AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0328
Study Code	D0190C00007
Edition Number	1
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A Phase IIa, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess Pharmacodynamics, Pharmacokinetics, Safety and Tolerability of Oral Multiple Ascending Doses of AZD0328 in Patients with Schizophrenia

Study dates: First patient enrolled: 2 April 2008
Last patient completed: 4 November 2008

Phase of development: Therapeutic exploratory (IIa)

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

Study center(s)

A total of 2 study centers in the United States participated in the study.

Publications

None at the time of writing this report.

Objectives

Primary objective: to prove the principle that AZD0328 improves cognition after 14 days of treatment in patients with stable schizophrenia being treated with a single atypical antipsychotic drug (quetiapine or risperidone) and who are active cigarette smokers. The effect of AZD0328 on cognition was to be assessed by the change from baseline to Day 14 in the Groton Maze Learning Task (GMLT) and One Card Learning Task (OCLT) standardized composite score as measured by the CogState[1] computerized test battery as compared to placebo.

Secondary objectives:

1. To evaluate the effect of AZD0328 on reasoning and problem solving as assessed by the change from baseline to Day 14 in the CogState battery GMLT score

2. To evaluate the effect of AZD0328 on visual learning as assessed by the change from baseline to Day 14 in the CogState battery OCLT score

3. To evaluate the effect of AZD0328 on processing speed as assessed by the change from baseline to Day 14 in the CogState battery Detection Task (DT) score

4. To evaluate the effect of AZD0328 on visual attention/vigilance as assessed by the change from baseline to Day 14 in the CogState battery Identification Task (IT) score

5. To evaluate the effect of AZD0328 on delayed recall as assessed by the change from baseline to Day 14 in the CogState battery Groton Maze Recall Task (GMRT) score

6. To evaluate the effect of AZD0328 on the additional domains of working memory, verbal learning and social cognition as assessed by the changes from baseline to Day 14 in the CogState battery One Back Memory Task (OBMT), the International Shopping List Task (ISLT) and the Social Matching Task (SMT) scores

7. To characterize the pharmacokinetics (PK) of AZD0328 in patients with schizophrenia stabilized on an antipsychotic medication (quetiapine or risperidone)

[1] CogState Limited; Melbourne, Australia.

by assessment of the time required to attain steady state, dose proportionality at steady state, the degree of accumulation and time dependency of the PK

8. To investigate any effect of AZD0328 on the PK of antipsychotic medications (quetiapine or risperidone) by assessment of steady state PK parameters of antipsychotic following administration of AZD0328 on Day 1, Day 7, and Day 14 versus no treatment of AZD0328 on Day –1 (baseline)

9. To assess the safety and tolerability of AZD0328 as an orally administered solution in patients with schizophrenia stabilized on antipsychotic medications through the incidence of adverse event (AE) and serious AE (SAE) reporting, physical examination abnormalities, laboratory values, vital signs, electrocardiograms (ECGs), and changes from baseline score from the following scales: Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale (SAS), Clinical Global Impression (CGI), Spielberger State-Trait Anxiety Inventory (STAI), and Calgary Depression Scale for Depression (CDSS).

10. To evaluate the effect of AZD0328 on positive and negative symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) from baseline to Day 14

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group study designed to prove the principle that 14 days of treatment with AZD0328 will improve cognition in patients with stable schizophrenia treated with atypical antipsychotic drugs (quetiapine or risperidone) who are active cigarette smokers. The study used a "play the winner" response-adaptive design in which more patients were allocated to those doses predicted to optimally improve cognition based on available data, thereby increasing the statistical power to establish proof of principle for AZD0328.

Target patient population and sample size

Male or non-fertile female; 18 to 55 years of age; diagnosis of schizophrenia according to the Structured Clinical Interview for DSM-IV[2] (SCID); receiving treatment with a single antipsychotic medication (quetiapine or risperidone) for a minimum of 8 weeks prior to enrollment and at a stable doses (±25% of the dose of enrollment) throughout the 4-week period prior to randomization; stable psychotic symptoms without a hospitalization for psychosis over the 8 weeks of clinical stability; actively smoking cigarettes as assessed by an average of ≥10 cigarettes per day.

Assuming a 1-sided test at an alpha level of 0.20, a sample size of 80 patients, in the response-adaptive randomization, completing Day 14 was considered sufficient to provide

[2] Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

approximately 90% power to detect an effect size of 0.60 or greater in the primary outcome variable. Assuming a 20% attrition rate prior to Day 14, 100 randomized patients were required to yield 80 patients completing Day 14.

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

AZD0328 or matching placebo was administered to the patients as an oral solution once daily. AZD0328 was provided as powder for oral solution (formulation number 4069-X-1, batch number C375/1) and was constituted using 9 mg/mL sodium chloride solution for injection. Placebo was provided as commercially available 9 mg/mL sodium chloride solution for injection. A total of 11 AZD0328 doses ranging from 0.00093 to 0.675 mg were used in the study.

Duration of treatment

Each patient received AZD0328 or placebo for 14 days (13 doses; patients were not dosed on Day 2).

