics, safety, and/or tolerability related to AZD3839 treatment or the target (BACE 1)	NA
	Pharmacokinetic	To obtain material (eg, plasma/urine) for possible exploratory analysis and investigate the presence and/or identity of drug metabolites of AZD3839	NA
	Pharmacodynamic	To obtain blood/plasma for possible exploratory analysis of biomarkers potentially related to the mechanism of action, neurodegeneration, and Alzheimer's disease	NA
	Pharmacodynamic	To collect and analyse biological samples (eg, plasma) for circulating biomarkers from consenting healthy male and female volunteers of non-childbearing potential before the administration of the investigational product	NA

[a] Results from the metabolite and pharmacogenetic analyses, if performed, will be reported separately.
[b] Part 2 of the study was not conducted and therefore the second objective was not achieved.

%CFB: percent change from baseline; $\%C_{min}$: minimum observed percent change from baseline; $\Delta AUC_{(0-24)}$: area under the plasma biomarker concentration curve from time zero to 24 hour that is below individual healthy volunteer baseline; ΔC_{min}: minimum observed plasma concentration below the individual healthy volunteer baseline (predose biomarker concentration prior to dosing); λ_z: terminal rate constant; A_e: amount of drug excreted unchanged in urine; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-24)}$: area under the plasma concentration-time curve from zero to 24 hours postdose; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the last quantifiable concentration; BACE 1: beta-site amyloid precursor protein cleaving enzyme 1; CFB: change from baseline; CL/F: apparent plasma clearance; CL_R: renal clearance; C_{max}: maximum observed plasma concentration; C_{min}: minimum observed plasma concentration; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; f_e: fraction of drug excreted unchanged in urine; NA: not applicable; $t_{1/2\lambda z}$: terminal half-life; t_{BBL}: duration of concentration below individual healthy volunteer baseline; $t_{BBL(0-24)}$: duration of concentration below individual healthy volunteer baseline from concentration-time data collected over 24 hours; t_{max}: time to C_{max}; t_{min}: time to minimum plasma concentration/ minimum observed percent change from baseline; V_z/F: apparent volume of distribution during the terminal phase.

Study design

This was a first in human, randomised, double-blind, placebo-controlled, parallel-group study. The study was to be conducted in 2 parts, however, based on the interim results of Part 1, it was decided not to proceed with Part 2, and only Part 1 was conducted.

The starting dose of AZD3839 was 1 mg and dose escalation continued up to 300 mg. In each dose group, 8 healthy volunteers were randomised in a 3:1 ratio to active treatment (6 healthy volunteers) or placebo (2 healthy volunteers) using the global randomisation system. After each dose group of 1 mg, 4 mg, 12 mg, 36 mg, 60 mg, 100 mg, 150 mg, 225 mg, and 300 mg, a Safety Review Committee evaluated the safety, tolerability, and the pharmacokinetics (PK) of AZD3839 while blinded to determine the next increased dose level.

Target subject population and sample size

A total of 72 male or female healthy volunteers (8 healthy volunteers in each of 9 dose groups) aged 18 to 55 years (inclusive) with a body mass index (BMI) between 19 and 30 kg/m^2 and weight between 50 and 100 kg (inclusive) who provided signed and dated, written informed consent. Female healthy volunteers were to be of non-childbearing potential.

Table S2 Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product	Strength and dosage form	Manufacturer	Batch number
AZD3839	1 mg/mL oral solution	AstraZeneca	11-001086AZ
AZD3839	5 mg/mL oral solution	AstraZeneca	11-001087AZ
Placebo	Oral solution	AstraZeneca	11-001084AZ

Duration of treatment

Single dose

Statistical methods

Continuous variables were summarised using descriptive statistics including number of healthy volunteers [n], mean, standard deviation, minimum, median, and maximum, by treatment group. Categorical variables were summarised in frequency tables (frequency and proportion) by dose group and treatment (AZD3839 or placebo).

All safety data (scheduled and unscheduled) were presented in the data listings and summarized when appropriate by dose group and treatment. Graphical presentations were used as appropriate.

AZD3839 plasma concentrations, urine amounts, and PK parameters were summarised by dose group using descriptive statistics. Graphical presentations of PK variables were used as appropriate.

For pharmacodynamic (PD) analyses, biomarker (amyloid-beta 1-40 and amyloid-beta 1-42) plasma concentrations were listed and summarised by dose group and/or treatment using descriptive statistics, along with change from baseline, and percentage change from baseline where applicable.

