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Name of Active Ingredient: Quetiapine fumarate		

SYNOPSIS

Title of Study:

Phase I Study of FK949E –Multiple Dose Study of Elderly Adult Patients with Major Depressive Disorder–

Responsible Officer or Designee:

[redacted], Astellas Pharma Inc.

Investigators:

[redacted], and others

Study Sites:

[redacted], and three other sites

Publication Based on the Study:

Unpublished

Study Period:

1 year and 8 months (duration from the starting day of the study to the day of study completion)

Study Initiation Date:

6 February 2010 (the day when the first subject signed the written informed consent)

Study Completion Date:

28 September 2011 (the day when the last subject was evaluated [the day of protocol-specified final assessments])

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Phase of Development:

Phase I

Study Objectives:

The objective of the study was to evaluate the safety and pharmacokinetics of FK949E administered as multiple oral doses of 300 mg for 7 days in elderly patients with major depressive disorder.

Study Design and Methodology:

Multicenter, open-label design

Planned Sample Size:

Group 1: 8 patients (Monotherapy: At least 2 of 8 patients [planned number of subjects])

Group 2: 8 patients

[Rationale]

The sample size was determined as the number of subjects that was considered sufficient to evaluate the safety and pharmacokinetics of the study drug, and also in consideration of the feasibility of the study. In association with the change in the indication of FK949E for "use as combination therapy for patients with major depressive disorder who had an inadequate response to existing antidepressants," based on the pre-phase IIb consultation (receipt number P1638) meeting held in March 2010, the description "at least 2 patients treated with monotherapy for Group 2" was deleted.

Diagnosis and Inclusion/Exclusion Criteria:

Elderly adult patients with major depressive disorder were eligible for the study if all of the following inclusion criteria applied and none of the exclusion criteria were met.

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1. Inclusion criteria

1. Provision of written informed consent.
2. Patients aged 65 to 80 years old, inclusive, at enrollment (written informed consent).
3. Documented clinical diagnosis of major depressive disorder meeting the DSM-IV-TR criteria for any of the following *:
   * In case of not receiving antidepressant treatment:
     Patients with a diagnosis within 6 months prior to provision of written informed consent
     In case of receiving antidepressant treatment:
     Patients continuously receiving antidepressant treatment at the time of providing written informed consent
4. Being able to understand and comply with the requirements of the study, as judged by the investigator/sub-investigator.
5. In case of female subjects, being confirmed to have no potential for pregnancy during the study period (e.g., the subject had been post-menopausal for at least 3 years; menopause had been confirmed; the potential for pregnancy could be ruled out because the subject had undergone hysterectomy or ovariectomy [only for Group 2]).

2. Exclusion criteria

1. A current or past history of a DSM-IV-TR Axis I disorder other than major depressive disorder within 6 months prior to provision of written informed consent.
2. Patients with a diagnosis of DSM-IV-TR Axis II disorder that had a major impact on the patient's current psychiatric status.
3. A history of substance or alcohol abuse or dependence excluding caffeine and nicotine.
4. Patients who were unable to abstain from drugs that induce or inhibit the drug-metabolizing enzyme CYP3A4 from 14 days before study drug administration throughout the study period.

   Phenobarbital, phenobarbital sodium, carbamazepine, glucocorticoids, phenytoin, rifampin, rifabutin, thioridazine, St John's wort, ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, fluvoxamine maleate, nefazodone, troleandomycin, indinavir, nelfinavir mesilate, ritonavir, saquinavir mesilate, ethotoin

5. Patients showing evidence or signs of renal or hepatic failure, serious heart disease, cerebrovascular disease, viral hepatitis B or C, or acquired immunodeficiency syndrome (AIDS) (carrier).
6. Patients with any diagnosis of a neurological condition, such as Parkinson's disease, Huntington's disease, essential tremor, multiple sclerosis, prior brain injury, space occupying lesion, etc.

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7. A clinical finding that is unstable (e.g., hypertension, unstable angina) or that, in the opinion of the investigator or sub-investigator, would be negatively affected by the study medication or that would affect the study medication (including patients under treatment for hypertension and those having concurrent hypotension or orthostatic hypotension in Group 2 [criteria for hypotension: systolic blood pressure of <100 mmHg]).
8. Conditions that could affect absorption and metabolism of study medication (e.g., malabsorption syndrome, liver disease).
9. A current diagnosis of cancer (except basal or squamous cell skin carcinoma), unless it has been in remission for at least 5 years.
10. Current or past diagnosis of transient ischemic attacks (TIA).
11. History of seizure disorder, except febrile convulsions.
12. Receipt of electroconvulsive therapy (ECT) within 90 days before study drug administration.
13. Use of a depot antipsychotic injection and inability to be off the drug for a period of twice the dosing interval prior to study drug administration throughout the study period.
14. Patients who, in the investigator's opinion, would require psychotherapy (other than supportive psychotherapy) during the study period, unless psychotherapy had been ongoing for a minimum of 90 days before study drug administration.
15. A score of ≥ 3 on the HAM-D_{17} Item (suicide) or a suicide attempt within the past 6 months. Patients judged to be at serious suicidal or homicidal risk in the opinion of the investigator/sub-investigator.
16. A current or past history of diabetes mellitus* or glycated hemoglobin (HbA_{1c}) of $\geq 6.5\%$ at screening within 2 months before the start of study drug administration (*refer to the guidelines for monitoring blood glucose levels in patients treated with atypical antipsychotics).
17. Clinically significant deviation from the reference range in clinical laboratory test results, as judged by the investigator/sub-investigator (refer to grade 3 adverse drug reactions according to the "Criteria for Classification of the Grade of Adverse Drug Reactions to Pharmaceutical Products" [Pharmaceutical Affairs Bureau/Safety Division (PAB/SD) Notification No. 80, dated 29 June 1992]).
18. White blood cell count (WBC) of $\leq 3{,}000/mm^3$ at screening assessment.
19. Thyroid-stimulating hormone (TSH) concentration >10% above the upper limit of the normal range of the laboratory used for sample analysis at the screening assessment, whether or not the patient is being treated for hypothyroidism.
20. Elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values at screening assessment (grade 2 or higher according to the "Criteria for Classification of the Grade of Adverse Drug Reactions to Pharmaceutical Products" [Pharmaceutical Affairs Bureau/Safety Division (PAB/SD) Notification No. 80, dated 29 June 1992]).
21. Treatment with epinephrine at the time of providing written informed consent.

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22. A known history of hypersensitivity to quetiapine or to any other component in the FK949E tablets at the time of providing written informed consent.
23. Treatment with quetiapine for depressive symptoms or bipolar disorder (manic phase) at the time of providing written informed consent.
24. Treatment with quetiapine at the time of providing written informed consent.
25. Involvement in the planning and conduct of the study (applying to Astellas staff and staff at the study site).
26. Previous randomization in a clinical study of quetiapine.
27. Participation in another clinical trial or post-marketing clinical study within 12 weeks before study drug administration
28. Patients who were judged to be inappropriate as subjects of this study by the investigator/sub-investigator.

Test Drug, Dose, and Dose Regimen:

1. Test drug and lot numbers

Test drug		Lot number
FK949E Tablets 50 mg	An oval, pale yellowish-red film-coated tablet, containing 50 mg of quetiapine.	[redacted] (Manufacturer: AstraZeneca)
FK949E Tablets 150 mg	An oval, white film-coated tablet, containing 150 mg of quetiapine.	

2. Dose and dose regimen

[Dose]

Group 1: 300 mg on Day 11 and subsequent days

Days 1 and 2 (50 mg)	One FK949E 50 mg Tablet
Days 3 and 4 (100 mg)	Two FK949E 50 mg Tablets
Days 5 and 6 (150 mg)	One FK949E 150 mg Tablet
Days 7 and 8 (200 mg)	One FK949E 50 mg Tablet and one FK949E 150 mg Tablet
Days 9 and 10 (250 mg)	Two FK949E 50 mg Tablets and one FK949E 150 mg Tablet
Days 11 to 17 (300 mg)	Two FK949E 150 mg Tablets

Group 2: 300 mg on Day 5 and subsequent days

Days 1 and 2 (50 mg)	One FK949E 50 mg Tablet

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Days 3 and 4 (150 mg) One FK949E 150 mg Tablet

Days 5 to 11 (300 mg) Two FK949E 150 mg Tablets

[Dose regimen and administration period]

Group 1: The prescribed number of FK949E tablets (50 mg or 150 mg) was orally administered once daily after breakfast (preferentially within 10 minutes after breakfast) for 17 days.

