Clinical Study Report Synopsis

Drug Substance	AZD1446
Study Code	D1950C00007
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A Phase IIa, Multi-center, Randomized, Double-blind, Placebo-controlled, Cross-Over Study to Assess the Efficacy, Safety and Pharmacokinetics of Three Oral AZD1446 Dose Regimens and Placebo During 2 weeks of Treatment in Adult Non-Users of Nicotine Containing Products and Two Oral AZD1446 Dose Regimens and Placebo during 2 weeks of Treatment in Adult Users of Nicotine Containing Products in Patients with Attention-Deficit/Hyperactivity Disorder (ADHD)

Study dates:	First subject enrolled: 6 November 2009 Last subject last visit: 23 August 2010
Phase of development:	Therapeutic exploratory (IIa)
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

A total of 6 study centers in the United States (US) participated in the study.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	To prove the principle that AZD1446 as compared to placebo improves ADHD core symptoms after 2 weeks of treatment in adult patients, who are not using nicotine containing products, with ADHD as measured by the Connor's Adult ADHD Rating Scale - Investigator Rated (CAARS-INV) Total ADHD Symptoms score (18 item)
	To prove the principle that AZD1446 improves ADHD core symptoms after 2 weeks of treatment in adult patients, who are using nicotine containing products, with ADHD as measured by the CAARS-INV Total ADHD Symptoms score (18 item)
Secondary	To evaluate the effect of 2 weeks of AZD1446 treatment compared to placebo on the respective inattentive, hyperactivity/impulsivity and ADHD index sub-scales as derived from the 30 item CAARS-INV scoring
	To assess the effects of 2 weeks treatment with AZD1446 compared to placebo on cognitive performance, measured by the CogState computerized test battery, including behavioral inhibition testing
	To evaluate the pharmacokinetics (PK) of AZD1446 in patients with ADHD, using population analysis
	To evaluate the effects of 2 weeks treatment with AZD1446 treatment compared to placebo on changes from baseline in Clinical Global Impression (CGI) of ADHD (Severity score [CGI-S], Global Improvement score [CGI-I])
	To assess the effect of 2 weeks treatment with AZD1446 compared to placebo on the 4 subscales from the 30 item CAARS-Self-Report Screening Version (CAARS-S:SV)
	To explore the exposure/response relationship of AZD1446 and efficacy (CGI-S, CGI-I, CAARS-S:SV and CAARS-INV, as applicable

Objectives	Outcome variables
Safety	To assess the safety and tolerability of AZD1446 as compared to placebo in patients with ADHD as measured by: • The incidence and nature of overall adverse events • Vital signs (blood pressure and pulse rate) • Electrocardiogram (ECG) • Physical Examination • Laboratory variables • Pharmacokinetics • Monitoring of emotional profile, using the Profile of Mood States (POMS) • In addition, all patients after baseline and up until the final follow-up assessments were to be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) for suicidal behavior and suicidal ideation occurrences.

Study design

This was a randomized, double-blind, placebo-controlled, 3-period crossover study. In each of the 3 treatment periods, patients took AZD1446 or placebo, 3-times daily, for 2 weeks. After each of the first 2 treatment periods, there was a 21-day washout period, during which patients received placebo 3 times a day to protect the treatment blind.

The study comprised 2 cohorts of patients: those who did not use nicotine-containing products and those who used nicotine-containing products. Non-nicotine users were randomly assigned to receive placebo and 2 of 3 AZD1446 treatment regimens (80mg tid, 80mg qd, or 10 mg tid). Nicotine users received placebo, AZD1446 80mg tid, and AZD1446 80mg qd.

Target subject population and sample size

The target population consisted nicotine product using and non-using of male and nonfertile female patients, aged 18 to 65 years, who met the following key inclusion criteria: a clinical diagnosis of ADHD according to criteria specified in the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV; APA 2000), a score of ≥ 4 (at least moderate severity) on the Clinical Global Impressions for ADHD Severity (CGI-S) test and a score of ≥ 2 on at least six of nine items in at least one of the subscales of the Conners' Adult ADHD Rating Scale-Investigator Rated (CAARS-INV) Total ADHD Symptoms score (18 item) at screening and randomisation.

The sample size for this study was selected to demonstrate PoP for the efficacy of AZD1446 over placebo and was calculated with regard to the primary outcome variable, change from baseline to Week 2 in the CAARS-INV Total ADHD Symptoms score. A sample size of 60 patients who completed the study (36 nicotine nonusers and 24 nicotine users) was deemed

sufficient to ensure >90% power, assuming an effect size of 0.625 in 1 dose of AZD1446 versus placebo in either cohort.

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

The details of investigational product and comparator are presented in the table below.

