SUMMARY

ZENECA INC

FINISHED PRODUCT:SEROQUEL™

ACTIVE INGREDIENT(S): ICI 204,636

Trial title (number): A Multicenter, Double-Blind, Randomized, Controlled, Multiple Fixed-Dose and Dose Regimen Comparison of SEROQUEL™ (ICI 204,636) and Haloperidol in the Prevention of Psychotic Relapse in Outpatients with Chronic or Subchronic Schizophrenia. (5077IL/0015)

Clinical phase: III

First patient entered: 27 July 1993 **Data cutoff date:** 1 June 1995

Publication: None at the time of writing this report.

OBJECTIVES: To delineate the dose response relationship for SEROQUEL, administered on either TID or BID dose regimens, in the prevention of psychotic relapse in outpatients with chronic or subchronic schizophrenia as measured by the time to withdrawal from the trial. To compare the efficacy, as measured by the changes from baseline in the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI), and the safety and tolerability among three fixed doses of SEROQUEL administered on either TID or BID dose regimens, with haloperidol in the prevention of psychotic relapse in the above population. To investigate the relative effects of multiple fixed doses of SEROQUEL and haloperidol, administered for up to 1 year, on negative symptoms, cognitive function, quality of life, and health outcomes assessments in the above population. To explore the relationship between the plasma concentrations of ICI 204,636 and response to treatment.

METHODS:

Design: US and Canadian, multicenter randomized, double-blind, two segment study comparing three fixed doses and two dose regimens of SEROQUEL with a standard dose of haloperidol. Segment A consisted of a screening period, and Segment B consisted of a double-blind phase (titration followed by fixed total daily doses of 75 mg, 300 mg, or 600 mg SEROQUEL).

Interim analyses were performed when approximately one-half of the total expected number of withdrawals from the trial had occurred.

Changes to the investigational plan: Due to a slow rate of patient accrual, recruitment for this trial was terminated early. As a result, the study objectives were amended on 1 March 1995 to combine the TID and BID regimens within dose groups for all inferential analyses. No comparisons between dose regimens were performed.

Population: A total of 301 adult men and women from 34 centers were randomized.

Key inclusion criteria: a) chronic or subchronic schizophrenia according to DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised -1987) criteria for any of the following subtypes: disorganized, catatonic, paranoid, residual, or undifferentiated; (b) no concurrent Axis I DSM-III-R diagnoses such as alcohol or psychoactive substance dependence not in full remission, concomitant organic mental disorder, or mental retardation; (c) full or partial remission according to DSM-III-R criteria upon entry into Segment A.

The following qualification criteria were met at entry to the trial and at completion of Segment A for the patient to have been randomized to treatment: (d)18-item BPRS (0- to 6- point system) positive symptom items rated ≤ 3 (moderate) for the following: Item 4: Conceptual disorganization; Item 11: Suspiciousness;Item 12: Hallucinatory behavior;Item 15: Unusual thought content; (e) CGI Severity of Illness item assessment ≤ 4 (moderately ill)

Key exclusion criteria: any significant clinical disorder, electrocardiogram (ECG), or laboratory finding which in the opinion of the investigator made the patient unsuitable for receiving an investigational drug

Dosage:

Segment A, Screening: All non-neuroleptic psychotropic agents, except medications for the treatment of extrapyramidal symptoms (EPS) (and lorazepam, added in US and Canadian protocol revision dated 29 July 1994), were discontinued before the start of Segment A. No trial treatment was administered during this screening phase. The duration of Segment A was 7 to 28 days depending on the need for tapering of previous neuroleptic medication.