Group 2: The prescribed number of FK949E tablets was orally administered once daily in the morning under fasting conditions for 11 days. Treatment was given at around 10:00. Subjects who had breakfast were instructed to start breakfast at 7:30 (preferentially), finish it within 30 minutes, and take the study drug after an interval of at least 2 hours (around 10:00).

Number of tablets administered

Treatment group	Study drug	Hospitalization (or outpatient)																
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17
Group 1	50 mg tablet	1	1	2	2			1	1	2	2							
	150 mg tablet					1	1	1	1	1	1	2	2	2	2	2	2	2
Group 2	50 mg tablet	1	1															
	150 mg tablet			1	1	2	2	2	2	2	2	2	–	–	–	–	–	–

[Rationale for the dose, dose regimen, and administration period]

In 7 of 8 overseas clinical studies of the extended-release formulation of quetiapine in patients with major depressive disorder that had been conducted to date, the extended-release formulation of quetiapine (50 to 300 mg) administered on a once daily regimen improved the depressive symptoms, and it has therefore been demonstrated to be effective for the treatment of major depressive disorder. The extended-release formulation of quetiapine administered at a dose of 300 mg/day has also been confirmed to be effective and safe in elderly patients with depression in the study evaluating the efficacy and safety of the extended-release formulation of

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quetiapine in elderly patients with depression (Study No. D1448C00014). The dose of 300 mg/day was therefore used as the maximum dose in the present study.

Drug-related adverse events such as somnolence and sedation have been reported with the use of FK949E due to its pharmacological action and similar adverse events may occur in clinical studies scheduled in Japan. In the completed Japanese phase I study (Study No. 6949-CL-0001), orthostatic hypotension was reported. Since the results of the food effect study (Study No. 6949-CL-0003) suggest that an increase in plasma FK949E concentrations arising from food effects may affect the occurrence of adverse events, it was decided to administer FK949E under fasting conditions in Group 2, as with the phase I study (Study No. 6949-CL-0009) that was conducted giving more careful consideration of safety. The fasting condition was defined as an interval of at least 2 hours after a meal, in reference to the definition “at least 1 hour before or 2 hours after a meal” given in the “FDA Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies (December 2002: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research [CDER]).”

The dose escalation schedule was established based on overseas clinical studies in non-elderly patients (Study Nos. D1448C00001 and D1448C00006), in which administration of FK949E was started at an initial dose of 50 mg, and the dose was increased every 2 days to 150 mg and 300 mg, as in Group 2 in the present study. FK949E was also administered at an initial dose of 50 mg and the dose was increased every 3 or 4 days in increments of 50 mg up to 150 mg by Day 8 in the clinical study in elderly patients (Study No. D1448C00014). The FK949E dose was further increased up to 300 mg by Day 22. With respect to the occurrence of adverse events, the incidence of adverse events was high on the day of dose escalation and the following day in these studies, and was independent of the maintenance dose period after dose escalation. It was therefore considered possible to set the maintenance period in Group 1 at 2 days. If it was also assessed that there were no safety concerns in Group 1, it was decided to start administering FK949E at an initial dose of 50 mg and increase the dose every 2 days to 150 mg and 300 mg in Group 2 so that treatment in the same increments as in non-elderly patients with depression could be evaluated.

Investigational period:

Pre-investigational period: No more than 28 days

Administration period: 17 days for Group 1 and 11 days for Group 2

Observation period after administration: 7 days

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Concomitant Medications and Therapies:

[Concomitant drugs and therapies permitted with restrictions]

1. Antidepressants

Only one of the antidepressants listed below was permitted provided that it had been ongoing since at least 28 days prior to the start of study drug administration. The dose was not to exceed the maximum approved daily dose of the drug, and the dosage and administration had to remain the same as those used from 28 days prior to the start of study drug administration.

Paroxetine hydrochloride hydrate, sertraline hydrochloride, and milnacipran hydrochloride

2. Hypnotics

Only one of the hypnotics listed below was permitted for insomnia provided that it had been ongoing since at least 28 days prior to the start of study drug administration. The dose was not to exceed the maximum approved daily dose of the drug.

Triazolam, zolpidem tartrate, zopiclone, brotizolam, rimazafone hydrochloride, and lormetazepam

3. Anticholinergics

Use of anticholinergics was allowed when extrapyramidal symptoms occurred (it was allowed to use only one of trihexyphenidyl hydrochloride, profenamine, biperiden, metixene hydrochloride, piroheptine hydrochloride, or mazaticol hydrochloride). However, prophylactic use was not allowed.

4. Psychotherapy

Psychotherapy was allowed if it had been ongoing since at least 90 days prior to the start of study drug administration.

5. Non-psychoactive medications

Non-psychoactive medications were allowed provided that they had been ongoing since at least 28 days prior to the start of study drug administration. The dosage and administration were not to be changed during the study period unless the drug was considered unnecessary (e.g., occurrence of adverse events, recovery of symptoms, etc.). Prophylactic use was also not allowed.

[Prohibited concomitant drugs and therapies]

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For drugs other than concomitant ones permitted with restrictions, the following drug washout periods were to be observed before the start of study drug administration:

1) Mood stabilizer: More than 5 times the $t_{1/2}$ prior to study drug administration
2) Antipsychotics: More than 5 times the $t_{1/2}$ prior to study drug administration
3) Anticholinergics: More than 5 times the $t_{1/2}$ prior to study drug administration
4) Anxiolytics, antidepressants, and hypnotics: More than 5 times the $t_{1/2}$ prior to study drug administration
5) Psychostimulants: More than 5 times the $t_{1/2}$ prior to study drug administration
6) Cytochrome P450 (CYP) 3A4 inhibitors or inducers: 14 days prior to study drug administration
7) Monoamine oxidase (MAO) inhibitors: 14 days prior to study drug administration
8) Depot antipsychotic injection: 2 times the specified dosing interval prior to study drug administration
9) Electroconvulsive therapy (ECT): 90 days prior to study drug administration

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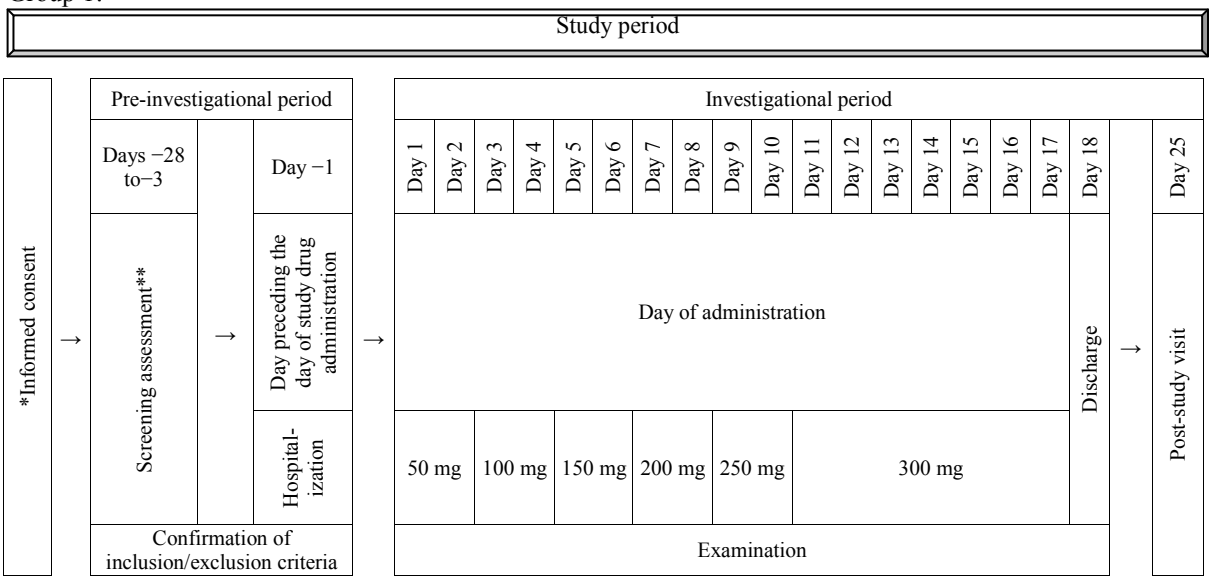
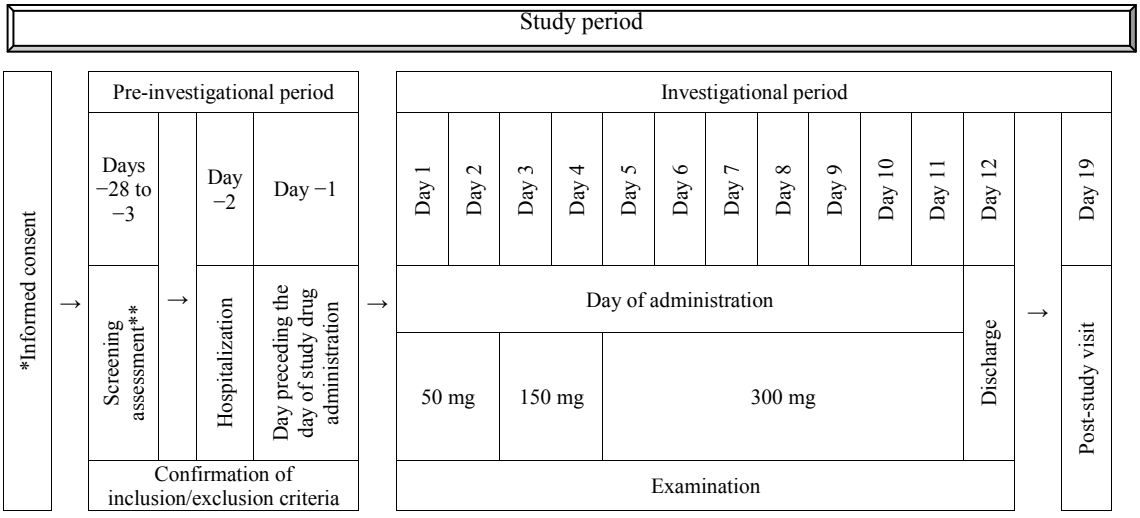
Assessments and Schedule of Procedures:

Evaluation schedule

Group 1:



Group 2:



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The study started when written informed consent was obtained from the first subject, and ended when the last subject completed the protocol-specified final assessment.

*:	In some cases, the site where the informed consent was obtained (screening site) was not the same as the site where the subject was hospitalized following the screening assessment up until the post-study visit (admission site). When a subject was transferred to the admission site, the investigator at the screening site had to provide the investigator at the admission site with all subject information obtained so far. The method of providing information was to be arranged for in advance by the investigators. Details of the collaboration between the two study sites were stipulated separately in a study site version of the study protocol.
**:	When a drug washout period was required, the screening assessment was performed after completion of the washout period.

Variables

1. Pharmacokinetics:

- Plasma unchanged FK949E concentration (C_{max}, t_{max}, AUC_{24h}, AUC_{inf}, $t_{1/2}$, C_{trough}, CL/F, MRT_{last}, MRT_{inf})

2. Safety:

- Adverse events
- Vital signs (axillary body temperature, blood pressure, and pulse rate)
- 12-lead ECGs
- Laboratory assessments (hematology, blood biochemistry, and urinalysis)

Statistical Analysis

1. Populations for analysis

The analysis sets were established as planned below, in principle, based on the data review.

Safety Analysis Set: The safety analysis set included all subjects who received the study drug.

Pharmacokinetic Analysis Set: The pharmacokinetic analysis set included all subjects who received the study drug and in which samples for pharmacokinetic assessment were measured (collected) for at least one time point after administration.

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2. Demographics and other baseline characteristics:

The following analyses were performed by treatment group on the SAF and PKAS.

- Frequency tabulation of the discrete data.
- Calculation of the descriptive statistics for continuous data.

3. Pharmacokinetics:

On the PKAS, the pharmacokinetic parameters were calculated from the measured plasma unchanged FK949E concentrations, and the descriptive statistics were summarized. Non-compartment model analysis of the time course of the plasma unchanged FK949E concentration by each subject was performed to estimate C_{max}, t_{max}, AUC_{24h}, AUC_{inf}, $t_{1/2}$, C_{trough}, CL/F, MRT_{last}, and MRT_{inf}. Plasma unchanged FK949E concentrations before administration on the day of drug administration or 24 hours post-dose were handled as C_{trough}. The actual time course after administration (time elapsed after the last study drug administration) was used for the calculation of the pharmacokinetic parameters. FK949E exposure (C_{max} and AUC_{24h}) on the first and last days of study drug administration at the maintenance dose and the steady state (C_{trough}) following multiple-dose administration of 300 mg for 7 days in Japanese elderly patients with depression were examined in an exploratory manner.

4. Safety:

The following analyses were performed by treatment group on the SAF.

1. Vital signs (axillary body temperature, blood pressure, and pulse rate)

- Descriptive statistics for the measured values of each item were calculated for each time point. Descriptive statistics for the difference between the supine and standing values for each item were calculated for each time point.
- The percentage of subjects with a decrease in systolic blood pressure of ≥20 mmHg or diastolic blood pressure of ≥10 mmHg in the standing position, compared with those in the supine position, was calculated for each time point.
- For each item, spaghetti plot and graphical representation of mean ± SD of the measured values were created. Graphical representations of the difference between the supine and standing values were created.

The following analyses were also performed in Group 2.

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- The number and percentage of subjects by the presence or absence of subjective symptoms (symptoms recorded as orthostatic hypotension-related events accompanied by subjective symptoms such as dizziness, dizziness on standing up, palpitations, syncope, and syncope-like symptoms following a postural change from the supine to standing position) were presented for each time point.
- The number and percentage of subjects with individual subjective symptoms following a postural change from the supine to standing position were presented for each time point.

2. Laboratory assessments (hematology, blood biochemistry, and urinalysis)

- For continuous data, descriptive statistics of the measured values were calculated for each time point.
- For continuous data, spaghetti plots of the measured values were created.
- For discrete data, shift table for the data before administration and at each time point of measurement was created.

3. Electrocardiogram

- Shift table for 12-lead ECGs on the day preceding the day of study drug administration and at each time point was created.

4. Adverse events

In case of the following 3 to 5, a subject who reported two or more different adverse event terms in the same SOC or a single PT during a given treatment was counted once in the calculation of the number of subjects with adverse events, but was counted for each adverse event in the calculation of the number of adverse events.

(1) The number and percentage of subjects by the presence or absence of adverse events and drug-related adverse events were presented. In Group 2, similar tabulation was performed by the presence or absence of adverse events assessed to be related to orthostatic hypotension (hereinafter, orthostatic hypotension-related events) and uncontrollable or unpredictable orthostatic hypotension-related events.

(2) The number of adverse events and drug-related adverse events was presented. In Group 2, similar tabulation was performed for the number of orthostatic hypotension-related events and uncontrollable and/or unpredictable orthostatic hypotension-related events.

(3) For adverse events and drug-related adverse events by symptom, the number and percentage of subjects with these adverse events and the number of these adverse events were presented by SOC and PT. In Group 2, similar tabulation was performed for orthostatic hypotension-related events accompanied by subjective symptoms following a postural change at the time of the vital sign measurement.

(4) For adverse events and drug-related adverse events by symptom, the number and percentage of subjects with these adverse events and the number of these adverse events were presented by SOC and PT and by severity. In Group 2, the number and percentage of subjects with orthostatic hypotension-related events

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by symptom and the number of orthostatic hypotension-related events by symptom were presented by SOC and PT and by severity.

(5) For adverse events and drug-related adverse events by symptom, the number and percentage of subjects with these adverse events were presented by SOC and PT and by the day of onset. In Group 2, the number and percentage of subjects with orthostatic hypotension-related adverse events by symptom were presented by SOC and PT and by the day of onset.

