

**Late phase II clinical study of FK949 (Quetiapine fumarate) for psychiatric symptoms and behavioral disorders in patients with Alzheimer's dementia-Double-blind, placebo-controlled, parallel-group, dose-finding study**

**ATTENTION:**

**Seroquel (Quetiapine fumarate) is not licensed for use in elderly patients with dementia in the world. There is a box warning on the US label highlighting that elderly patients with dementia related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo and this information is reflected in the European Summary of Product Characteristics (SmPC).**

**Study Sponsor: Astellas Pharma Inc.**

**Original Company: Astra Zeneca**

**Name of Finished Product: Seroquel**

**Name of Active Ingredient: Quetiapine fumarate**

**Study centers:** A total of 58 centers (No patient was enrolled at five centers.)

**Study period:** 1 year and 7 months

**Date of the first informed consent:** October 3, 2003

**Date of the last observation completed:** May 2, 2005

**Development phase:** Late phase II

**Objective:**

The objective of the study was to investigate the efficacy, safety and standard dose of FK949 in patients with Alzheimer's dementia accompanied by delusions or hallucinations in a randomized, double-blind, placebo-controlled, parallel-group manner.

**Methodology:**

The efficacy, safety and standard dose of FK949 were investigated in patients with Alzheimer's dementia accompanied by delusions or hallucinations in a randomized, double-blind, placebo-controlled, parallel-group manner. The subjects received FK949 200 mg/day, FK949 100 mg/day group or placebo. The active drug groups started the study treatment at a dose of 25 mg/day and completed dose increase in 2 weeks. The study consisted of a 2-week observation period receiving placebo and a subsequent 6-week double-blind period. The 2-week observation period was prior to the 2-week dose escalation period. The efficacy of FK949 was evaluated based on 1) psychiatric symptoms and behavioral disorders (NPI), 2) ADL (DAD), 3) cognitive function (MMSE), 4) patient's

QOL [demented elderly's health-related QOL questionnaire (QOL-D)] and 5) caregiver's burden (NPI). The investigator, etc. (other than doctors responsible for assessment of global improvement and safety evaluation) assessed efficacy endpoints 1), 2), 3) and 5) above, using the respective worksheets shown in parentheses, and instructed to subjects' caregivers to complete the worksheet shown in parentheses for assessment of 4). Based on the information regarding DAD, MMSE, QOL-D and other information collected from subjects and their caregivers, global improvement in clinical symptoms was assessed. The primary efficacy variable was a change in the total score of delusions and hallucinations on NPI scale (NPI-2) from the start of the double-blind period and at the final point. The safety of FK949 was evaluated based on accompanying symptoms, body weight, blood pressure, pulse rate, ECG and abnormal changes in laboratory test values.

### **Number of subjects:**

No. of subjects planned: 195 (65 per group)

No. of subjects registered (1<sup>st</sup> registration): 262 (total number)

No. of subjects registered (2<sup>nd</sup> registration):

214 (placebo: 69, 100 mg: 71, 200 mg: 74)

No. of subjects administered with investigational drugs:

214 (placebo: 69, 100 mg: 71, 200 mg: 74)

No. of subjects analyzed: Subjects included in the efficacy analysis:

183 (placebo: 60, 100 mg: 60, 200 mg: 63)

Subjects included in the safety analysis: 214

(placebo: 69, 100 mg: 71, 200 mg: 74)

### **Diagnosis and main criteria for inclusion:**

#### **1. Inclusion criteria**

1) Diagnostic criteria for Alzheimer's dementia

(1) Patients who met the diagnostic criteria for Probable AD according to NINCDS-ADRDA Work Group

(2) Patients with a Hachinski ischemic score of  $\leq 4$

(3) Patients with no localized lesions nor multiple cerebral infarctions indicative of cognitive diseases other than Alzheimer's dementia as diagnosed by diagnostic imaging methods such as CT, MRI and SPECT

2) Patients with the following delusion or hallucination profile on the NPI scale at the start of the observation period and the start of the double-blind period

(1) Frequency score of  $\geq 2$  (about once weekly), and

(2) Severity score of  $\geq 2$  (causing distress and deterioration in patients)

3) Patients with an MMSE score of  $\leq 23$  at the start of the observation period and the start of the double-blind period

- 4) Inpatients or outpatients: While both inpatients and outpatients were eligible for the study, changes in the inpatient or outpatient status was not to be expected from at least 2 weeks before the start of the observation period until the end of the study period.
- 5) Patients who had caregivers able to grasp patients' conditions and ensure compliance to the study requirements including study treatment

