AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD2624 |
| Study Code | D0970C00004 |
| Edition Number | 1 |
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# A Phase IIa, Double-blind, Double-dummy, Placebo-controlled, Randomized, Parallel-group Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of AZD2624 in Adult Schizophrenia Patients

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|---|---|
| **Study dates:** | First patient enrolled: 13 May 2008<br>Last patient completed: 02 March 2009 |
| **Phase of development:** | Phase IIA |
| **Co-ordinating Investigator**<br>**Sponsor's Responsible Medical Officer:** | |

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

## Study centers

This was a multicenter study.

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

The primary objective of the study was to demonstrate the superior efficacy of AZD2624 when administered as 40-mg oral doses once daily (QD) for 28 days compared to placebo in the treatment of patients diagnosed with schizophrenia and as measured by a change from baseline in total Positive and Negative Syndrome Scale (PANSS) score at Day 28.

The secondary objectives of the study were:

1. To assess the safety and tolerability of oral doses of 40 mg QD of AZD2624 when administered to adult patients with schizophrenia as assessed by vital signs measurements, physical examination, clinical laboratory evaluations, electrocardiograms (ECGs), and the incidence of adverse events.

2. To characterize the pharmacokinetics of AZD2624 (parent) and its metabolite AZ12592232 when given as oral doses over 28 days by assessment of concentration in plasma.

## Study design

This was a randomized, double-blind, double-dummy, placebo-controlled, and active-controlled, parallel-group study conducted in male and female patients diagnosed with schizophrenia between the ages of 18 and 65 years old, inclusive.

## Target patient population and sample size

The target population comprised male and female patients (of non-childbearing potential) between the ages of 18 and 65 years old, inclusive, who were diagnosed with schizophrenia and who were symptomatic at admission.

## Investigational product and comparators: dosage, mode of administration, and batch numbers

AZD2624 was administered as an oral suspension in Ora-Plus (a proprietary oral suspending vehicle) containing 0.05% w/v sodium lauryl sulphate (SLS) as a wetting agent.

AZD2624 placebo was administered as an oral suspending vehicle containing 0.05% w/v SLS.

Patients were administered AZD2624 placebo in the morning and olanzapine placebo capsules in the evening during the washout period from approximately Day –7 through Day –1. If patients were not currently on medication for schizophrenia, they were admitted to the clinical research unit (CRU) on approximately Day –3 and began the placebo run-in period.

After a washout/run-in period of up to 7 days, 106 patients were randomly assigned to receive AZD2624 (batch no. WK80122.005, formulation no. F13550), placebo (batch no. WK80122.003, formulation no. F13324), or olanzapine (batch no. WK80122.004, formulation no. F13076) at a randomization ratio of 2:2:1.

**Treatment A:** Oral dose of 40 mg of AZD2624 in the morning and an oral dose of placebo to match 15 mg of olanzapine in the evening for 28 days.

**Treatment B:** Oral dose of placebo to match 40 mg of AZD2624 in the morning and an oral dose of placebo to match 15 mg of olanzapine in the evening for 28 days.

**Treatment C:** Oral dose of placebo to match 40 mg of AZD2624 in the morning and an oral dose of 15 mg of olanzapine in the evening.

**Duration of treatment**

The duration of the patient's participation was up to 70 days including up to a 21-day screening period. Patients may have been admitted to the CRU during the screening visit, at the discretion of the investigator, while eligibility was determined. This period was not to exceed 2 days. Once a patient had been determined to be eligible, he/she at that time was to begin the washout period. Patients who were currently on treatment for schizophrenia were required to complete a 7-day washout period. Patients who were not currently on treatment for schizophrenia were to complete a 3-day run-in period. During the 7-day washout or 3-day run-in period, all patients were administered AZD2624 placebo in the morning and olanzapine placebo in the evening. Patients then began a 28-day/27-night inpatient treatment period to be followed by an inpatient period when resumption of treatment for schizophrenia took place. This post-treatment hospitalization was a minimum of 4 days up to a maximum of 14 days prior to discharge. Patients were discharged from the study when, at the discretion of the investigator, the patient had been stabilized on treatment following standard inpatient care. The investigator facilitated appropriate discharge planning at the completion of the study period.