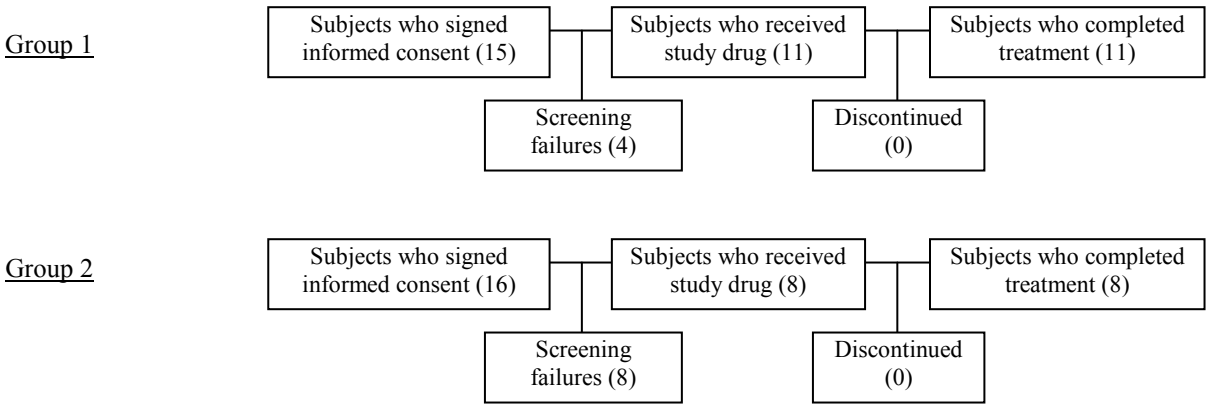
Results:

1. Disposition of Subjects and Analysis Set:

The disposition of subjects in the present study is shown in Figure 1. Written informed consent was obtained from a total of 31 subjects, consisting of 15 subjects in Group 1 and 16 subjects in Group 2. In Group 1, there were 4 subjects who were reported as screening failures and 11 subjects received the study drug. After the completion of study treatment in Group 1, the sponsor examined whether to proceed to Group 2 or not in consultation with the medical expert based on the safety data, and judged it possible to proceed to Group 2. The study treatment in Group 2 was started after receiving the report that permissible safety results had been obtained in the phase I study which was conducted to reevaluate the safety in non-elderly patients with major depressive disorder (Study No. 6949-CL-0009). In Group 2, there were 8 of 16 subjects who were reported as screening failures and 8 subjects received the study drug.

The most frequently reported reason for screening failures was “Not fulfill the inclusion or exclusion criteria” (3 subjects in Group 1 and 8 subjects in Group 2). None of the subjects discontinued the study treatment in either group.

Figure 1 Disposition of Subjects



The analysis set is presented in Table 1. All subjects in each group who received the study drug were included in the SAF and PKAS.

Table 1 Number of Subjects in Analysis Sets

Analysis set	Group 1	Group 2
SAF (n)	11	8
PKAS (n)	11	8

2. Demographics and Other Baseline Characteristics:

Table 2 shows the major demographics of the PKAS and SAF of each group. In Group 1, the proportion of male subjects was as high as 90.9% (10/11 subjects); mean age ± SD were 71.5 ± 4.37 years and mean BMI ± SD

were 21.61 ± 2.504 kg/m^2. In Group 2, the proportion of male and female subjects was the same (4 subjects each); mean age ± SD were 68.9 ± 3.72 years and mean BMI ± SD were 23.02 ± 3.859 kg/m^2.

Table 2 Major Demographics and Other Baseline Characteristics

Variable		Group 1 N=11 †	Group 2 N=8 †
Sex	Male	10 (90.9%)	4 (50.0%)
	Female	1 (9.1%)	4 (50.0%)
	Total	11	8
Past disease	No	11 (100.0%)	8 (100.0%)
	Yes	0 (0.0%)	0 (0.0%)
	Total	11	8
Concurrent disease	No	5 (45.5%)	1 (12.5%)
	Yes	6 (54.5%)	7 (87.5%)
	Total	11	8
Age (yrs) (at the time of informed consent)	Mean ± SD Median Min - Max	71.5 ± 4.37 73.0 65 to 76	68.9 ± 3.72 68.0 65 to 77
Body weight (kg) (on the day preceding the day of study drug administration)	Mean ± SD Median Min - Max	57.50 ± 8.075 59.60 43.5 to 68.4	59.68 ± 12.611 57.90 42.5 to 84.9
BMI (kg/m^2) (at the time of screening assessment)	Mean ± SD Median Min - Max	21.61 ± 2.504 21.58 15.4 to 25.1	23.02 ± 3.859 23.32 17.1 to 29.4

†SAF and PKAS

Number of subjects (%)

3. Study drug exposure:

All the subjects in each group completed the study drug administration and none discontinued the study drug administration.

4. Pharmacokinetics:

Table 3 shows the pharmacokinetic parameters of unchanged FK949E in plasma at each measurement time point in Group 1 (Day 1 of the 50 mg dose period, and Day 1 and Day 7 of the 300 mg dose period) and Figure 2 shows the mean plasma unchanged FK949E concentration-time profile. The C_{max} of unchanged FK949E in plasma (mean ± SD, the same hereinafter) was 68.38 ± 29.94 ng/mL on Day 1 of the 50 mg dose period, 494.48 ± 163.53 ng/mL on Day 1 of the 300 mg dose period, and 483.59 ± 169.94 ng/mL on Day 7 of the 300 mg dose period. Similarly, the AUC_{24h} of unchanged FK949E in plasma was 584.66 ± 242.49 ng·h/mL, 4163.20 ± 1608.32 ng·h/mL, and 4091.09 ± 1510.34 ng·h/mL, respectively. Both the C_{max} and AUC_{24h} increased with increasing dose. The mean t_{max} ranged from 5.1 to 5.8 hours at each measurement time point.

Table 4 shows the pharmacokinetic parameters of unchanged FK949E in plasma at each measurement time point in Group 2 (Day 1 of the 50 mg dose period, and Day 1 and Day 7 of the 300 mg dose period) and Figure 3 shows the mean plasma unchanged FK949E concentration-time profile. The C_{max} of unchanged FK949E in plasma (mean ± SD, the same hereinafter) was 43.99 ± 18.44 ng/mL on Day 1 of the 50 mg dose period, 390.57 ± 173.47 ng/mL on Day 1 of the 300 mg dose period, and 434.42 ± 184.20 ng/mL on Day 7 of the 300 mg dose

period. Similarly, the AUC_{24h} of unchanged FK949E in plasma was 580.98 ± 198.59 ng·h/mL, 4588.85 ± 1747.19 ng·h/mL, and 4912.00 ± 1996.19 ng·h/mL, respectively. Both the C_{max} and AUC_{24h} increased with increasing dose. The mean t_{max} ranged from 6.0 to 8.7 hours at each measurement time point.

When FK949E was administered at a dose of 50 mg (single dose) or 300 mg (multiple doses), the interindividual and intraindividual changes in the plasma unchanged FK949E concentrations were great; however, the plasma unchanged FK949E concentration gradually increased following administration of FK949E.

The present study examined steady state in each group and accumulation following multiple-dose administration in an exploratory manner. For steady state, when the GMR was determined using C_{trough} as an indicator, by reference to 24 hours after the last administration of the final dose, the results demonstrated that the GMR changed slightly in all groups and it was almost constant. Therefore, the steady state appeared to be achieved immediately after the start of multiple-dose administration. With respect to accumulation following multiple-dose administration, the GMR between the first day and the last day of the final dose period following a multiple dose regimen was determined using C_{max} and AUC_{24h} as indicators. From the results, it was considered that comparable steady state concentrations were obtained on the first day and the last day of multiple dose administration.

Table 3 Pharmacokinetic Parameters of Plasma Unchanged FK949E Concentrations (Mean ± SD) (Group 1)

Pharmacokinetic parameter	Day 1 at 50 mg dose N=11	Day 1 at 300 mg dose N=11†	Day 7 at 300 mg dose N=11†
C_{max} (ng/mL)	68.38 ± 29.94	494.48 ± 163.53	483.59 ± 169.94
t_{max} (h)	5.1 ± 1.6	5.6 ± 2.3	5.8 ± 2.2
AUC_{24h} (ng·h/mL)	584.66 ± 242.49	4163.20 ± 1608.32	4091.09 ± 1510.34
AUC_{inf} (ng·h/mL)	618.59 ± 273.73	–	–
$t_{1/2}$ (h)	4.8 ± 1.1	5.2 ± 1.0	5.3 ± 0.7
CL/F (L/h)	101.42 ± 54.13	83.33 ± 39.69 ††	84.19 ± 38.53
MRT_{last} (h)	8.5 ± 1.8	–	–
MRT_{inf} (h)	10.1 ± 2.0	–	–

† N=10 for $t_{1/2}$

†† For reference, it was calculated assuming that the data were those at the steady state although the steady state had not been achieved.

