SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: **SEROQUEL™**

ACTIVE INGREDIENT: **quetiapine fumarate (ICI 204,636)**

Trial title (number): A Multicentre, Open, Randomised Comparison of ICI 204,636 (SEROQUEL™) and Usual Care on Health Outcomes in Subjects With Schizophrenia and Schizoaffective Disorder (5077IL/0056).

Clinical phase: IIIb

First subject recruited: 10 January 1996
Last subject completed: 27 May 1998
AstraZeneca approval date: 17 June 2005

Publications: None at the time of writing this report.

OBJECTIVES
Primary: To compare the rates of hospitalisation for psychiatric, medical, or social consequences of schizophrenia or schizoaffective disorder for subjects treated with quetiapine or usual care. **Secondary:** To compare the effects of quetiapine and usual care on service use as determined by the number of hospitalisations, number of days of hospitalisation (and for each day, the level of care), and use of crisis shelters and out-patient services for psychiatric, medical, or social consequences of schizophrenia or schizoaffective disorder, and quality of life.

Tertiary: To compare the effects of quetiapine and usual care on efficacy, exacerbation of psychotic symptoms, safety, compliance with the administration of antipsychotic medication, and subject satisfaction with antipsychotic medication.

METHODS

Design: A 53-week, multicentre, open, randomised, parallel-group trial, conducted in the US, consisting of 3 segments: A (screening, Weeks -1 to 0), B (tapering of maintenance antipsychotic medication and titration onto quetiapine or usual care, Weeks 0 to 4), and C (continued/flexible dosing of quetiapine or usual care, with or without additional first-line oral or depot antipsychotic medications, Weeks 4 to 52).

Population: Subjects with schizophrenia or schizoaffective disorder, not to exceed 540 subjects with a target of 364 subjects (182 per treatment group) remaining as active study participants throughout the entire study period.

Key inclusion criteria: Men or women, aged 18 years or older who fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, (DSM-IV) criteria for schizophrenia (disorganised, catatonic, paranoid, residual, or undifferentiated types) or schizoaffective disorder (bipolar or depressive types); registered with an out-patient psychiatric facility; currently receiving an oral antipsychotic medication unless treated with a depot antipsychotic; recent history of hospitalisation and crisis shelter use for psychiatric, medical, or social consequences of schizophrenia or schizoaffective disorder; clinical remission from acute exacerbation of schizophrenia or schizoaffective disorder for at least 2 months.

Key exclusion criteria: Pregnancy or lactation; currently receiving, or history of non-responsiveness to, clozapine; clinically unstable haematological, hepatic, cardiovascular, pulmonary, gastrointestinal, endocrine/metabolic, renal, or other systemic disease or laboratory abnormality; white blood cell (WBC) or neutrophil counts below the lower limits of normal; history of drug-induced agranulocytosis.

Dosage: Quetiapine dosing was titrated during Segment B and continued during Segment C to a maximum dose of 800 mg/day (administered orally, twice daily) according to subject response and tolerability. Usual care was titrated during Segment B and continued during Segment C in accordance with a dose and regimen determined by the standard of care.

Key assessments:

Health outcome assessments: Primary: Proportion of subjects who were hospitalised at least once during trial treatment for psychiatric, medical, or social consequences of schizophrenia or schizoaffective disorder. **Secondary:** number of hospitalisations, number of days of hospitalisation by type of in-patient bed occupied, and use of crisis shelter and out-patient services for psychiatric, medical, or social consequences of schizophrenia or schizoaffective disorder; quality of life (assessed by the standard US version of the Medical Outcomes Study [MOS] 36-item Short-form Health Survey [SF-36] and the 32-item Behavior and Symptom Identification Scale [BASIS-32]).

Efficacy assessments: Efficacy was determined by the severity of, and improvement in, psychiatric symptoms for each subject. The Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) Severity of Illness item were used to assess the severity of symptoms, the CGI Global Improvement item was used to assess the improvement.

Subject satisfaction with antipsychotic medication was measured by the Subject Satisfaction with Antipsychotic Treatment item. Compliance with the administration of antipsychotic medication was assessed by tablet counts.
Safety assessments: Adverse event reporting, clinical laboratory tests, electrocardiograms (assessed as needed post-baseline), physical examination results, Simpson Scale, vital signs (assessed as needed post-baseline), and body weight.

RESULTS
Demography: Of the 508 subjects screened for entry into this trial, 449 were randomised to treatment: 227 (50.6%) to quetiapine and 222 (49.4%) to usual care. The intention-to-treat (ITT) population consisted of 436 subjects (quetiapine 225, usual care 211). The majority of these subjects were Caucasian (306/436, 70.2%). The mean age of all subjects was 38.2 years (range 18 to 71 years). No statistically significant differences were evident between the two treatment groups for any of the demographic characteristics recorded (age [and age at onset of schizophrenia], sex, race, weight).
Health outcomes: Among the ITT population, quetiapine subjects were more likely to be hospitalised (due to schizophrenia and for any reason), were hospitalised more often, and were hospitalised for more days than usual care subjects. These treatment group differences, reported in Tables I and II, were statistically significant.