**Statistical methods**

The change from baseline in PANSS total score was compared between each treatment and placebo, at each observed case (OC) assessment and at the end of treatment (EOT) assessment, in the intent-to-treat (ITT) analysis set using an analysis of covariance (ANCOVA) model. The primary efficacy result was the EOT (ie, 28 weeks Last Observation Carried Forward [LOCF] during the treatment phase). The ANCOVA model included treatment and baseline score as fixed effects. The analysis of the change from baseline to EOT between AZD2624 and placebo was considered as the primary efficacy analysis. Active control was considered as a reference, and used to test for assay sensitivity.

ANCOVA analyses were performed repeatedly for other secondary variables such as the change from baseline in PANSS positive symptom subscale score, the change from baseline in

the PANSS negative symptom subscale score, and change from baseline in Clinical Global Impression of Severity (CGI-S) score at each OC visit, and at EOT.

PANSS total score response was presented for 10%, 20%, and 30% improvement from baseline.

Baseline was defined as the last assessment prior to the first dose of study medication. Due to the exploratory nature and relatively small sample size, all the statistical tests were 2-sided at $\alpha$=20% unless otherwise specified. Descriptive statistics were used to present efficacy and safety variables.

### Patient population

The demographic and key baseline characteristics of study patients are presented in Table S1.

**Table S1 Demographic and baseline characteristics (ITT analysis set)**

| | | AZD2624 (N=43) | Placebo (N=41) | Olanzapine (N=22) | Total (N=106) |
|---|---|---|---|---|---|
| **Demographic characteristics** | | | | | |
| Sex: n (%) | Male | 40 (93.0%) | 39 (95.1%) | 22 (100.0%) | 101 (95.3%) |
| | Female | 3 (7.0%) | 2 (4.9%) | 0 | 5 (4.7%) |
| Age: years | Mean (SD) | 40.1 (12.0) | 40.2 (11.6) | 35.3 (8.7) | 39.2 (11.3) |
| | Min to max | 22 to 63 | 18 to 65 | 25 to 55 | 18 to 65 |
| Race: n (%) | Caucasian | 10 (23.3%) | 13 (31.7%) | 5 (22.7%) | 28 (26.4%) |
| | Black or African American | 32 (74.4%) | 27 (65.9%) | 16 (72.7%) | 75 (70.8%) |
| | Asian | 1 (2.3%) | 0 | 0 | 1 (0.9%) |
| | Other | 0 | 1 (2.4%) | 1 (4.5%) | 2 (1.9%) |
| **Baseline disease characteristics** | | | | | |
| CGI Severity at baseline: | | | | | |
| Moderately ill | | 9 (20.9) | 10 (24.4) | 4 (18.2) | 23 (21.7) |
| Markedly ill | | 32 (74.4) | 30 (73.2) | 18 (81.8) | 80 (75.5) |
| Severely ill | | 2 (4.7) | 1 (2.4) | 0 | 3 (2.8) |
| BMI ($kg/m^2$) | Mean (SD) | 26.442 (4.212) | 28.478 (5.051) | 28.409 (6.562) | 27.638 (5.139) |
| Baseline PANSS total score | Mean (SD) | 103.77 (14.50) | 102.10 (13.14) | 100.59 (15.06) | 102.46 (14.03) |

BMI Body mass index. CGI-S Clinical Global Impression Severity scale. ITT Intent-to-treat. n Number of patients. N Number of patients in treatment group. PANSS Positive and Negative Syndrome Scale. SD Standard deviation.