Segment B, Double-Blind: On entry into Segment B, patients were randomized to one of the following seven treatment groups: total daily dose of 75 mg, 300 mg, or 600 mg SEROQUEL (administered BID or TID), or 12 mg haloperidol (administered TID). The initial 2 to 3 weeks of Segment B were allowed for titration and the remaining 50 weeks (or until psychotic relapse) were fixed dose. Formulation and lot numbers for trial treatments follow, respectively:

SEROQUEL	25-mg tablets	F7134	92-0707T, 92-0052, 94-0195, 94-3085T
	25-mg matched placebo	F7142	92-0473, 93-0098, 93-3075, 93-0099
	100-mg tablets	F7133	92-0725T, 92-0741T, 92-0745T, 93-0781T, 93-0775T, 93-0776T, 93-0782T, 94-3036T, 94-0237, 94-0237T, T43093
	100-mg matched placebo	F7143	92-0477, 92-0475, 93-0103, 93-0100, 93-0101, 93-0102, 93-3074
Haloperidol	2-mg tablets	F10108	92-3216, 94-3053
	2-mg matched placebo	F10109	92-3217
	5-mg tablets	F10110	92-3218, 94-3054
	5-mg matched placebo	F10111	92-3219, 94-3055

Key assessments:

The primary efficacy variable was time to withdrawal from Segment B for any reason, in days from randomization. Patients who completed Segment B were censored at their completion date, and patients who remained in Segment B were considered censored as of 1 June 1995. The time to psychotic relapse was also analyzed, where all patients who did not withdraw due to psychotic relapse were censored.

Psychiatric rating scale measures included BPRS positive symptom cluster score, CGI Severity of Illness and Global Improvement scores, and Modified Scale for the Assessment of Negative Symptoms (SANS). These were secondary efficacy variables. Tertiary measures of efficacy included health outcomes assessments (Questionnaire and Quality of Life Scale [QLS]) and cognitive function tests. These assessments were monitored as per the protocol.

Safety: Adverse events and neurologic measures (Simpson Scale and AIMS) were monitored as per the protocol. Safety also was assessed by physical examinations, vital signs, ECGs, ophthalmologic examinations, and clinical laboratory tests.

Statistical considerations:

The primary population for the time to withdrawal and the time to relapse (Criteria I and II) included all randomized patients. The secondary population for the time to withdrawal and the time to relapse (Criteria I and II) included all patients who were considered protocol compliant and who successfully completed the titration phase of Segment B. The remaining efficacy variables were analyzed for all randomized patients with baseline and at least one post-baseline BPRS or CGI measurement. All patients randomized to treatment were included in the safety analyses.

Formal analyses of the time to withdrawal and the time to relapse (Criteria I and II combined) were performed on all available data through Week 52, when the last randomized patient would have had the opportunity to complete 3 months of treatment. For the remaining efficacy and safety variables, last observation carried forward (LOCF) analyses were performed on all data available up through Week 12, and analyses based on observed data were performed on all available data up through Week 52. Summary statistics for Health Economics and QOL were provided yet no formal analyses were performed.

All inferential analyses with respect to efficacy and safety were performed for the total daily dose of trial treatment received (SEROQUEL 75, 300, or 600 mg, or haloperidol 12 mg). No attempt was made to inferentially compare the TID and BID dose regimens within each total daily dose group. All dose group comparisons were declared statistically significant at the 0.05 level using 2-tailed tests. Descriptive statistics were provided by treatment arm (randomized treatment) and dose group (SEROQUEL 75, 300, or 600 mg, or haloperidol 12 mg) in the T-tables.

RESULTS:

Demography: Due to the early termination of recruitment, a total of 331 patients entered into the trial. Of these, 301 patients from 34 centers entered the double-blind phase, with 85 patients randomized to SEROQUEL 75 mg, 88 patients randomized to SEROQUEL 300 mg, 87 patients randomized to SEROQUEL 600 mg, and 41 patients randomized to haloperidol. No center enrolled more than 6% of all randomized patients. The treatment groups were generally well balanced with respect to demographic characteristics, psychiatric diagnosis and illness history, and psychiatric assessments at baseline. The overall mean age was 38 years (range 19 to 66 years). The majority of patients were men (80%) and white (70%)

Chronic paranoid schizophrenia was the most common diagnostic category among randomized patients (50% of patients). The vast majority of patients had chronic schizophrenia (93%). There were no clinically meaningful differences among the treatment groups with respect to psychiatric diagnosis or illness history.