The relationship between AZD3839 PK (concentrations) and PD (amyloid-beta 1-40 and amyloid-beta 1-42 percent change from baseline) was also graphically investigated in this study.

Subject population

Planned:	72 healthy volunteers (AZD3839: 54 healthy volunteers and placebo: 18 healthy volunteers)
Enrolled:	72 healthy volunteers (AZD3839: 54 healthy volunteers and placebo: 18 healthy volunteers)
Completed:	72 healthy volunteers (AZD3839: 54 healthy volunteers and placebo: 18 healthy volunteers)

The treatment groups (AZD3839 and placebo) were well balanced with regards to demographic characteristics, but the mean and median age and weight varied between the dose groups. Though females of non-childbearing potential were allowed in this study, no female volunteers were randomised.

The age of healthy volunteers who received AZD3839 ranged from 19 to 47 years (mean 30 years and median 27 years) and healthy volunteers who received placebo from 19 to 47 years (mean and median 31 years). The BMI of healthy volunteers who received AZD3839 ranged from 19.4 to 29.6 kg/m^2 (mean 24.1 kg/m^2 and median 23.9 kg/m^2) and healthy volunteers who received placebo from 20.9 to 29.8 kg/m^2 (mean 24.6 kg/m^2 and median 24.5 kg/m^2).

Summary of pharmacokinetic results

Following a single oral dose (up to 300 mg), AZD3839 PK was characterised by rapid dose independent absorption (median t_{max}, 20 minutes to 1 hour) and rapid initial decline, followed by a slower terminal phase (geometric mean $t_{1/2\lambda z}$, 10 to 14 hours for AZD3839 4 mg to 300 mg). Based on the statistical assessment of dose proportionality, the point estimate for the slope of AUC, $AUC_{(0\text{-}t)}$, and C_{max} was greater than 1 and the lower bound of the confidence interval was also greater than 1 indicating that AZD3839 exposure parameters increased in a greater than dose-proportional fashion (Table S4). A marked increase in AZD3839 exposure was observed at the 300 mg dose in plasma. Correspondingly, apparent oral clearance from plasma appeared to decrease with increasing dose, especially at 300 mg.

Renal excretion is not a significant route of elimination for AZD3839 since less than 0.5% of the dose was excreted unchanged in urine over the dose range studied.

The percentage of unbound AZD3839 in plasma ranged from 2.12% to 4.71%.

In the last planned dose group of 300 mg AZD3839, the geometric mean C_{max} exceeded the predefined stopping limit of 2000 nmol/L by 1.7-fold (3400 nmol/L). Geometric mean AZD3839 AUC did not exceed the predefined stopping limit at any dose level. In the highest (300 mg) dose group, geometric mean AUC was approximately 17.3-fold below the stopping criteria of 140,000 nmol*h/L.

Table S3 Summary statistics of key AZD3839 pharmacokinetic parameters following single escalating oral dose

Parameter (units)	Statistic	1 mg	4 mg	12 mg	36 mg	60 mg	100 mg	150 mg	225 mg	300 mg
AUC (nmol*h/L)	Geo mean (CV%)	ND	20.9 (85.0)	65.9 (85.7)	218 (31.5)	492 (77.1)	966 (40.0)	1720 (65.7)	2320 (82.3)	8100 (73.7)
	n		4	6	6	6	6	6	6	6
C_{max} (nmol/L)	Geo mean (CV%)	0.696 (63.0)	4.83 (91.9)	18.8 (97.8)	104 (52.0)	206 (99.4)	334 (39.4)	671 (49.6)	1230 (80.3)	3400 (57.1)
	n	6	6	6	6	6	6	6	6	6
t_{max} (h)[a]	Median (range)	0.62 (0.35-1.5)	0.35 (0.33-1.53)	0.68 (0.33-1.02)	0.52 (0.35-0.68)	0.68 (0.67-1.02)	1.03 (0.67-1.52)	0.84 (0.67-1.53)	0.51 (0.33-0.67)	1.02 (0.67-1.52)
	n	6	6	6	6	6	6	6	6	6
$t_{1/2\lambda z}$ (h)	Geo mean (CV%)	4.72 (62.1)	10.1 (39.9)	10.4 (40.2)	10.3 (28.4)	10.2 (12.1)	9.83 (26.6)	13.7 (28.3)	11.4 (30.2)	10.3 (7.8)
	n	6	5	6	6	6	6	6	6	6
CL/F (L/h)	Geo mean (CV%)	ND	445 (85.2)	422 (85.7)	382 (31.7)	282 (77.0)	240 (39.9)	202 (65.7)	226 (82.4)	85.6 (73.6)
	n		4	6	6	6	6	6	6	6
CL_R (L/h)	Geo mean (CV%)	ND	0.615 (51.1)	0.409 (55.8)	0.218 (89.1)	0.255 (55.0)	0.529 (71.5)	0.454 (28.3)	0.481 (37.5)	0.366 (63.6)
	n		3	6	6	6	6	6	6	5

[a] Presented as median (range)

ND not deretmined; Geo geometric; CV% geometric coefficient of variation.