Figure 2 Mean Plasma Unchanged FK949E Concentrations (Group 1)

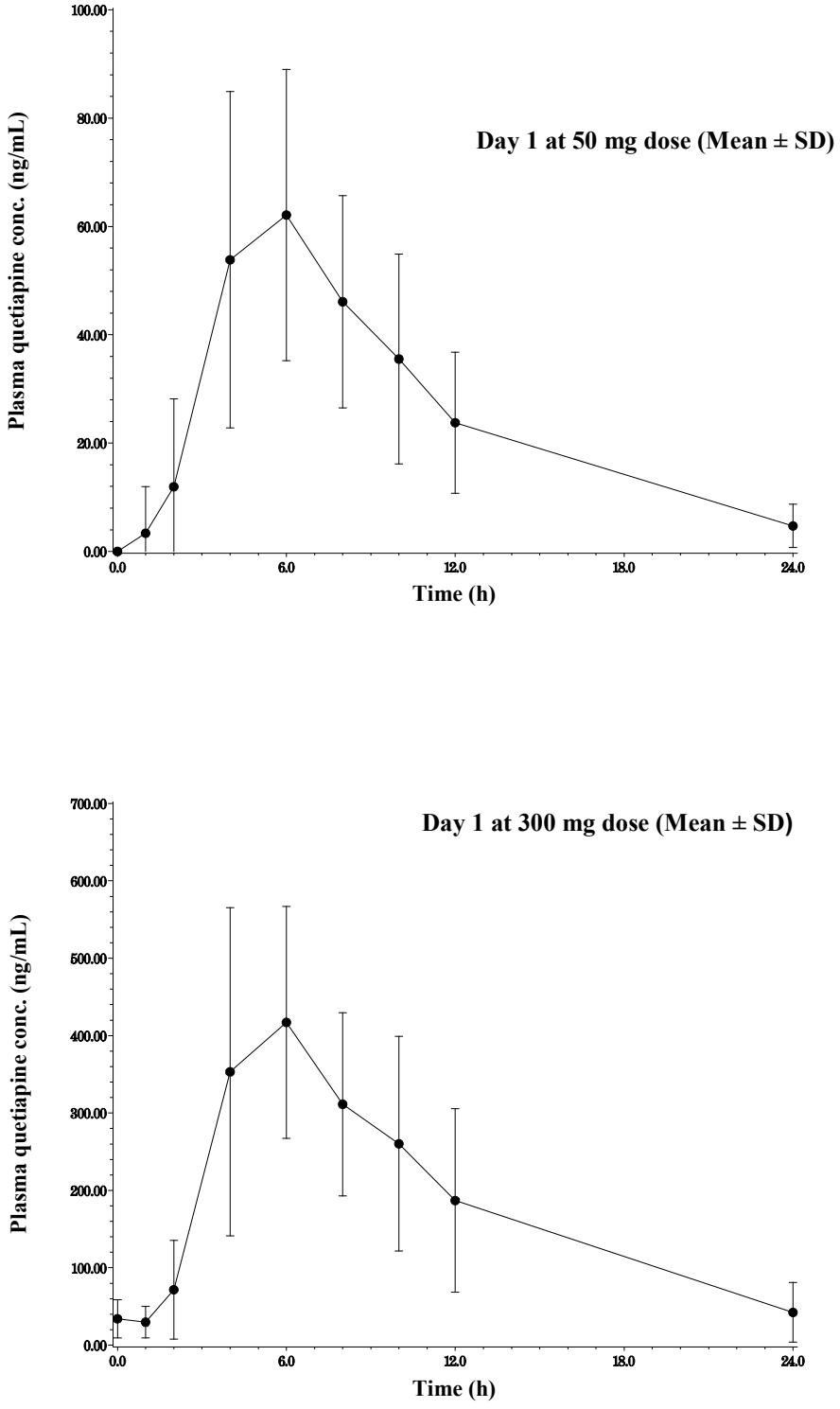


Table 2 Mean Plasma Unchanged FK949E Concentrations (Group 1) (Continued)

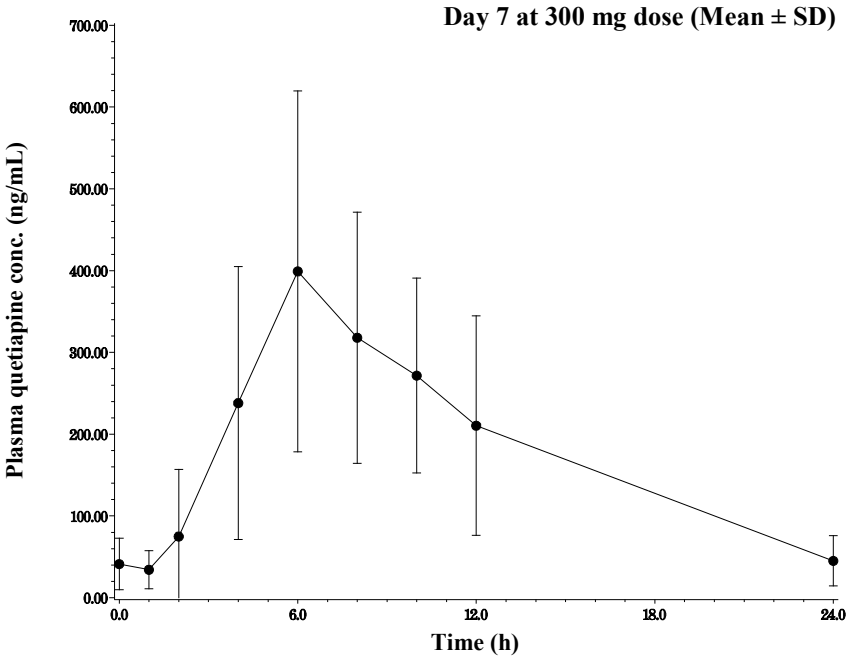


Table 4 Pharmacokinetic Parameters of Plasma Unchanged FK949E Concentrations (Mean ± SD) (Group 2)

Pharmacokinetic parameter	Day 1 at 50 mg dose N=8†	Day 1 at 300 mg dose N=8‡	Day 7 at 300 mg dose N=8††
C_{max} (ng/mL)	43.99 ± 18.44	390.57 ± 173.47	434.42 ± 184.20
t_{max} (h)	8.7 ± 1.5	7.0 ± 2.1	6.0 ± 2.8
AUC_{24h} (ng·h/mL)	580.98 ± 198.59	4588.85 ± 1747.19	4912.00 ± 1996.19
AUC_{inf} (ng·h/mL)	908.09 ± 113.84	–	–
$t_{1/2}$ (h)	7.1 ± 0.7	8.0 ± 2.8	7.9 ± 2.3
CL/F (L/h)	55.61 ± 6.57	77.98 ± 41.66 ‡‡	77.33 ± 51.42
MRT_{last} (h)	12.0 ± 1.4	–	–
MRT_{inf} (h)	13.8 ± 1.3	–	–

† N=3 for AUC_{inf}, $t_{1/2}$, CL/F, MRT_{inf}
‡ N=7 for $t_{1/2}$
†† N=6 for $t_{1/2}$
‡‡ For reference, it was calculated assuming that the data were those at the steady state although the steady state had not been achieved.