## **2. Exclusion criteria**

### 1) Criteria established from the efficacy viewpoints

- (1) Patients confined to bed
- (2) Patients unable to undergo cognitive function test due to any visual or auditory disorder, or aphasia
- (3) Patients with alcohol dependence
- (4) Patients with the initial onset of delusions or hallucinations within 1 month before the start of the observation period
- (5) Patients with a known history of delusions or hallucinations before confirmed diagnosis of dementia had been given
- (6) Patients with delusions or hallucinations only during the onset of deliriums
- (7) Patients with psychiatric symptoms definitely due to psychiatric diseases other than Alzheimer's dementia
- (8) Patients treated with donepezil hydrochloride for less than 12 weeks before the start of the observation period
- (9) Patients treated with a long-acting injectable preparation of antipsychotic within 6 months before the start of the observation period
- (10) Patients treated with quetiapine fumarate within 6 months before the start of the observation period
- (11) Patients enrolled in an early phase II clinical study of FK949

### 2) Criteria established from the safety viewpoints

- (1) Patients with any serious cardiac disease
- (2) Patients with any serious hematological disease
- (3) Patients with any serious hepatic disease
- (4) Patients with any serious renal disease
- (5) Patients with any malignant tumor as a complication
- (6) Patients in coma
- (7) Patients under the strong influence of a central nervous system depressant such as barbiturates
- (8) Patients being treated with epinephrine
- (9) Patients with existing or previous diabetes
- (10) Patients with any one of the following values as measured by standard laboratory tests at the start of the observation period: AST of  $\geq 100$  IU/L, ALT of  $\geq 100$  IU/L, serum creatinine of  $\geq 2$  mg/dL, causal blood glucose of  $\geq 200$  mg/dL or HbA<sub>1c</sub> of  $\geq 6.5\%$

- (11) Patients on drug therapy for hypotension
- (12) Patients with a history of drug allergy
- (13) Pregnant women, women intending to become pregnant or nursing mothers
- 3) Patients enrolled in another clinical study or postmarketing clinical study within 3 months before providing the informed consent
- 4) Patients who were, in the investigator's opinion, otherwise ineligible to participate in the study

## **Test drugs, dose and mode of administration:**

### **1. Doses and mode of administration**

#### - Doses

FK949 200 mg group: 200 mg/day as quetiapine

FK949 100 mg group: 100 mg/day as quetiapine

Placebo group: 0 mg/day as quetiapine

#### - Mode of administration

During the observation period (placebo single-blind period), one placebo tablet was administered once daily in the evening.

During the double-blind period, the dose was to be increased with reference to the following dose-increase schedule. Administration up to four tablets/day was acceptable until day 7 of the double-blind period\*. The study treatment was started with one tablet (once daily) to reach eight tablets at the maximum on day 15\*. The acceptable range of dose increase was one or two tablets/day.

\*: The acceptable range of a deviation from the schedule was  $\pm 3$  days, depending on the status of clinical examinations. When the dose was set at one or two tablets/day, the investigational drug was administered once daily in the evening. After the dose was increased to more than two tablets/day, the investigational drug was administered twice daily in the morning and in the evening. After the dose was reached to eight tablets/day, the dose could be reduced by two tablets/day at maximum if dose reduction was deemed necessary, for example, in the case of occurrence of moderate or severer adverse events (AEs). Dose increase up to eight tablets/day was allowed even after dose reduction.

### **2. Test drugs**

[Observation period]

FK949 placebo tablet: Light yellowish-red film-coated tablet indistinguishable from FK949  
25 mg tablet

[Double-blind period]

FK949 25 mg tablet: Light yellowish-red film-coated tablet containing 25 mg of quetiapine

FK949 placebo tablet: Light yellowish-red film-coated tablet indistinguishable from FK949  
25 mg tablet

**Duration of administration:**

Observation period (placebo single-blind period): 2 weeks

Double-blind period: 6 weeks

**Evaluation criteria:**

Global improvement

1. Markedly improved: Complete or almost complete improvement in all the symptoms
2. Improved: Partial improvement in the symptoms, leading to better subject management
3. Slightly improved: Slight improvement in clinical pictures, not leading to better subject management
4. Unchanged: No change in clinical pictures
5. Slightly aggravated: Slight aggravation of clinical pictures, not leading to poor subject management
6. Aggravated: Partial aggravation of the symptoms, leading to poor subject management
7. Markedly aggravated: Complete or almost complete aggravation of all the symptoms

**Statistical methods:**

A significance level of 0.05 (two-sided) was used, and confidence intervals (CIs) were presented in two-sided 95%.