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary variable: CogState GMLT and OCLT standardized change composite score at Day 14

Secondary efficacy variables: CogState GMLT, OCLT, DT, IT, and GMRT standardized change from baseline scores at Day 14. Changes from baseline to Day 13 in the CogState OBMT, ISLT, International Shopping List Recall Task, and SMT scores.

(Note: In the Statistical Analysis Plan, the descriptions of the primary variable and the secondary efficacy variables were updated from the descriptions included in the study protocol. These changes were made to more accurately reflect the variable calculations.)

Pharmacokinetic variables:

PK parameters of AZD0328: AUC; $AUC_{(0\text{-}t)}$; AUC_{τ}; C_{trough}; C_{max}; $C_{ss,max}$; t_{max}; $t_{ss,max}$; CL/F; $t_{1/2}$; V_z/F. PK parameters of quetiapine, norquetiapine (active metabolite), risperidone, and 9-hydroxy-risperidone (active metabolite): AUC_{τ}; $C_{ss,av}$; $C_{ss,max}$; $t_{ss,max}$; C_{trough}

Criteria for evaluation - safety (main variables)

Safety variables were as follows: incidence of AE and SAE reporting; results of physical examination, laboratory studies, vital sign assessments, and ECGs; changes from baseline in BARS, SAS, CGI, CDSS, STAI, and PANSS scores.

Statistical methods

For analysis purposes, the 11 AZD0328 doses tested were grouped around the "optimal" dose of 0.011 mg. The optimal dose was identified as the best AZD0328 dose, relative to the other AZD0328 doses tested in the study, via quadratic regression analysis of blinded data. The

dose groups were as follows: low (3 doses from 0.0009 to 0.0028 mg), optimal (5 doses from 0.0048 mg [1/3 × optimal dose] to 0.0329 mg [3 × optimal dose]), and high (3 doses from 0.075 to 0.675 mg). Except for the primary analysis, all statistical tests were 2-sided with a significance level of 5%, ie, α=0.05 unless otherwise specified. No adjustments for multiplicity were made for any secondary analyses.

The primary analysis used a mixed-effects repeated-measures model that included treatment, baseline composite score, day, and day-by-treatment interaction terms as explanatory variables. The comparison of interest was the difference between AZD0328 and placebo. Proof of principle was to be declared if the 1-sided p-value, based on a permutation test, for the AZD0328 ("optimal") group and placebo comparison was less than 0.20. Secondary efficacy variables were analyzed in similar fashion.

Dose proportionality was assessed by regressing log (AUC) and log (C_{max}) for Day 1 or log (AUC_{τ}) and log ($C_{ss,max}$) for Day 14 on log (dose) with patient as a random factor; dose proportionality was to be concluded if the slope (β) is close to 1. A repeated-measures linear mixed model was used to explore the possible effect of AZD0328 on the PK parameters of quetiapine, risperidone, and their metabolites.

Subject population

A total of 158 patients were enrolled in the study, and 100 patients were randomized to study treatment as follows: 78 to AZD0328 and 22 to placebo. The 78 patients randomized to AZD0328 were distributed as follows: 23 in the low-dose group, 37 in the optimal-dose group, and 18 in the high-dose group. In all, 85.9% of AZD0328-treated patients and 81.8% of placebo-treated patients completed randomized treatment. All 100 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.

The treatment groups (the 3 AZD0328 dose groups and the placebo group) were generally balanced with respect to demographic, patient, and baseline disease characteristics. Of the 100 patients in the full analysis set, most were male (83% to 96% across treatment groups) and most were black (78% to 94% across treatment groups). Mean age ranged from 38.3 to 41.7 years across groups. Overall, 82 (83%) of randomized patients were taking quetiapine and 17 (17%) were taking risperidone at enrollment. (One patient, not included in these percentages, was classified as taking risperidone but was actually taking quetiapine). Most patients (96.2% for AZD0328 overall and 100% for placebo) met DSM-IV diagnostic criteria for paranoid schizophrenia. Mean PANSS and CGI scores indicated similar psychiatric status for patients across treatment groups, and mean CDSS scores indicated minimal depressive symptoms in the study population.

Summary of efficacy results

The results of the primary analysis to test proof of principle are summarized in Table 1.

Table 1 GMLT and OCLT standardized change composite score at Day 14 (OC) - MMRM analysis (FAS)

			Change score			Difference versus placebo		
Day	**Treatment**	**N**	**LS mean[a]**	**SE**	**95% CI**	**LS mean**	**95% CI**	**p-value**
Day 14	AZD0328 Low	23	0.234	0.122	(-0.008, 0.476)	-0.033	(-0.348, 0.283)	0.837
	AZD0328 Optimal	32	0.240	0.072	(0.096, 0.384)	-0.026	(-0.271, 0.219)	0.833
	AZD0328 High	13	0.194	0.216	(-0.235, 0.622)	-0.073	(-0.539, 0.394)	0.758
	Placebo	19	0.266	0.099	(0.069, 0.463)			

