Clinical Study Report Synopsis

Drug Substance	AZD3480
Study Code	D3690C00011
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A Multi-Center Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase IIb Proof of Concept Study with 3 Oral Dose Groups of AZD3480 during 12 Weeks Treatment of Cognitive Deficits in Patients with Schizophrenia

Study dates:	First healthy volunteer/patient enrolled: 13 August 2007 Last healthy volunteer/patient completed: 29 October 2008
Phase of development:	Therapeutic exploratory (IIb)
International Coordinating Investigator:	
Sponsor's Responsible Medical Officer:	

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

Study center(s)

A total of 81 study centers in the United States (66 centers) and Canada (15 centers) enrolled patients in the study.

Publications

None at the time of writing this report.

Objectives

Primary: To prove the concept that AZD3480 improves cognition in patients with stable schizophrenia who are being treated with an atypical antipsychotic medication and who are active cigarette smokers. Cognition was assessed by change from baseline (time of randomization) to Week 12 (last observation carried forward [LOCF], during randomized treatment) in the IntegNeuro computerized test battery of cognitive function scores in the domains of Attention/Vigilance, Working Memory, Verbal Learning, Speed of Processing, and Reasoning & Problem Solving [which replaced Verbal Fluency].

Secondary: To assess the effect of AZD3480, as compared to placebo, on the change from baseline to Week 12 on the UCSD Performance Based Skills Assessment (UPSA2) measure of functional capacity and on the Social Functioning Scale (SFS) patient and informant measure of functional capacity.

Exploratory: There were additional, exploratory objectives of further elucidating the effects of AZD3480 on 1) IntegNeuro, UPSA2, and SFS scores at different timepoints; 2) patient-reported outcomes (PROs) as assessed by the Personal Evaluation of Transitions in Treatment (PETiT) and the Medical Outcomes Cognitive Function (MOS-Cog) measures, 3) selected paper-and-pencil tests from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB; Visual WMSIII Spatial Span Test, Brief Visuospatial Memory Test, BACS Symbol Coding Test); 4) positive and negative symptoms of schizophrenia as measured by change on the Positive and Negative Syndrome Scale (PANSS), and 5) behavioral and biochemical markers of smoking using the Fagerström Test for Nicotine Dependence and blood levels of nicotine and cotinine. Finally, pharmacokinetic (PK) sampling was done for population PK and PK/pharmacodynamic analysis, and standard safety assessments were included to assess the safety of 3 doses of AZD3480.

Study design

This multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase IIb study comprised an 8-week stability period, a 12-week treatment period with 1 of 4 treatment regimens (AZD3480: low dose [5 mg], middle dose [20 mg] and high exposure dose [35 mg or 100 mg for slow or rapid metabolizers respectively] or placebo) and a 2-week follow-up period. Rapid metabolizers (RMs) were defined as patients with ≥1.5 functional CYP2D6 alleles and not concomitantly treated with drugs known to be strong or moderate inhibitors of CYP2D6. Slow metabolizers (SMs) were defined as patients with <1.5 functional CYP2D6

alleles and/or concomitantly treated with drugs known to be strong or moderate inhibitors of CYP2D6.

Target patient population and sample size

Patients with stable schizophrenia who were taking an atypical antipsychotic medication and were active cigarette smokers were included. A sample size of 90 evaluable patients per treatment group was considered sufficient to detect 1 dose with an effect size (ie, treatment difference/standard deviation [SD]) of 0.5 SD in 1 of the 5 IntegNeuro domains in the primary analysis.

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

Study patients were randomly assigned to 1 of 3 AZD3480 treatment groups (5 mg, 20 mg, or 35/100 mg) or to placebo. Study drug was taken orally, once daily. The batch numbers are provided in the study report.

Duration of treatment

12 weeks

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary proof of concept analysis (Group A variables): IntegNeuro domain scores for Attention/Vigilance, Working Memory, Verbal Learning, Speed of Processing, and Reasoning & Problem Solving

Secondary proof of concept analysis (Group B variables): IntegNeuro Reasoning & Problem Solving domain score, UPSA2 score, SFS score

Criteria for evaluation - safety (main variables)

Incidence of adverse events (AEs), physical examination results, laboratory studies, electrocardiogram (ECG), the Barnes Akathisia Rating Scale (BARS), Clinical Global Impression (CGI) scale, Calgary Depression Scale (CDSS), Simpson-Angus Scale (SAS), and PANSS.