Table S 2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number
AZD1446	10-mg capsules, oral	AstraZeneca	09-006986AZ, 09-005442AZ
AZD1446	80-mg capsules, oral	AstraZeneca	09-006987AZ, 09-005446AZ
Placebo	Capsules, oral	AstraZeneca	09-006990AZ

Duration of treatment

The study began with a screening/run in period for a maximum of 30 days for patients to discontinue medications or therapy not permitted by protocol. Once the patient was randomised, the total duration of this trial utilizing the crossover design was 12 weeks: 2 weeks for each of 3 treatment assignments plus a 21 day washout between each treatment period.

Statistical methods

This study had 2 co-primary objectives, to show efficacy in each of 2 cohorts of patients: those not using nicotine containing products, and those using nicotine containing products. Identical and parallel analyses were performed for the 2 cohorts.

Proof of principle was to be declared in a cohort if at least 1 dose of AZD1446 was statistically significantly superior to placebo with respect to change from baseline in the primary variable, with a 1-sided test of superiority. A mixed effects repeated measures model (MRMM) was used to analyze the primary variable in each cohort.

Descriptive statistics (including n, mean, median, standard deviation, minimum and maximum for continuous variables and n, frequency and percentage for categorical values) were produced for all efficacy and safety variables, as well as for the changes from randomization and from last predose value for each treatment period.

The PK parameters of AZD1446 were summarized by cohort using descriptive and graphical methods. Population PK/PD analysis was performed by exploratory modelling.

Subject population

Patient enrolment and disposition are summarized in the table below:

Table S 3 Patient disposition (All patients)

	Number of Patients		
	Nicotine Nonuser (N=105)	**Nicotine User (N=30)**	**Total (N=135)**
Patients Enrolled [a]	105 (100)	30 (100)	135 (100)
Patients randomized	52 (50)	27 (90)	79 (59)
Patients who received treatment	52 (50)	27 (90)	79 (59)
-- Period 1	52 (50)	27 (90)	79 (59)
-- Period 2	42 (40)	19 (63)	61 (45)
-- Period 3	36 (34)	17 (57)	53 (39)
Patients who completed treatment	34 (32)	14 (47)	48 (36)
Patients who discontinued treatment	18 (17)	13 (43)	31 (23)
Patients who completed follow up	45 (43)	21 (70)	66 (49)

[a] Informed consent received.

All 79 randomized patients received at least 1 dose of study treatment and were included in the safety analysis set. No patients were excluded from the full analysis set in either cohort. All but 12 of the 79 patients in the full analysis set were also included in the PP analysis set: 8 (out of 52) nicotine nonusers and 4 (out of 27) nicotine users. The PK analysis set included 48 nicotine nonusers and 22 nicotine users.

There were generally no imbalances in either cohort between treatment groups in any demographic or subject characteristic baseline variables, concomitant medication or treatment compliance that could have had a potential influence on the results or their interpretation.

Summary of efficacy results

The results of the primary analysis to test proof of principle are summarized for nicotine nonusers and nicotine users separately below.

Table S 4 CAARS - IR DSM-IV Total score change from baseline at Week 2, AZD1446 vs placebo - nicotine nonusers (Full analysis set)

			Difference versus Placebo		
Treatment	**N**	**LS mean**	**LS Mean**	**95% CI**	**P-Value**
Placebo	40	29.05	.		.

			Difference versus Placebo		
Treatment	**N**	**LS mean**	**LS Mean**	**95% CI**	**P-Value**
80 mg tid	26	29.14	0.08734	(-3.26 , 3.44)	0.8039
80 mg qd	26	27.77	-1.2764	(-4.65 , 2.10)	0.3893
10 mg tid	26	28.54	-0.5103	(-3.89 , 2.87)	0.6382

CAARS-IR Conners Adult Attention Deficit Hyperactivity Disorder Rating Scale - Investigator Rated. CI Confidence interval. DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition. LS Least squares. n Number of patients in analysis. qd Once daily. tid Three times daily.

Note: p-value is one-sided. LSMean is the estimated mean score after adjusting for differences in covariates (eg, visit, period)

The results for nicotine non-users do not support proof of principle. AZD1446 did not statistically significantly improve (P-value <0.10) ADHD core symptoms in any of the treatment groups compared to placebo, after 2 weeks of treatment, as measured by the CAARS-INV Total ADHD Symptoms score. Mean numerical improvement compared to placebo was shown in the AZD1446 80 mg qd and 10 mg tid groups; mean numerical worsening compared to placebo was shown in the AZD1446 80 mg tid group.