**1) Subject baseline characteristics**

Between-group homogeneity of the subject baseline characteristics was assessed. The subject baseline characteristic data for each group were analyzed using a contingency table  $\chi^2$ -test, analysis of variance or Kruskal-Wallis test, depending on the scale or characteristics of the data. If there was a between-group difference in a parameter, the data were statistically adjusted, using such a method as a linear regression model to assess the effects of the difference on the analysis results of the primary endpoint. Analysis without adjustment was used as the primary analysis.

**2) Efficacy**

(Primary endpoint)

For the change in the NPI-2 score from the start of the double-blind period and at the final point, the mean and standard deviation were determined for each group. A statistical significance in the 100 mg and 200 mg groups vs. the placebo control group was evaluated by parametric Dunnett's multiple comparison test.

(Secondary endpoints)

A statistical significance was evaluated by parametric or non-parametric Dunnett's multiple comparison test, depending on the scale or characteristics of the data.

**3) Safety**

The incidences of AEs (accompanying symptoms and abnormal changes in laboratory test values) and adverse drug reactions (ADRs) were determined and compared between the groups by Fisher's exact test. AE data were collected separately during the observation period and during the period after the start of the double-blind period.

### **Efficacy results:**

A total of 183 subjects (placebo: 60, 100 mg: 60, 200 mg: 63) were included in the efficacy analysis.

#### **1. Primary endpoint**

A change in the total score of delusions and hallucinations on the NPI scale (NPI-2) at the final point

The change in NPI-2 score at the final point [between-group difference in the difference between pre-dose and post-dose scores (SEM) (vs. placebo group)] was -1.3 (1.0) in the 100 mg group and -0.3 (1.0) in the 200 mg group. No significant difference was noted in either of the active drug groups (100 mg:  $p=0.323$  vs. placebo, 200 mg:  $p=0.788$  vs. placebo, hereinafter only p-values are presented in the same order).

#### **2. Secondary endpoints**

- The NPI-2 score was decreased after the start of the study in each group. No significant difference from the placebo group was observed in either of the active drug groups up to week 6.
- The NPI-10 score was decreased after the start of the study in each group. No significant difference from the placebo group was observed in either of the active drug groups up to week 6. The change (mean (SEM)) from baseline in the NPI-10 score at the final point was as follows: [placebo] -2.6 (2.3), [100 mg] -11.9 (2.5), and [200 mg] -9.5 (1.9). The decrease was statistically significant in the 100 mg group but not in the 200 mg group ( $p=0.007$  and  $0.053$ , respectively).
- In each of the following NPI parameters, the decreases were statistically significant compared to the placebo group: disinhibition (at the final point) and aberrant motor activity (at the final point) in the 100 mg group, and irritability (at week 6 and the final point) in the 200 mg group. More than half the subjects in each group had no euphoria nor disinhibition after the start of the study.
- The severity (percentage) of DAD showed little change after the start of the study in any group, indicating no decrease in ADL.
- The MMSE score showed little change after the start of the study in any group, indicating no decrease in the cognitive function.
- The score of positive feeling, ability for communication, attachment to others and spontaneity/activity of the patient's QOL scale showed little change after the start of the study in any group. On the other hand, the decreases in the following parameters were