Statistical methods

Most efficacy variables, including the primary variable, were analyzed using a fixed-effect analysis of covariance (ANCOVA) model with treatment and metabolic capacity (slow or rapid metabolizer) as fixed effects and baseline score as a covariate. Dunnett's multiple-comparison method was used to control for multiplicity in the 3 comparisons of AZD3480 dose versus placebo. Hypothesis tests were 1-sided for most analyses, including the primary analysis, with p-values for the differences between the least-squares (LS) mean scores.

Pivotal proof of concept: The concept was to be considered proven if, for ≥1 of the 5 Group A cognitive domain scores, ≥1 dose was statistically significantly better than placebo at a

1-sided, adjusted alpha level of $p<0.04$. Within each domain, p-values were adjusted for multiple comparisons between each of the 3 doses and placebo using a 1-sided Dunnett's test, while the critical p-value of $p<0.04$ was a Bonferroni adjustment to ensure that the overall probability to prove the concept for a placebo-like drug (ie, a "false positive") did not exceed 20%.

Supporting proof of concept: A secondary concept incorporating functional capacity outcomes was also tested. This concept was to be considered proven if, for ≥1 of the 5 Group A cognitive domain scores, ≥1 dose was statistically significantly better than placebo at a 1sided alpha level of $p<0.0149$. The concept was also to be considered proven if, for the Reasoning &Problem Solving domain, or the SFS, or the UPSA2 (ie, for any of the Group B variables), ≥1 dose was statistically significantly better than placebo at a 1-sided alpha level of $p<0.0149$ and for the same dose, ≥1 Group A variable exhibited a positive trend (1-sided, $p <0.05$). In this analysis, the critical p-value controls for multiple comparisons among all domain and dose comparisons, and the overall probability to prove the secondary concept for a placebo-like drug did not exceed 20%.

The safety data were summarized by treatment using descriptive statistics.

Subject population

Of the 675 enrolled patients, 445 were randomized, 440 received study treatment, and 308 completed the study. Of the 440 treated patients, 410 were included in the full analysis set and 379 were included in the per-protocol analysis set. They were predominantly male (70%) and white (45%) or black (47%), with a mean age of 41 years; 43% were RMs and 57% were SMs. The majority (88%) had a diagnosis of 'schizophrenia, paranoid'. The 4 treatment groups were balanced with respect to demography, baseline characteristics, and concomitant medications.

Summary of efficacy results

AZD3480 was not shown to have an effect on any of the primary or secondary measures of cognition or life functioning (see Table S1 and Table S2). Nor was an effect observed in any of the subgroups analyzed, including those defined by by metabolic stratum, antipsychotic treatment, age, and sex.

Table S1 Group A cognitive domain scores: changes from baseline to EOT, ANCOVA, superiority vs placebo (Full analysis set)

			Change from baseline		Difference from placebo		One-sided p-values	
Domain	**AZD3480 dose**	**N**	**LS Mean (SE)**	**95% CI**	**LS Mean (SE)**	**Adjusted 95% CI**	**Unadjusted**	**Adjusted**
Attention/ Vigilance	5 mg	90	-0.14 (0.09)	(-0.31, 0.02)	-0.05 (0.12)	(-0.33, 0.24)	0.649	0.872
	20 mg	83	-0.08 (0.09)	(-0.26, 0.10)	0.01 (0.13)	(-0.28, 0.31)	0.455	0.713
	35/100 mg	80	-0.10 (0.09)	(-0.28, 0.08)	-0.00 (0.13)	(-0.30, 0.29)	0.510	0.765
	0 (placebo)	93	-0.10 (0.09)	(-0.27, 0.07)	na	na	na	na
Reasoning & Problem Solving	5 mg	110	0.22 (0.06)	(0.10, 0.34)	0.03 (0.09)	(-0.18, 0.23)	0.368	0.617
	20 mg	85	0.11 (0.07)	(-0.03, 0.24)	-0.09 (0.09)	(-0.30, 0.13)	0.822	0.960
	35/100 mg	90	0.11 (0.07)	(-0.02, 0.24)	-0.08 (0.09)	(-0.29, 0.14)	0.800	0.951
	0 (placebo)	102	0.19 (0.06)	(0.07, 0.31)	na	na	na	na
Speed of Processing	5 mg	90	0.21 (0.06)	(0.08, 0.33)	0.08 (0.09)	(-0.14, 0.29)	0.196	0.387
	20 mg	72	0.02 (0.07)	(-0.12, 0.16)	-0.11 (0.10)	(-0.33, 0.12)	0.863	0.975
	35/100 mg	77	0.12 (0.07)	(-0.01, 0.26)	-0.01 (0.10)	(-0.23, 0.22)	0.524	0.777
	0 (placebo)	86	0.13 (0.06)	(0.00, 0.26)	na	na	na	na
Verbal Learning	5 mg	112	0.09 (0.08)	(-0.08, 0.25)	-0.16 (0.12)	(-0.44, 0.13)	0.903	0.986
	20 mg	89	0.27 (0.09)	(0.09, 0.45)	0.03 (0.13)	(-0.27, 0.33)	0.415	0.669
	35/100 mg	94	0.19 (0.09)	(0.01, 0.37)	-0.06 (0.13)	(-0.36, 0.24)	0.670	0.883
	0 (placebo)	102	0.24 (0.09)	(0.07, 0.42)	na	na	na	na
Working Memory	5 mg	97	0.02 (0.08)	(-0.15, 0.18)	-0.15 (0.12)	(-0.43, 0.13)	0.900	0.986
	20 mg	78	0.00 (0.09)	(-0.18, 0.18)	-0.16 (0.12)	(-0.46, 0.13)	0.907	0.987
	35/100 mg	81	-0.01 (0.09)	(-0.18, 0.17)	-0.17 (0.12)	(-0.46, 0.12)	0.920	0.990
	0 (placebo)	96	0.17 (0.08)	(0.00, 0.33)	na	na	na	na