Table S 5 CAARS - IR DSM-IV Total score change from baseline at Week 2, AZD1446 vs placebo - nicotine users (Full analysis set)

			Difference versus Placebo		
Treatment	**N**	**LS mean**	**LS Mean**	**95% CI**	**P-Value**
Placebo	17	29.38	.		.
80 mg tid	18	32.75	3.3735	(-2.36 , 9.11)	0.9685
80 mg qd	20	31.57	2.1875	(-3.49 , 7.87)	0.9136

CAARS-IR Conners Adult Attention Deficit Hyperactivity Disorder Rating Scale - Investigator Rated. CI Confidence interval. DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition. LS Least squares. n Number of patients in analysis. qd Once daily. tid Three times daily.

Note: p-value is one-sided. LSMean is the estimated mean score after adjusting for differences in covariates (eg, visit, period)

The results for nicotine users do not support proof of principle. AZD1446 did not statistically significantly improve (P-value <0.10) ADHD core symptoms in any of the treatment groups compared to placebo, after 2 weeks of treatment, as measured by the CAARS-INV Total ADHD Symptoms score. Mean numerical worsening compared to placebo was shown in both the AZD1446 80 mg tid and qd groups.

The results for the secondary efficacy analyses showed that:

- There were no significant effects, compared to placebo, after 2 weeks of treatment with AZD1446 on CAARS-INV sub-scales, CGI-S, and CAARS-S including subscales in adult patients with ADHD (non-nicotine users and nicotine users)

- Significant improvement was observed for AZD1446 80 mg qd compared to placebo on 1 test of the CogState Computerized test battery (the Groton Maze Learning Task) in nicotine non-users. All other the tests were non-significant for both nicotine nonusers and nicotine users.

Summary of pharmacokinetic results

The geometric mean (CV%) of key, model predicted PK results for AZD1446 were as follows. In the 10 mg group (nonusers): mean $C_{ss,max,pred}$ was 196 (21) nmol/L and mean $AUC_{ss,pred}$ was 2120 (21) nmol*h/L. In the 80 mg qd group, mean $C_{ss,max,pred}$ was 1240 (44) nmol/L in nonusers vs 1360 nmol/L (29) in users, and mean $AUC_{ss,pred}$ was 5710 (19) nmol*h/L in nonusers vs 5730 nmol*h/L (19) in users. In the 80 mg tid group, mean $C_{ss,max,pred}$ was 1460 nmol/L (36) in non users vs 1440 (27) nmol/L in users and $AUC_{ss,pred}$ was 17600 (28) nmol*h/L nmol/L in nonusers vs 17000 (17) nmol*h/L in users.

Summary of safety results

There were no deaths and no Serious Adverse Events in the study.

There were 4 Adverse Events (AEs) leading to discontinuation of treatment (1 in the placebo group and 3 in the AZD1446 80 mg tid group) in nicotine nonusers and 2 AEs leading to discontinuation of treatment (1 in the AZD1446 80 mg qd group and 1 in the AZD1446 80 mg tid group) in nicotine users.

In the cohort of nicotine nonusers, greater frequencies of AEs were shown in AZD1446 10 mg (50.0%) and 80 mg tid (61.3%) groups than in the AZD1446 80 mg qd (37.0%) and placebo (40.9%) groups. In the cohort of nicotine users, greater frequencies of AEs were shown in the AZD1446 80 mg qd (72.7%) and 80 mg tid (65.0%) groups than in the placebo group (37.0%). In both cohorts, most AEs were of mild or moderate intensity.

In both cohorts, the haematology, clinical chemistry, urinalysis, ECG and vital signs results showed no clinically meaningful mean changes over time and no clinically meaningful trends in the individual subject changes (ie shifts) among the AZD1446 dose groups compared to placebo. There were no physical findings in patients during treatment with AZD1446 in either cohort. There were no clinically meaningful trends in the Profile of Mood States or Columbia Suicide Severity Rating Scale results in either cohort for any of the AZD1446 treatment groups compared to placebo.

Result(s)

- AZD1446 did not, compared to placebo, improve ADHD core symptoms after 2 weeks of treatment in adult patients with ADHD as measured by the Connor's Adult ADHD Rating Scale - Investigator Rated (CAARS-INV) Total ADHD Symptoms score (18 item) in either nicotine or non-nicotine users

- There were no significant effects, compared to placebo, after 2 weeks of treatment with AZD1446 on CAARS-INV sub-scales, CGI-S, and CAARS-S including subscales in adult patients with ADHD (non-nicotine and nicotine users)

- Significant improvement was observed for AZD1446 80 mg qd compared to placebo on 1 test of the CogState Computerized test battery (the Groton Maze Learning Task) in nicotine non-users. All other the tests were non-significant, across both cohorts.

- Results indicate that AZD1446, at daily doses up to 80 mg tid during 2 weeks had acceptable safety and tolerability in adult patients with ADHD (non-nicotine and nicotine users).

- The pharmacokinetics of AZD1446 in ADHD patients was similar to what has been observed in previous studies in healthy volunteers. No difference in exposure could be seen between nicotine users and non-users