Figure 3 Mean Plasma Unchanged FK949E Concentrations (Group 2)

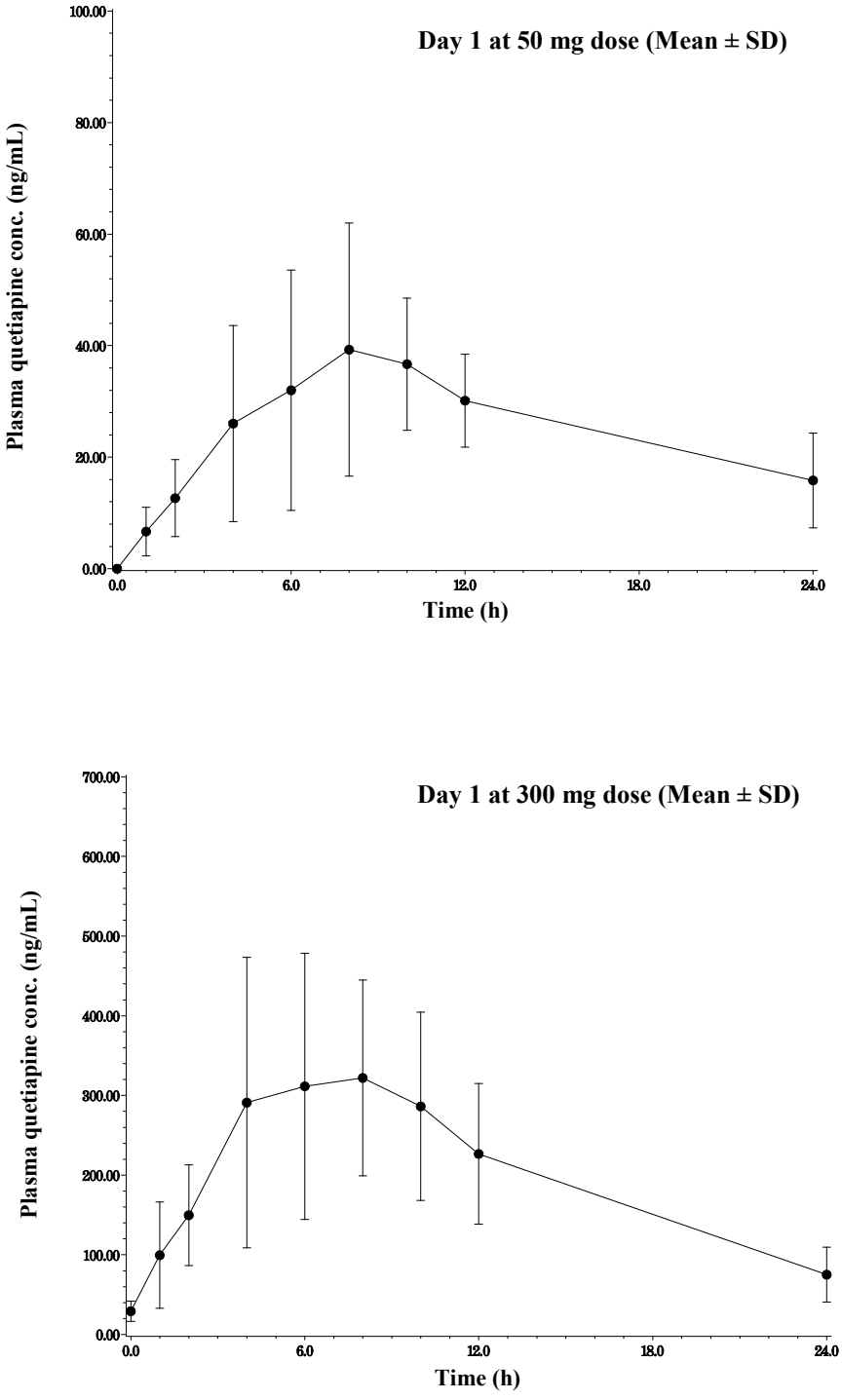
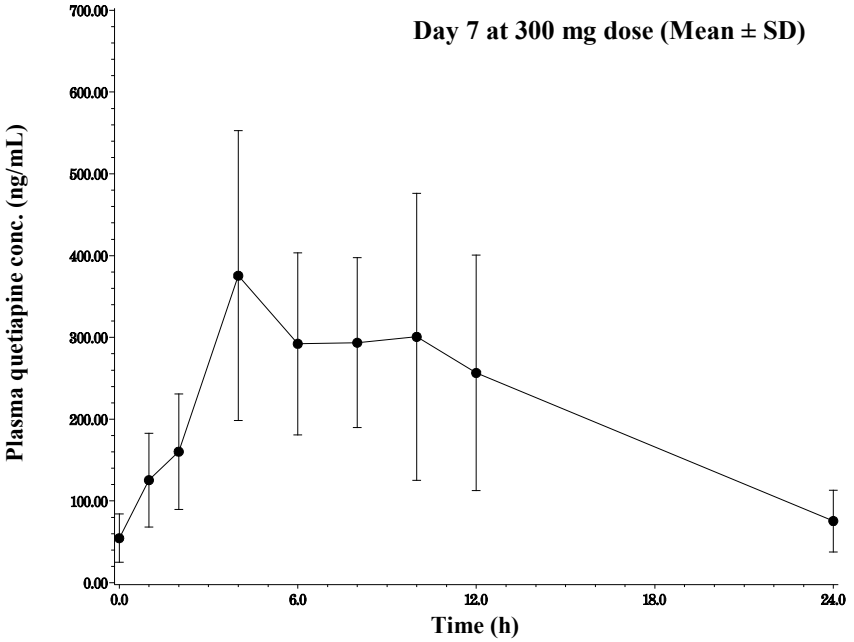


Table 3 Mean Plasma Unchanged FK949E Concentrations (Group 2) (Continued)



5. Safety:

Adverse events

A summary of adverse events in each group is shown in Table 5. Adverse events and drug-related adverse events occurred in all the subjects consisting of 11 subjects in Group 1 and 8 subjects in Group 2. The number of adverse events was 60 in Group 1 and 52 in Group 2; the number of drug-related adverse events was 55 in Group 1 and 51 in Group 2.

Adverse events resulting in death or leading to discontinuation of the study were not observed in either group. One serious adverse event (panic disorder) occurred in 1 subject in Group 2, but a causal relationship with study drug was ruled out.

Table 5 Summary of Adverse Events

	Group 1 N=11		Group 2 N=8	
	Number of subjects with an AE†	Number of AEs	Number of subjects with an AE†	Number of AEs
SAF	11		8	
Adverse events	11 (100.0%)	60	8 (100.0%)	52
Drug-related adverse events	11 (100.0%)	55	8 (100.0%)	51
Death	0	0	0	0
Serious adverse events	0	0	1 (12.5%)	1
Adverse events resulting in discontinuation	0	0	0	0

† Number of subjects (incidence)

The incidence of adverse events and drug-related adverse events in each group are shown in Table 6 and Table 7, respectively.

The most common adverse event was somnolence, which was reported in all the subjects in both groups.

Adverse events with incidences of at least 20% in Group 1 were somnolence (100%), dry mouth (63.6%), malaise (45.5%), orthostatic hypotension (45.5%), and blood creatinine increased (27.3%). The status of the occurrence of drug-related adverse events was similar to that of adverse events. All adverse events were mild in severity.

Adverse events with incidences of at least 20% in Group 2 were somnolence (100%), orthostatic hypotension (75.0%), dry mouth (50.0%), constipation (25.0%), asthenia (25.0%), thirst (25.0%), tri-iodothyronine free decreased (25.0%), and headache (25.0%). The status of the occurrence of drug-related adverse events was similar to that of adverse events. All adverse events were mild in severity.

In the evaluation of adverse events by the time of onset, somnolence occurred in the early phases after the start of study drug administration (Days 1 to 3), and was reported in 10 of 11 subjects on the day of the first dose (Day 1, 50 mg) in Group 1. In Group 2, somnolence occurred in all of the 8 subjects on the day of the first dose (Day 1, 50 mg), and was subsequently reported in 1 subject each on Day 3, Day 5, Day 7, Day 9, and Day 10; however, there was no tendency indicating that the number of events increased with increasing dose.

Table 6 Incidence of Adverse Events

System Organ Class/Preferred Term†	Group 1 N=11	Group 2 N=8
Ear and labyrinth disorders	**1 (9.1%)**	**0 (0.0%)**
Vertigo positional	1 (9.1%)	0 (0.0%)
Cardiac disorders	**0 (0.0%)**	**1 (12.5%)**
Palpitations	0 (0.0%)	1 (12.5%)
Eye disorders	**1 (9.1%)**	**0 (0.0%)**
Vision blurred	1 (9.1%)	0 (0.0%)
Gastrointestinal disorders	**8 (72.7%)**	**6 (75.0%)**
Constipation	2 (18.2%)	2 (25.0%)
Diarrhoea	2 (18.2%)	0 (0.0%)
Dry mouth	7 (63.6%)	4 (50.0%)
General disorders and administration site conditions	**6 (54.5%)**	**4 (50.0%)**
Malaise	5 (45.5%)	0 (0.0%)
Pyrexia	1 (9.1%)	0 (0.0%)
Asthenia	0 (0.0%)	2 (25.0%)
Thirst	1 (9.1%)	2 (25.0%)
Infections and infestations	**1 (9.1%)**	**0 (0.0%)**
Nasopharyngitis	1 (9.1%)	0 (0.0%)

Table 6 Incidence of Adverse Events (Continued)