The 3 treatment groups were well-balanced in baseline characteristics; however, some minor differences were noted in the demographic data. There were no females in the olanzapine group, and the percentage of Blacks (or African Americans) in the placebo group was lower when compared to the other 2 groups.

### Summary of efficacy results

The key efficacy results of the study are presented in Table S2.

**Table S2 PANSS total score change from baseline to end of treatment (ITT analysis set)**

| | | AZD2624 (N=43) | Placebo (N=41) | Olanzapine (N=22) |
|---|---|---|---|---|
| n | | 42 | 39 | 21 |
| Baseline | Mean (SD) | 103.90 (14.65) | 100.62 (11.62) | 99.71 (14.85) |
| EOT | Mean (SD) | 104.74 (20.44) | 105.44 (15.67) | 91.48 (14.75) |
| Change | Mean (SD) | 0.83 (15.14) | 4.82 (14.99) | -8.24 (14.84) |
| ANCOVA results | LS mean change | 1.40 (2.27) | 4.51 (2.35) | -8.79 (3.20) |
| | 95% CI | -3.10, 5.91 | -0.15, 9.17 | -15.15, -2.44 |
| Difference vs placebo | LS mean | 3.10 (3.28) | | -13.30 (3.96) |
| | 95% CI | -9.60, 3.40 | | -21.17, -5.43 |
| | p-value | 0.346 | | 0.001 |

ANCOVA Analysis of covariance. CI Confidence interval. EOT End of treatment. ITT Intent-to-treat. LS Least squares. n Number of patients. N Number of patients in treatment group. PANSS Positive and Negative Syndrome Scale. SD Standard deviation.

AZD2624 did not demonstrate superior efficacy as measured by change from baseline PANSS total score at Day 28 compared to placebo. In contrast, the active control, olanzapine, demonstrated a substantial, clinically relevant effect on the PANSS total score in comparison with placebo. Furthermore, supporting measurements, which included the Clinical Global Impression of Improvement (CGI-I) and CGI-S scores, showed similar findings.

### Summary of pharmacokinetic results

Summary pharmacokinetic statistics for plasma AZD2624 and metabolite are presented in Table S3.

**Table S3 Summary statistics, geometric mean, of pharmacokinetic parameters for plasma AZD2624 and AZ12592232 (ITT)**

| Parameter | Day | AZD2624 | AZ12592232 |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 1 | 324.01 | 89.03 |
| | 28 | 331.09 | 126.44 |
| $AUC_{0-24}$ (ng•h/mL) | 1 | 3294.70 | 1517.19 |
| | 28 | 3300.86 | 2135.84 |
| $t_{1/2}$ (h) | 1 | 8.47 | 27.10 |
| | 28 | 8.04 | 11.12 |
| $t_{max}$ (h)[a] | 1 | 2.84 | 7.53 |
| | 28 | 2.35 | 4.94 |

$AUC_{0-24}$ Area under plasma concentration-time curve from zero to 24 hours. $C_{max}$ Maximum plasma concentration. $t_{max}$ Time to reach $C_{max}$ following drug administration. $t_{1/2}$ Apparent terminal half-life in plasma.

The pharmacokinetic data were considered to be consistent with other previous pharmacokinetic studies of AZD2624.

### Summary of pharmacodynamic results

There were no pharmacodynamic results in this study.

### Summary of pharmacokinetic/pharmacodynamic relationships

Pharmacokinetic/pharmacodynamic relationships were not analyzed in this study.

### Summary of pharmacogenetic results

There were no pharmacogenetic results.

### Summary of safety results

A summary of adverse events in each category is presented in Table S4. The overall incidence of adverse events was highest in the olanzapine group (82%), followed by the AZD2624 and placebo groups (67% and 66%, respectively). Most adverse events were mild to moderate in severity. There were no deaths in the study. The incidence of non-fatal serious adverse events was highest in the AZD2624 group (9%) and placebo group (5%), and no serious adverse events were reported in the olanzapine group. Similarly, the numbers of patients withdrawing from the study due to an adverse event were highest in the AZD2624 and placebo groups.