Table I Proportion of subjects hospitalised at least once

	Number (%) of subjects			
	Quetiapine (N = 225)		Usual care (N = 211)	
Proportion of subjects hospitalised at least once due to schizophrenia	111	(49.3)	76	(36.0)
Proportion of subjects hospitalised at least once for any reason	118	(52.4)	81	(38.4)

Table II Proportion of subjects hospitalised: estimated treatment effects

	Odds ratio estimate [a]	95% CI [a]	p-values [a]	
			CMH test	Breslow-Day test
Proportion of subjects hospitalised at least once due to schizophrenia	0.588	0.399 to 0.867	0.007	0.281
Proportion of subjects hospitalised at least once for any reason	0.566	0.384 to 0.833	0.004	0.360

a CMH test, odds ratio, and CI pertain to treatment comparisons of hospitalisation rates stratified by pooled sites; the Breslow-Day Test reflects the homogeneity of results across pooled sites.
CI Confidence interval.
CMH Cochran-Mantel-Haenszel.

There were no statistically significant treatment group differences in crisis shelter and out-patient services utilisation among the ITT population.
Both treatment groups showed some improvement in quality of life measures (SF-36 MCS and BASIS-32 daily living/role functioning, depression/anxiety, psychosis and overall) from baseline to Week 52 and endpoint. This pattern was similar across both treatment groups. There were no statistically significant treatment group differences in any of the measures at any time point.
Efficacy: Quetiapine was shown to be similar to usual care antipsychotic medication in the treatment of schizophrenia and schizoaffective disorder. Both treatment groups showed improvement in PANSS scores, CGI–Severity of Illness, and CGI-Global Improvement items. This same pattern of improvement was reflected in the assessment of subject satisfaction. There were no statistically significant treatment group differences in PANSS scores, CGI-Severity of Illness, and CGI-Global Improvement for the ITT population (subject satisfaction was not tested for treatment group differences).
Safety: Quetiapine was generally well tolerated. Two deaths occurred among quetiapine subjects although both of these occurred after quetiapine treatment had ended. No deaths were reported among usual care subjects.
A higher proportion of quetiapine subjects (14.1%) than usual care subjects (9.6%) experienced serious adverse events. However, no treatment group differences were evident among specific events. The most commonly reported serious adverse events were events related to, or common among, subjects with schizophrenia or schizoaffective disorder (overdose, suicide attempt, and depression).
No treatment group differences were evident and no patterns emerged in terms of adverse events leading to withdrawal of trial medication (quetiapine: 13.2%; usual care: 11.0%), especially as these patterns may differ from overall incidences of adverse events.
Somnolence was clearly the most frequently reported adverse event amongst quetiapine subjects (48.9%) and disproportionately more common than among usual care subjects (22.9%). Other common adverse events which were more likely to occur among quetiapine subjects than in usual care subjects were dizziness (quetiapine: 19.4%; usual care: 11.0%) and

agitation (quetiapine: 10.6%; usual care 3.7%). Adverse events reported more frequently among usual care subjects than in quetiapine subjects included diarrhoea (quetiapine: 6.6%; usual care 14.2%), akathisia (quetiapine: 4.4%; usual care: 8.7%), and extrapyramidal syndrome (quetiapine: 1.3%; usual care: 8.7%).

Extrapyramidal symptoms were more likely to be reported as adverse events for usual care subjects than for quetiapine subjects in certain EPS-related adverse events. These events, which were less frequent among quetiapine subjects, were akathisia and extrapyramidal syndrome. The results from the analysis of the Simpson Scale summarising EPS over time were consistent with this finding. At each measured time point after Week 16, quetiapine subjects were more likely than usual care subjects to show improvement in EPS and less likely than usual care subjects to show worsening.

No notable problems and no treatment group differences were noted in haematology and liver function laboratory tests. A small number of subjects had clinically significant laboratory values for neutrophils (quetiapine: 6, usual care: 0) and ALT and/or AST (quetiapine: 16; usual care: 10) though most of these returned to non-clinically significant values at the next measurement.

High incidences of clinically significant weight gain (at least a 7% increase of baseline body weight) were evident in both treatment groups at Week 52 (quetiapine: 33.6%; usual care: 27.8%). Quetiapine subjects were slightly more likely than usual care subjects to experience weight gain at all measured time points though the treatment group differences were statistically significant only at Week 16 (quetiapine: 18.2%; usual care: 10.4%).

No notable problems or treatment group differences were found in other safety measures (ECG or physical examinations).