System Organ Class/Preferred Term†	Group 1 N=11	Group 2 N=8
Investigations	**5 (45.5%)**	**4 (50.0%)**
Alanine aminotransferase increased	1 (9.1%)	0 (0.0%)
Aspartate aminotransferase increased	0 (0.0%)	1 (12.5%)
Blood creatine phosphokinase increased	0 (0.0%)	1 (12.5%)
Gamma-glutamyltransferase increased	0 (0.0%)	1 (12.5%)
Blood creatinine increased	3 (27.3%)	0 (0.0%)
Blood potassium increased	1 (9.1%)	0 (0.0%)
Blood pressure decreased	1 (9.1%)	0 (0.0%)
Blood uric acid increased	1 (9.1%)	0 (0.0%)
Tri-iodothyronine free decreased	1 (9.1%)	2 (25.0%)
Thyroxine free decreased	1 (9.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	**2 (18.2%)**	**0 (0.0%)**
Arthralgia	1 (9.1%)	0 (0.0%)
Myalgia	1 (9.1%)	0 (0.0%)
Pain in extremity	1 (9.1%)	0 (0.0%)
Nervous system disorders	**11 (100.0%)**	**8 (100.0%)**
Dizziness	2 (18.2%)	0 (0.0%)
Dizziness postural	2 (18.2%)	1 (12.5%)
Headache	1 (9.1%)	2 (25.0%)
Somnolence	11 (100.0%)	8 (100.0%)
Psychiatric disorders	**2 (18.2%)**	**2 (25.0%)**
Hallucination, visual	1 (9.1%)	0 (0.0%)
Insomnia	1 (9.1%)	0 (0.0%)
Nervousness	0 (0.0%)	1 (12.5%)
Panic disorder	0 (0.0%)	1 (12.5%)
Respiratory, thoracic and mediastinal disorders	**2 (18.2%)**	**1 (12.5%)**
Epistaxis	1 (9.1%)	0 (0.0%)
Nasal congestion	1 (9.1%)	1 (12.5%)
Skin and subcutaneous tissue disorders	**1 (9.1%)**	**0 (0.0%)**
Eczema	1 (9.1%)	0 (0.0%)
Vascular disorders	**5 (45.5%)**	**6 (75.0%)**
Orthostatic hypotension	5 (45.5%)	6 (75.0%)

Number of subjects (incidence)
† MedDRA/J ver.12.0 (SOC / PT)

Table 7 Incidence of Drug-Related Adverse Events

System Organ Class/Preferred Term†	Group 1 N=11	Group 2 N=8
Ear and labyrinth disorders	**1 (9.1%)**	**0 (0.0%)**
Vertigo positional	1 (9.1%)	0 (0.0%)
Cardiac disorders	**0 (0.0%)**	**1 (12.5%)**
Palpitations	0 (0.0%)	1 (12.5%)
Eye disorders	**1 (9.1%)**	**0 (0.0%)**
Vision blurred	1 (9.1%)	0 (0.0%)
Gastrointestinal disorders	**8 (72.7%)**	**6 (75.0%)**
Constipation	2 (18.2%)	2 (25.0%)
Diarrhoea	1 (9.1%)	0 (0.0%)
Dry mouth	7 (63.6%)	4 (50.0%)
General disorders and administration site conditions	**6 (54.5%)**	**4 (50.0%)**
Malaise	5 (45.5%)	0 (0.0%)
Pyrexia	1 (9.1%)	0 (0.0%)
Asthenia	0 (0.0%)	2 (25.0%)
Thirst	1 (9.1%)	2 (25.0%)
Investigations	**5 (45.5%)**	**4 (50.0%)**
Alanine aminotransferase increased	1 (9.1%)	0 (0.0%)
Aspartate aminotransferase increased	0 (0.0%)	1 (12.5%)
Blood creatine phosphokinase increased	0 (0.0%)	1 (12.5%)
Gamma-glutamyltransferase increased	0 (0.0%)	1 (12.5%)
Blood creatinine increased	3 (27.3%)	0 (0.0%)
Blood potassium increased	1 (9.1%)	0 (0.0%)
Blood pressure decreased	1 (9.1%)	0 (0.0%)
Blood uric acid increased	1 (9.1%)	0 (0.0%)
Tri-iodothyronine free decreased	1 (9.1%)	2 (25.0%)
Thyroxine free decreased	1 (9.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	**1 (9.1%)**	**0 (0.0%)**
Arthralgia	1 (9.1%)	0 (0.0%)
Nervous system disorders	**11 (100.0%)**	**8 (100.0%)**
Dizziness	2 (18.2%)	0 (0.0%)
Dizziness postural	2 (18.2%)	1 (12.5%)
Headache	1 (9.1%)	2 (25.0%)
Somnolence	11 (100.0%)	8 (100.0%)
Psychiatric disorders	**2 (18.2%)**	**1 (12.5%)**
Hallucination, visual	1 (9.1%)	0 (0.0%)
Insomnia	1 (9.1%)	0 (0.0%)
Nervousness	0 (0.0%)	1 (12.5%)
Respiratory, thoracic and mediastinal disorders	**1 (9.1%)**	**1 (12.5%)**
Nasal congestion	1 (9.1%)	1 (12.5%)
Skin and subcutaneous tissue disorders	**1 (9.1%)**	**0 (0.0%)**
Eczema	1 (9.1%)	0 (0.0%)
Vascular disorders	**5 (45.5%)**	**6 (75.0%)**
Orthostatic hypotension	5 (45.5%)	6 (75.0%)

Number of subjects (incidence)
† MedDRA/J ver.12.0 (SOC / PT)

Orthostatic hypotension, the most common adverse event in the phase I study (Study No. 6949-CL-0001) conducted before the present study, was further investigated. In the present study, blood pressure and pulse rate were measured in the supine position and 1 minute after standing up, as in the phase I study (Study No. 6949-CL-0001), to assess the effects of a postural change from the supine to standing position on the blood pressure and pulse rate.

In Group 2, besides orthostatic hypotension, orthostatic hypotension-related events such as dizziness postural and palpitations were investigated (Table 8 and Table 9). The results showed that 11 events of orthostatic hypotension occurred in 6 of 8 subjects (75.0%). When orthostatic hypotension-related events such as dizziness postural and palpitations were included in the evaluation, 14 orthostatic hypotension-related events were observed in 7 subjects (87.5%). However, none of these events were assessed as uncontrollable or unpredictable adverse events by the investigator/sub-investigator: all were controllable or predictable. Among subjects with orthostatic hypotension, some experienced a decrease in standing systolic blood pressure to below 80 mmHg, but all of these events recovered promptly without intervention and were assessed to be mild in severity. Evaluation of orthostatic hypotension-related events was conducted in Group 2, but was not carried out in Group 1, in which 5 events of orthostatic hypotension were observed in 5 of 11 subjects (45.5%). All of these events recovered without intervention and were assessed to be mild in severity.

Table 8 Summary of Orthostatic Hypotension-Related Events (Group 2)

	Group 2 N=8	
	Number of subjects with an AE†	Number of AEs
Orthostatic hypotension	6 (75.0%)	11
Orthostatic hypotension-related events	7 (87.5%)	14
Uncontrollable or unpredictable orthostatic hypotension-related events	0	0

† Number of subjects (incidence)

Table 9 Incidence of Orthostatic Hypotension-Related Events (Group 2)

System Organ Class/Preferred Term†	Group 2 N=8
Cardiac disorders	**1 (12.5%)**
Palpitations	1 (12.5%)
Nervous system disorders	**1 (12.5%)**
Dizziness postural	1 (12.5%)
Vascular disorders	**6 (75.0%)**
Orthostatic hypotension	6 (75.0%)

Number of subjects (incidence)
† MedDRA/J ver.12.0 (SOC / PT)

Clinical laboratory evaluations

In hematology and blood biochemistry after the start of study drug administration, mean values deviating from the reference range include low tri-iodothyronine free in Group 1 and high LDL cholesterol, high triglyceride, high total cholesterol, and low tri-iodothyronine free in Group 2. However, mean values of triglyceride and total cholesterol were already at high levels before the start of study drug administration and no aggravation was noted after the start of study drug administration. Mean values of LDL cholesterol and tri-iodothyronine free (Group 1 and Group 2) returned to within the reference range at the post-study visit. In urinalysis, 1 subject in Group 1 tested positive (+) for protein urine at the post-study visit; however, none of the other subjects showed any laboratory data deviating from the reference range after the start of study drug administration.