ANCOVA Analysis of covariance. CI Confidence interval. EOT End of treatment. LS Least squares. N Number of patients in treatment group. n number of patients. na Not applicable. SE Standard error.
All p-values are 1 sided. Adjusted 95% CI and adjusted p-value are adjusted for multiple dose comparisons vs placebo by Dunnett's method.

Table S2 Life functioning scores: changes from baseline to EOT, ANCOVA, superiority vs placebo (Full analysis set)

			Change from baseline		Difference from placebo		One-sided p-values	
Domain	**AZD3480 dose**	**N**	**LS Mean (SE)**	**95% CI**	**LS Mean (SE)**	**Adjusted 95% CI**	**Unadjusted**	**Adjusted**
SFS score	5 mg	104	1.97 (1.96)	(-1.88, 5.82)	-1.31 (2.83)	(-7.99, 5.37)	0.679	0.892
	20 mg	78	0.15 (2.27)	(-4.32, 4.62)	-3.13 (3.05)	(-10.34, 4.08)	0.848	0.971
	35/100 mg	79	1.72 (2.25)	(-2.71, 6.14)	-1.57 (3.03)	(-8.73, 5.60)	0.697	0.903
	0 (placebo)	96	3.29 (2.04)	(-0.73, 7.30)	na	na	na	na
UPSA2 score	5 mg	101	4.11 (0.98)	(2.18, 6.03)	-1.94 (1.40)	(-5.26, 1.37)	0.917	0.990
	20 mg	78	4.49 (1.12)	(2.28, 6.69)	-1.56 (1.49)	(-5.10, 1.97)	0.852	0.973
	35/100 mg	77	4.21 (1.13)	(1.99, 6.43)	-1.84 (1.51)	(-5.41, 1.72)	0.889	0.984
	0 (placebo)	98	6.05 (1.00)	(4.08, 8.02)	na	na	na	na

ANCOVA Analysis of covariance. CI Confidence interval. EOT End of treatment. LS Least squares. N Number of patients in treatment group. n number of patients. na Not applicable. SE Standard error. SFS Social Functioning Scale. UPSA2 University of California at San Diego Performance Based Skills Assessment, Version 2.
All p-values are 1 sided. Adjusted 95% CI and adjusted p-value are adjusted for multiple dose comparisons vs placebo by Dunnett's method.

Summary of safety results

AZD3480 was generally well tolerated in these patients with stable schizophrenia who were taking an atypical antipsychotic medication and who were active cigarette smokers. The frequency of AEs, including AEs of a psychiatric nature, was similar across treatments. AEs of a psychiatric nature were more often serious and/or led to discontinuation in AZD3480-treated patients than in placebo-treated patients. The results for clinical laboratory tests, vital signs, and ECGs were similar across treatments.

A lack of change in PANSS and CGI scores indicated that the patients' underlying disease remained stable during the study treatment period in all treatment groups. A lack of change in CDSS, SAS, and BARS scores indicated no onset of or increase in depressive symptoms or extrapyramidal symptoms.

Date of the report

16 September 2009