Table S4 Statistical assessment of dose proportionality of AZD3839

Analyte	Parameter (unit)	n[a]	Slope estimate (SE)	(95%CI)	Intercept estimate (SE)	(95%CI)	Coefficient of determination
AZD3839	AUC (nmol*h/L)	46	1.32 (0.07)	(1.17, 1.46)	0.91 (0.31)	(0.28 1.54)	0.8846
	$AUC_{(0-t)}$ (nmol*h/L)	54	1.37 (0.05)	(1.28, 1.46)	0.64 (0.19)	(0.27, 1.02)	0.9447
	C_{max} (nmol/L)	54	1.42 (0.05)	(1.33, 1.51)	-0.46 (0.19)	(-0.84, -0.08)	0.9460

SE standard error
[a] The 'n' represents number of observations used in the model.
$AUC_{(0-t)}$ was included in the analysis since AUC could not be determined for any subject at the lowest dose (1mg) and in 2 volunteers at 4 mg AZD3839.

Summary of pharmacodynamic results

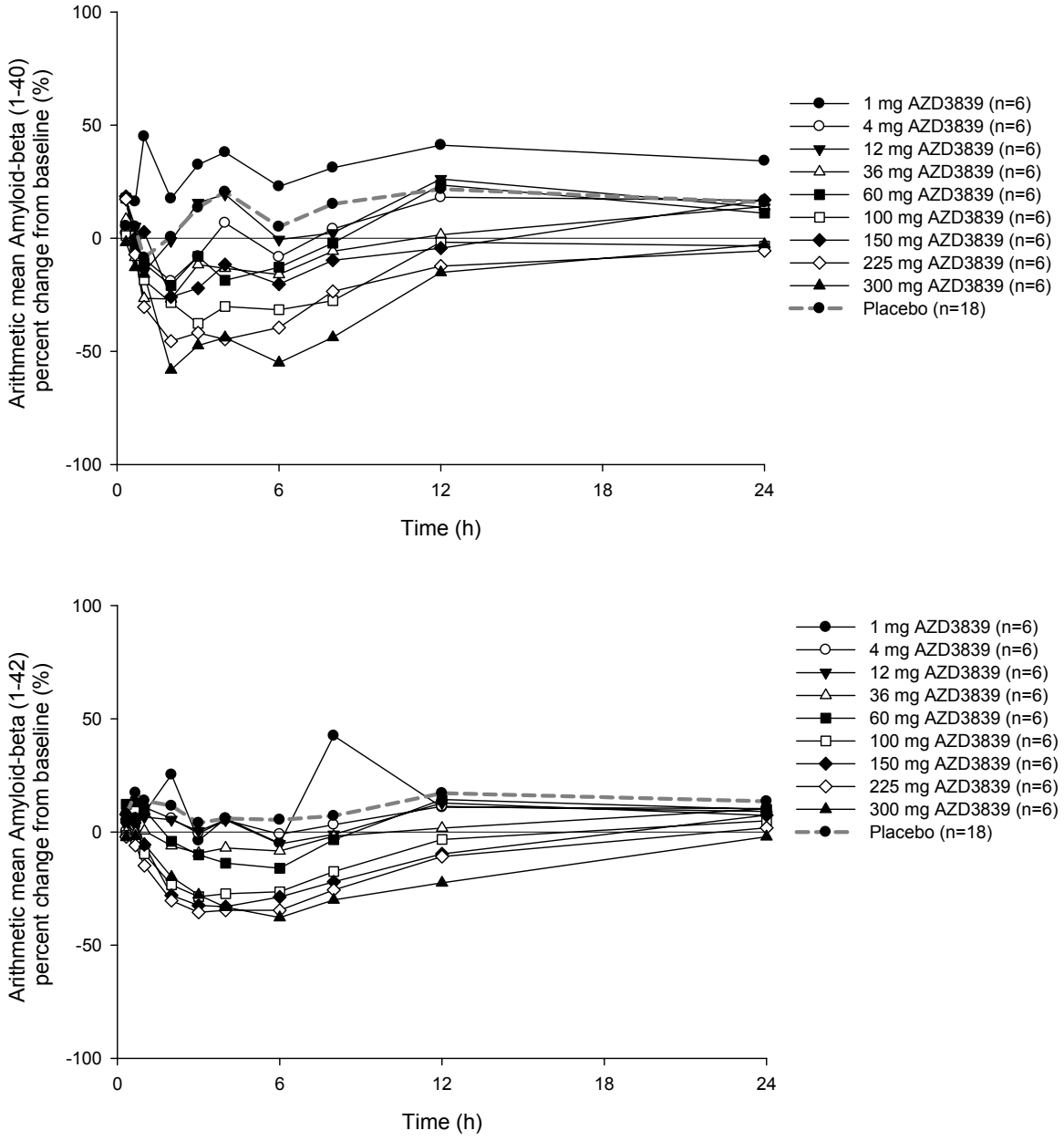
Arithmetic mean percent-change-from-baseline versus time for amyloid-beta 1-40 and amyloid-beta 1-42 over the 0-24 hour time period for all AZD3839 doses groups and the placebo group (Figure S1) suggest that there was a trend for the percent change from baseline (%CFB) for both amyloid-beta 1-40 and amyloid-beta 1-42 to decrease following AZD3839 administration and then to return to approximate baseline levels by 24 hours postdose.