The overall proportion of patients who completed the trial was low. Eight percent of patients in the SEROQUEL 75-mg group, 13% of patients in the SEROQUEL 300-mg group, 16% of patients in the SEROQUEL 600-mg group, and 32% of patients in the haloperidol group completed the trial. The majority of withdrawals in the SEROQUEL groups were for psychotic relapse and the majority of withdrawals in the haloperidol group were for adverse events or intercurrent illnesses.

Efficacy: There was no statistically significant dose response among SEROQUEL groups in the time to withdrawal from the trial, which was the primary efficacy variable. Pairwise comparison showed no statistically significant differences among any treatment groups, including haloperidol, in the time to withdrawal from the trial. There was also no statistically significant dose response among the SEROQUEL groups in the time to withdrawal from the trial for psychotic relapse. Times to psychotic relapse were generally longer in the haloperidol group. Pairwise comparisons of the time to withdrawal for psychotic relapse revealed statistically significant differences between the haloperidol group and each SEROQUEL group. However, there was an imbalance in the reasons for withdrawal from the trial between the SEROQUEL and haloperidol treatment groups with proportionally more patients in the haloperidol group withdrawing for adverse events. Some of these adverse events, among haloperidol patients, may have been surrogates for relapse (eg, anxiety, suicide attempt, depression). Since proportionally more censoring for relapse occurred in the haloperidol treatment group, any contrasts between the haloperidol and SEROQUEL groups for time to withdrawal for psychotic relapse may not reflect true differences in the relapse distributions among the groups and therefore are noninformative. Results of the analysis of the time to withdrawal in the secondary population showed a similar trend for the primary population. The analysis of prognostic variables indicated that only the interaction between treatment groups and the need for

neuroleptic medication to be tapered during Segment A were significantly associated with time to withdrawal.

Statistically significant differences in favor of haloperidol when compared with each SEROQUEL group were seen in the change from baseline to the final evaluation for the BPRS positive symptom cluster score and the CGI Severity of Illness score. Additionally, a significantly greater proportion of patients in the haloperidol group demonstrated an improvement at the final evaluation on the CGI Global Improvement item. These results are consistent with the results of the primary efficacy analysis of time to withdrawal, since proportionally more patients in the SEROQUEL groups compared to the haloperidol groups withdrew for psychotic relapse and psychotic relapse was defined in terms of worsening BPRS positive symptoms cluster and CGI Global Improvement item scores. Similar trends were seen on the analysis of the change from baseline to final evaluation for the SANS summary score. The higher SANS summary scores in the SEROQUEL groups compared to the haloperidol group may be reflective of increased levels of negative symptoms which may be secondary to increased positive symptoms, demonstrated by higher BPRS positive symptom cluster scores in the SEROQUEL groups.

Tertiary objectives included investigations of the relative effects of multiple fixed doses of SEROQUEL and haloperidol on negative symptoms, cognitive function, quality of life, and health outcomes assessments as well as exploring the relationship between the plasma concentrations of ICI 204,636 and response to treatment. Results of note include the dose-related improvement in tests of selective attention (Stroop color test) and executive function (Trail making test [Trails A]) during treatment with SEROQUEL. Additionally, a small dose-related improvement in the QLS total score occurred in the SEROQUEL groups. These findings require further exploration in controlled clinical trials.

Safety: The median time on randomized treatment was approximately 2 to 3 months. Overall, the use of psychotropic medications (ie, benztropine mesylate, chloral hydrate, and lorazepam) was greatest in the haloperidol group (66% of patients) and similar in the SEROQUEL groups (range 41 to 44% of patients).