[a] Positive values indicate improvement.
CI Confidence interval. FAS Full analysis set. GMLT Groton Maze Learning Task.
LS Least squares. MMRM Mixed-model repeated-measures. N Number of patients.
OC Observed cases. OCLT One Card Learning Task. SE Standard error.
/csre/prod/azd0328/d0190c00007/sp/output/tlf/csr13.rtf cstat400.sas 02FEB2009:13:46 laportes

The results of the primary analysis did not provide proof of the principle that AZD0328 improves cognition, relative to placebo, after 14 days of treatment in patients with stable schizophrenia being treated with a single atypical antipsychotic drug and who are active cigarette smokers. AZD0328 in the optimal dose range (0.0048 to 0.0329 mg) did not significantly improve the GMLT and OCLT standardized change composite score compared with placebo at Day 14 (p=0.833). In addition, none of the AZD0328 optimal-dose groups differentiated statistically from placebo at Day 14 on any of the 9 individual cognitive tasks that were defined as secondary efficacy variables..

Summary of pharmacokinetic results

Pharmacokinetic results apply to those doses for which plasma concentrations were above the limit of quantification. The small number of risperidone-treated patients limited the scope of PK analyses for this group.

Steady state was reached within 3 days following once-daily administration of AZD0328. Maximal AUC and C_{max} values were 1367 h*nmol/L and 129 nmol/L, respectively, and were obtained for the highest dose given (0.675 mg); these values were below the predefined exposure limits of 1500 h*nmol/L (AUC) and 600 nmol/L (C_{max}). For quetiapine-treated patients, peak AZD0328 plasma concentrations occurred across doses at median times ranging from 0.5 to 1.9 hours on Day 1 and 0.5 to 2.5 hours on Day 14; oral plasma clearance (CL/F, geometric mean) was 12.9 to 22.5 L/h on Day 1 and 6.6 to 22.1 L/h on Day 14; $t_{1/2}$ was 6.2 to 9.1 hours with an overall mean of approximately 7.8 hours, based on sampling 36 hours following a single dose on Day 1. For risperidone-treated patients, peak AZD0328 plasma concentrations occurred at median times ranging from 0.9 to 2.6 hours on Day 1 and 0.5 to 2.0 hours on Day 14; CL/F (geometric mean) was 17.0 to 28.4 L/h on Day 1 and 15.0 to 22.0 L/h on Day 14; $t_{1/2}$ (geometric mean) was 5.4 to 9.2 hours with an overall mean of approximately 7.1 hours, based on sampling 36 hours following a single dose on Day 1.

The mean accumulation ratio (R_{ac}, Day 14/Day 1) was 0.99 to 1.47 based on $C_{ss,max}/C_{max}$ and 0.96 to 1.29 based on $AUC_{\tau}/AUC_{(0-t)}$, for quetiapine-treated patients; and 0.51 to 1.39 based

on $C_{ss,max}/C_{max}$ and 0.83 to 1.45 based on $AUC_{\tau}/AUC_{(0-t)}$, for risperidone-treated patients; indicating accumulation of AZD0328 was limited. For quetiapine-treated patients, AUC_{τ} for AZD0328 (Day 14) increased in proportion to dose (slope 0.960, 95% CI 0.782 to 1.138), and $C_{ss,max}$ increased somewhat less than in proportion to dose (slope 0.891, 95% CI 0.786 to 0.997). For risperidone-treated patients, no conclusion could be made regarding dose proportionality.

There was no apparent effect of AZD0328 on the PK of quetiapine or norquetiapine. There was no apparent effect of AZD0328 on the $C_{ss,max}$ of risperidone or 9-hydroxy risperidone. However, an effect of AZD0328 on AUC_{τ} of risperidone or 9-hydroxy risperidone could not be excluded.

Summary of safety results

Approximately 77% of AZD0328-treated patients overall reported at least 1 AE compared with approximately 59% of placebo-treated patients. There was no apparent dose-related pattern in the overall frequency of AEs for patients treated with AZD0328. There was 1 serious AE during randomized treatment, pulmonary embolism in a placebo-treated patient; this patient was withdrawn from the study as a result of the AE. No deaths were reported. Four patients treated with AZD0328 (3 in the high-dose group and 1 in the optimal-dose group) withdrew from the study as a result of nonserious cardiovascular AEs (atrioventricular block, congestive cardiomyopathy, and tachycardia [2 patients]); 3 of the 4 patients had ECG abnormalities at screening.

Dyspepsia was the most frequently reported AE for AZD0328 compared with placebo (30.8% versus 18.2%). The frequency of dyspepsia was highest in the AZD0328 low-dose group (39.1%) and occurred with similar frequency in the optimal-dose and high-dose groups (27.0% and 27.8%, respectively). Other GI-associated AEs (nausea, constipation) were also reported more frequently for AZD0328 compared with placebo. The frequencies of nausea suggested a dose-related trend in the AZD0328 groups (4.3% in the low-dose group, 5.4% in the optimal-dose group, 22.2% in the high-dose group, and 0% in the placebo group). Constipation was most frequent in the low-dose group (13.0%), with decreasing frequency as dose increased.

The results of other safety assessments did not indicate any major safety or tolerability concerns.