- statistically significant compared to the placebo group: negative feeling/negative action and restlessness (at week 6 and the final point for both the parameters) in the 100 mg group, and negative feeling/negative action (at the final point) in the 200 mg group.
- The NPI-10 caregiver's burden score was decreased after the start of the study in each group. The decrease at week 6 was statistically significant in the 100 mg group compared to the placebo group, but not in the 200 mg group. The change (mean (SEM)) from baseline in the NPI-10 caregiver's burden score at the final point was as follows: [placebo] -0.6 (1.0), [100 mg] -4.8 (1.1), and [200 mg] -3.2 (1.0). The decrease was statistically significant in the 100 mg group but not in the 200 mg group ( $p=0.007$  and  $0.126$ , respectively).
  - The NPI-2 caregiver's burden score was slightly decreased after the start of the study in each group. No significant difference from the placebo group was observed in either of the active drug groups up to week 6. The change (mean (SEM)) from baseline in the NPI-2 caregiver's burden score at the final point was as follows: [placebo] -0.6 (0.3), [100 mg] -1.4 (0.4), and [200 mg] -1.0 (0.3). No significant difference from the placebo group was observed in either of the active drug groups ( $p=0.173$  and  $0.648$ , respectively).
  - In each of the following NPI parameters regarding caregiver's burden, the decreases were statistically significant compared to the placebo group: disinhibition (at week 6 and the final point) and aberrant motor activity (at the final point) in the 100 mg group, and irritability (at the final point) in the 200 mg group.
  - The global improvement rates (i.e., the percentage of "improved" and "markedly improved") at the final point were as follows: [placebo] 31.7% (19/60 subjects), [100 mg] 48.3% (29/60 subjects), and [200 mg] 44.4% (28/63 subjects). The improvement rates in the two active drug groups were higher than in placebo group. However, the difference of the rates between each of the two active drug groups and the placebo drug groups was not statistically significant ( $p=0.112$  and  $0.248$ , respectively). Although some subjects were rated as "slightly aggravated" or "aggravated" in each group, no subject was rated as "markedly aggravated" in either of the active drug groups.

### **Safety results (AEs seen during the double-blind period):**

All the 214 subjects (placebo: 69, 100 mg: 71, 200 mg: 74) were included in the safety analysis.

- No death occurred during the study.
- The following AEs were considered serious: [placebo] 8 events (pneumonia aspiration, gastritis haemorrhagic, hepatic function abnormal, AST increased, ALT increased, blood ALP increased,  $\gamma$ -GTP increased and blood bilirubin increased) in 3 subjects; [100 mg] 4 events (2 events of femoral neck fracture, 1 event each for musculoskeletal stiffness and dysphagia) in 3 subjects; and [200 mg] 4 events (blood pressure decreased, injury corneal, upper respiratory tract inflammation and pyrexia) in 3 subjects. Of these serious adverse

events (SAEs), the following were judged as ADRs: [placebo] hepatic function abnormal, AST increased, ALT increased, blood ALP increased,  $\gamma$ -GTP increased and blood bilirubin increased, [100 mg] musculoskeletal stiffness and dysphagia, and [200 mg] blood pressure decreased. For all the other events, the causal relationship with the investigational drug was ruled out. The reasons for the above seriousness assessments included “the event may result in disability/incapacity” for femoral neck fracture (group 47, No. 5) in the 100 mg group, “the event is an important medical event other than (1)-(5) in the evaluation criteria for safety (seriousness)” for blood pressure decreased in the 200 mg group, and “the event requires inpatient hospitalization for treatment or prolongation of existing hospitalization” for all the other events. All the other events were recovered or relieved, than blood ALP increased and  $\gamma$ -GTP increased in the placebo group, and femoral neck fracture in the 100 mg group. All the SAEs seen in the active drug groups were known events with FK949.

- Accompanying symptoms that led to study treatment discontinuation, other than the SAEs, occurred with following breakdown: [placebo] 6 subjects (15 events), [100 mg] 12 subjects (18 events), and [200 mg] 11 subjects (16 events). In addition, one abnormal change in the laboratory test value in 1 subject on placebo led to study treatment discontinuation. Of the AEs leading to study treatment discontinuation in the placebo group, 3 events (disinhibition, somnolence and blood cholesterol increased) were judged as ADRs. All the events except for 1 event (excitability) were recovered after study treatment discontinuation. On the other hand, all the AEs leading to study treatment discontinuation in the active drug groups were judged as ADRs. All the events except for 1 event (delusion) in the 200 mg group were recovered during the study period or after study treatment discontinuation.
- The AEs (all events) were seen with the following breakdown: [placebo] 121 events in 46/69 subjects (66.7%), [100 mg] 123 events in 47/71 subjects (66.2%), and [200 mg] 195 events in 62/74 subjects (83.8%). The incidence of AEs in the 200 mg group was significantly higher than in the placebo group ( $p=0.020$ ). The difference in the incidence between the two active drug groups was also statistically significant ( $p=0.020$ ). Of these events, the following events were judged as ADRs: [placebo] 38 events in 24/69 subjects (34.8%), [100 mg] 52 events in 29/71 subjects (40.8%), and [200 mg] 109 events in 49/74 subjects (66.2%). The incidence of ADRs in the 200 mg group was significantly higher than in the placebo group ( $p=0.000$ ). The difference in the incidence between the two active drug groups was also statistically significant ( $p=0.003$ ).
- The accompanying symptoms (all events) were seen with the following breakdown: [placebo] 79 events in 41/69 subjects (59.4%), [100 mg] 91 events in 42/71 (59.2%), and [200 mg] 145 events in 54/74 subjects (73.0%). No significant difference in the incidence was noted between the placebo group and either of the active drug groups. The difference between the two active drug groups was not statistically significant either. Of these accompanying symptoms, the following events were judged as ADRs: [placebo]