TABLE A Summary of adverse events

Category	Treatment group			
	SEROQUEL			Haloperidol
	75 mg (n = 85)	300 mg (n = 88)	600 mg (n = 87)	(n = 41)
Number of patients (number of adverse events)				
Adverse events associated with death	0	0	0	0
Adverse events leading to withdrawal	7 (9)	13 (13)	13 (15)	14 (21)
Serious adverse events not leading to withdrawal	1 (1)	0	4 (7)	2 (2)
Other adverse events	68 (269)	58 (281)	58 (269)	24 (108)
No adverse events	9	17	12	1

The most frequently reported adverse event was somnolence. The only frequently reported adverse events in the SEROQUEL groups with an apparent dose-response relationship were

somnolence, dizziness, nervousness, and weight gain. The proportion of patients who withdrew from the trial due to adverse events was similar among SEROQUEL groups and these proportions were all lower than that observed in the haloperidol group. The most common adverse events leading to withdrawal were somnolence in the SEROQUEL groups and EPS adverse events in the haloperidol group. A total of 11 serious adverse events which did not lead to withdrawal were reported by 8 patients during the trial. There was no consistency with regard to serious adverse events reported; each serious adverse event was reported by one patient only. Few severe adverse events were reported during the trial and there were no trends apparent.

The results of the Simpson Scale analysis failed to show any dose-related increase in EPS associated with SEROQUEL treatment. In each SEROQUEL group, the incidence of EPS was less than that observed in the haloperidol group. These results are supported by the analyses that the proportions of patients administered medications for EPS and proportions of patients with EPS adverse events were lower in the SEROQUEL groups. The results of the AIMS analysis showed no dose-related worsening or improvement in abnormal involuntary movements over time in the SEROQUEL or haloperidol groups.

SEROQUEL treatment was associated with benign fluctuations in white blood cells (WBCs) and absolute neutrophil counts (ANCs); however, the incidence of clinically significant WBC and ANC decreases was similar to that in the haloperidol group.

SEROQUEL was associated with transient elevations in LFTs. There was no dose-response relationship among the SEROQUEL groups and no clear difference between the TID and BID dose regimens in terms of the proportions of patients with clinically significant LFT elevations.

SEROQUEL was associated with dose-related decreases from baseline in total T_4, free T_4, and total T_3. These decreases were seen early in the trial (within the first four weeks) and no progressive decreases were seen over time. There were no substantial elevations from baseline in TSH associated with the decreases in total T_4, free T_4, and total T_3 and no progressive increases in TSH were seen over time.

The analysis of plasma prolactin concentrations indicates that SEROQUEL, in contrast to standard antipsychotic agents, generally produced decreases from baseline in prolactin levels.

Overall, the results of the slit lamp and LOCS III evaluations of the ocular lens support the view that SEROQUEL had no clinically relevant effect on the ocular lens. Ocular changes were of a very minor nature, were noted in all treatment groups, and were not related to the dose of SEROQUEL administered. LOCS III scores showed no dose-related increase in the proportions of patients with worsening scores in the SEROQUEL groups, and similar proportions of patients in the SEROQUEL and haloperidol treatment groups had worsening scores. The magnitude of worsening in any LOCS III category did not represent a clinically significant change from baseline examination in any treatment group.

Although this trial was not capable of establishing definitively that SEROQUEL does not induce cataracts in man, SEROQUEL did not appear to have any clinically relevant effects on the ocular lens in this trial.

Other than slight mean increases in heart rate in the SEROQUEL groups, there were no consistent clinically relevant changes in ECGs during the trial. There was no evidence of conduction abnormalities, no arrhythmias, and no conformation changes associated with SEROQUEL treatment.

Vital signs measurements revealed a greater mean increase in pulse and weight in the SEROQUEL groups compared with the haloperidol group. The proportions of patients with clinically significant postural changes in both systolic blood pressure and pulse were relatively small, although there appeared to be a dose-related increase in the proportions of patients in the SEROQUEL groups. There also appeared to be a dose-related increase in the proportion of patients with clinically significant weight gain among the SEROQUEL groups.

Trough plasma concentrations of ICI 204,636 show mean concentrations that increase with dose at each trial day. No definitive conclusions can be drawn from these data with regard to the relationship between ICI 204,636 plasma concentrations and trial outcome.