**Table S4 Patients who had an adverse event in any category (safety analysis set)**

| Category of adverse event | AZD2624 (N=43) n (%) | Placebo (N=41) n (%) | Olanzapine (N=22) n (%) |
|---|---|---|---|
| Any adverse event | 29 (67.4%) | 27 (65.9%) | 18 (81.8%) |
| Serious adverse event | 4 (9.3%) | 2 (4.9%) | 0 |
| Serious adverse event leading to death | 0 | 0 | 0 |
| Adverse events leading to discontinuation | 3 (7.0%) | 2 (4.9%) | 0 |
| Any other significant adverse event | 0 | 0 | 0 |

n Number of patients. N Number of patients in treatment group.
Note: Percentages are calculated as n/N*100.

The incidence of common adverse events (occurring at an incidence of ≥5% in any treatment group) is shown by preferred term in Table S5.

**Table S5 Common (≥5%) adverse events by preferred term (safety analysis set)**

| MedDRA preferred term | AZD2624 (N=43) n (%) | Placebo (N=41) n (%) | Olanzapine (N=22) n (%) |
|---|---|---|---|
| Any adverse event | 29 (67.4%) | 27 (65.9%) | 18 (81.8%) |
| Headache | 7 (16.3%) | 0 | 3 (13.6%) |
| Vomiting | 6 (14.0%) | 1 (2.4%) | 1 (4.5%) |
| Nausea | 5 (11.6%) | 1 (2.4%) | 1 (4.5%) |
| Psychotic disorder | 4 (9.3%) | 3 (7.3%) | 0 |
| Sedation | 4 (9.3%) | 1 (2.4%) | 3 (13.6%) |
| Decreased appetite | 3 (7.0%) | 1 (2.4%) | 0 |
| Somnolence | 3 (7.0%) | 1 (2.4%) | 4 (18.2%) |
| Stomach discomfort | 2 (4.7%) | 3 (7.3%) | 0 |
| Constipation | 1 (2.3%) | 4 (9.8%) | 1 (4.5%) |
| Dizziness | 1 (2.3%) | 4 (9.8%) | 0 |
| Musculoskeletal pain | 1 (2.3%) | 5 (12.2%) | 1 (4.5%) |
| Weight increased | 0 | 0 | 9 (40.9%) |
| Back pain | 0 | 3 (7.3%) | 0 |
| Dry mouth | 0 | 0 | 2 (9.1%) |

**Table S5 Common (≥5%) adverse events by preferred term (safety analysis set)**

| MedDRA preferred term | AZD2624 (N=43) n (%) | Placebo (N=41) n (%) | Olanzapine (N=22) n (%) |
|---|---|---|---|
| Increased appetite | 0 | 1 (2.4%) | 4 (18.2%) |

MedDRA Medical Dictionary of Regulatory Activities. n Number of patients. N Number of patients in treatment group.
Note: Common adverse event is defined as an event occurring at an incidence of ≥5% in any treatment group.
Note: Events sorted by decreasing frequency in the AZD2624 treatment group.
Note: Percentages are calculated as n/N*100.

The most common adverse events differed among the 3 groups. The adverse events occurring at the highest frequency in the AZD2624 group were headache, vomiting, and nausea. Musculoskeletal pain, constipation, and dizziness were the most common adverse events in the placebo group; and weight increased, somnolence, and increased appetite were the most common in the olanzapine group.

None of the differences among the treatment groups in the changes from baseline were judged to be clinically relevant for any hematology assessments. No clinically relevant changes in clinical chemistry results were observed for any of the patients, and none of the abnormalities in clinical chemistry values were considered to be clinically significant. There were no clinically relevant changes in individual or mean vital sign data, and no differences between treatment groups for any vital sign parameters were noted.

Date of the report

17 September 2009