17 events in 15/69 subjects (21.7%), [100 mg] 41 events in 25/71 subjects (35.2%), and [200 mg] 78 events in 38/74 subjects (51.4%). The incidence of ADRs in the 200 mg group was significantly higher than in the placebo group ( $p=0.000$ ), while the difference in the incidence between the two active drug groups was not statistically significant. In the placebo group, no identical AE occurred on more than three occasions. On the other hand, major ADRs included somnolence (12 events; “events” to be applied to all the following parentheses in this paragraph), dizziness (4) and constipation (3) in the 100 mg group, and somnolence (23), dizziness (8), speech disorder (4) and constipation (4) in the 200 mg group. Most of the events in each group were mild or moderate in intensity. By system organ class (SOC), nervous system disorders accounted for most of the events in both active drug groups, compared with the placebo group. The following patients in each group were withdrawn from the study treatment for the intervention of accompanying symptoms (ADRs): [placebo] 3 subjects (4.3%), [100 mg] 12 subjects (16.9%), and [200 mg] 11 subjects (14.9%).

- The incidence of extrapyramidal symptoms were seen with the following breakdown: [placebo] 1/69 subjects (1.4%), [100 mg] 2/71 subjects (2.8%), and [200 mg] 4/74 subjects (5.4%). All of these AEs were judged as ADRs. All the extrapyramidal symptoms seen in the active drug groups were recovered with no treatment or appropriate treatment (study treatment discontinuation etc.).
- The abnormal changes in laboratory test values (all events) were seen with the following breakdown: [placebo] 42 events in 23/69 subjects (33.3%), [100 mg] 32 events in 16/71 subjects (22.5%), and [200 mg] 50 events in 27/74 subjects (36.5%). No significant difference in the incidence was noted between the placebo group and either of the active drug groups. The difference between the two active drug groups was not statistically significant either. Of these abnormal changes in laboratory test values, the following events were judged as ADRs: [placebo] 21 events in 12/69 subjects (17.4%), [100 mg] 11 events in 7 /71 subjects (9.9%), and [200 mg] 31 events in 18/74 subjects (24.3%). No significant difference was noted between the placebo group and either of the active drug groups, while the difference in the incidence between the two active drug groups was statistically significant ( $p=0.027$ ). In the 100 mg group, no identical AE occurred on more than three occasions. On the other hand, major ADRs included blood prolactin increased (4 events; “events” to be applied to all the following parentheses in this paragraph) in the placebo group, and blood prolactin increased (5), blood ALP increased (3),  $\gamma$ -GTP increased (3) and blood CPK increased (3) in the 200 mg group. Most of the events in each group were mild in intensity. In endocrine function-related parameters, abnormal changes were commonly observed in the placebo and 200 mg groups. The study was discontinued in only 1 subject (1.4%) on placebo for the intervention of abnormal changes in laboratory test values (ADRs).

## **Conclusion:**

The efficacy results in this study suggested that FK949 improved some behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's dementia accompanied by delusions or hallucinations, but failed to demonstrate the effectiveness of FK949 in terms of the primary endpoint of NPI-2 (delusions or hallucinations).

No death occurred during the study. All the SAEs seen in the active drug groups were known events with FK949. No considerable difference was noted in the number of SAEs between the placebo group and either of the active drug groups. However, the incidences of AEs and ADRs in the 200 mg group were significantly higher than in the placebo or 100 mg group. Most common (N>4 any FK949 group) ADRs in the study due likely to the pharmacological action of FK949. These ADRs were also observed in the preceding clinical studies, which could be expected at the time of planning the present study. The number of subjects who could increase the dose to the maintenance dose does not differ much among the groups. Therefore, this study suggests that ADRs can be managed by taking adequate measures including careful observation and examination after the start of FK949 administration at a low dose. In conclusion, this study suggests that FK949 is generally safe and well tolerated up to a dose of 200 mg/day in patients.