For amyloid-beta 1-40, after AZD3839 administration, the mean minimum value of percent change from baseline ($\%C_{min}$) tended to decrease in a dose-dependent manner with the highest mean decrease of approximately -57.8% occurring at the 300 mg dose groups compared to -25.0% for placebo. There was considerable variability in the duration of amyloid-beta 1-40 concentration below individual healthy volunteer baseline over 24 hours ($t_{BBL(0-24)}$). Treatments groups of 100 mg AZD3839 or greater had a median $t_{BBL(0-24)}$ which were approximately 2-fold or greater that for placebo. At the 2 highest doses (225 and 300 mg), amyloid-beta 1-40 concentration below individual healthy volunteer baseline were maintained for close to 24 hours. A dose dependent effect on amyloid-beta 1-40 concentrations is also apparent in the average percent change-from-baseline over 24 hours post AZD3839 administration (Av%CFB) seemed to decrease with increasing dose at doses above 36 mg. At the 300 mg dose the Av%CFB was -22.5% compared to 13.4% for placebo.

For amyloid-beta 1-42, after AZD3839 administration, the mean minimum value of percent change from baseline tended to decrease in a dose-dependent manner with the highest mean decrease of approximately -40.9 and -39.3% occurring at the 225 mg and 300 mg dose groups, respectively, compared to –7.56% for placebo. All AZD3839 treatments groups had a median $t_{BBL(0-24)}$ above that for placebo. At the 2 highest doses (225 and 300 mg), amyloid-beta 1-42 concentration below individual healthy volunteer baseline were maintained for close to 24 hours. The average percent change-from-baseline over 24 hours post AZD3839

administration (Av%CFB) seemed to decrease with increasing dose. In the 300 mg dose group the Av%CFB was -19.2% compared to 11.9% for placebo.

Figure S1 Percent change from baseline for amyloid-beta 1-40 and 1-42 versus time (0-24 hours Postdose)



Summary of pharmacokinetic/pharmacodynamic relationships

Visual inspection of the data indicated that there is a trend towards a decrease in plasma amyloid-beta %CFB (for both amyloid-beta 1-40 and 1-42) with increasing plasma AZD3839 concentrations.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), or discontinuations of the investigational product due to adverse events (DAEs) reported in this study. At least 1 adverse event (AE) was reported for 17 healthy volunteers (31%) who received AZD3839 and for 7 healthy volunteers (39%) who received placebo. The most frequently reported AEs were dizziness, headache, and orthostatic hypotension. Most of the AEs were considered to have a causal relationship to the investigational product and 1 moderate AE (presyncope) was reported in the 300 mg AZD3839 dose group. No severe AEs were reported.

A total bilirubin value of ≥2 x the upper limit of normal (ULN) (ULN=20.7 µmol/L) was reported for 1 healthy volunteer in the 4 mg AZD3839 dose group on Day 2 (a change from baseline of 13.5 µmol/L). A dose-dependent effect on QTcF was observed, with a mean QTcF prolongation of 5 to 6 ms at the 60 mg dose, 9 to 10 mg at the 100 mg dose, and 16 ms at the 300 mg dose.

Conclusion(s)