Laboratory-related adverse events observed in more than 1 subject were blood creatinine increased (3 subjects) in Group 1 and tri-iodothyronine free decreased (2 subjects) in Group 2. Other laboratory-related adverse events include alanine aminotransferase increased, aspartate aminotransferase increased, blood creatine phosphokinase increased, γ-glutamyltransferase increased, blood potassium increased, blood pressure decreased, blood uric acid increased, and free thyroxine decreased in 1 subject each. All of these laboratory-related adverse events were mild in severity.

Vital signs

In order to assess the effects of a postural change from the supine to standing position on blood pressure and pulse rate, the blood pressure and pulse rate were measured in the supine position and 1 minute after standing up. Differences in measurements in the supine position and 1 minute after standing up (1 minute after standing up – supine) in each group are presented in Figure 4 and Figure 6 for blood pressure and in Figure 5 and Figure 7 for pulse rate.

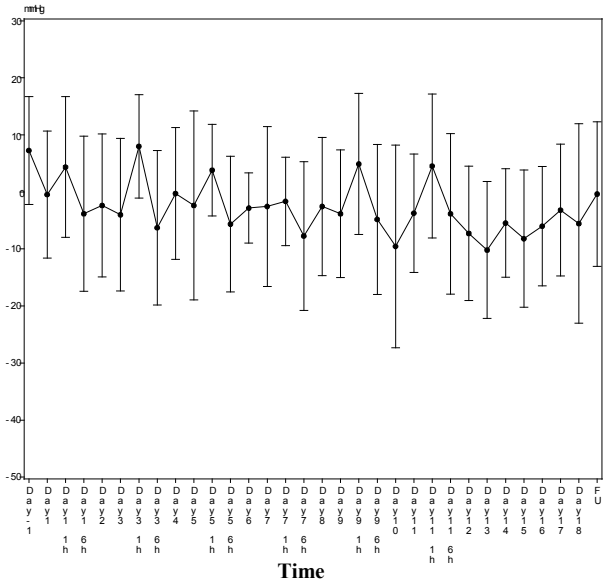
When the time course of changes (pre-dose, 1 hour post-dose, and 6 or 8 hours post-dose) on each day of the evaluation period was followed, the differences in blood pressure and pulse rate between the postures (1 minute after standing up – supine) became the greatest at 6 or 8 hours post-dose and the parameters tended to recover by the time of study drug administration on the following day.

Mean axillary body temperature ranged from 35.96 to 36.30°C in Group 1, and from 36.00 to 36.59°C in Group 2, indicating no notable changes.

Figure 4 **Changes in Systolic and Diastolic Blood Pressure (1 Minute after Standing Up – Supine) (Mean ± SD) (Group 1)**

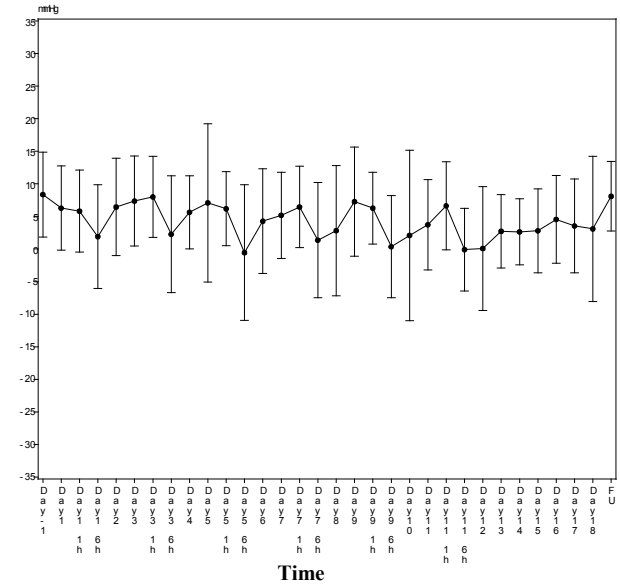
Treatment group = Group 1

Systolic blood pressure (1 minute after standing up – supine)



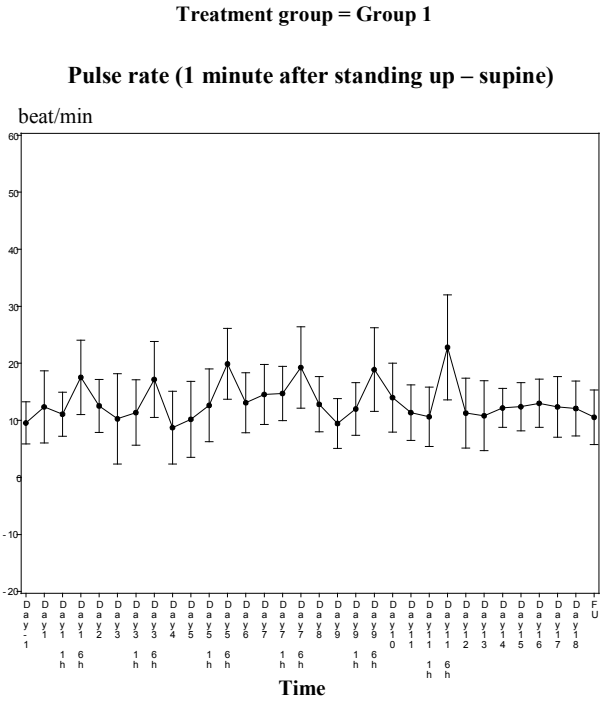
Treatment group = Group 1

Diastolic blood pressure (1 minute after standing up – supine)



Time points of measurement: 1 h, 1 hour post-dose; 6 h, 6 hours post-dose; no description, before administration;
FU: Post-study visit

Figure 5 Changes in Pulse Rate (1 Minute after Standing Up – Supine) (Mean ± SD) (Group 1)

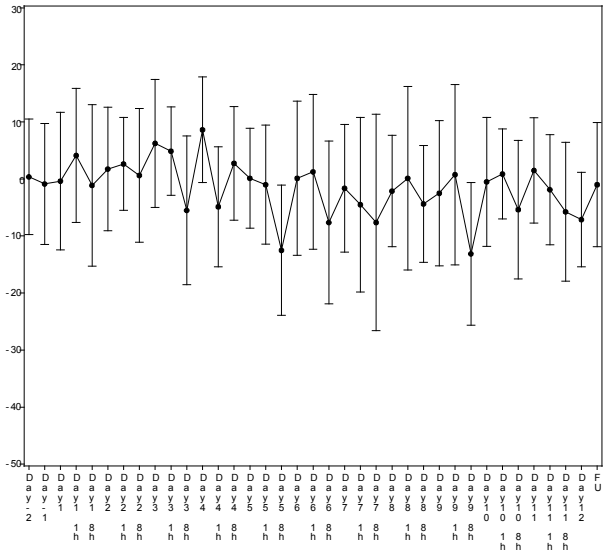


Time points of measurement: 1 h, 1 hour post-dose; 6 h, 6 hours post-dose; no description, before administration;
FU: Post-study visit

Figure 6 **Changes in Systolic and Diastolic Blood Pressure (1 Minute after Standing Up – Supine) (Mean ± SD) (Group 2)**

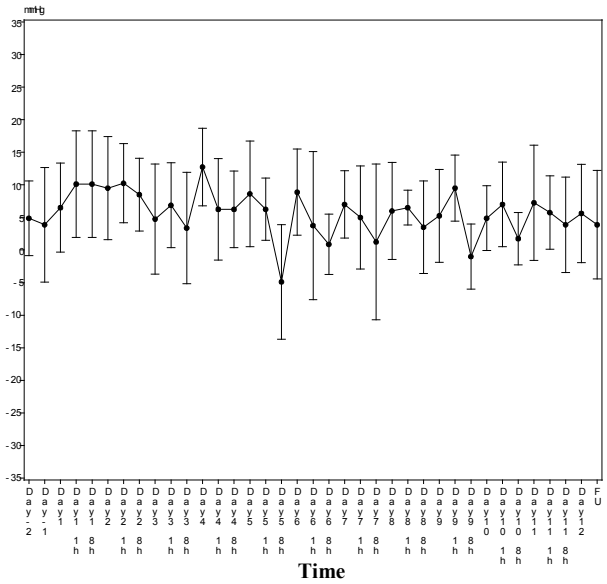
Treatment group = Group 2

Systolic blood pressure (1 Minute after Standing Up – Supine)



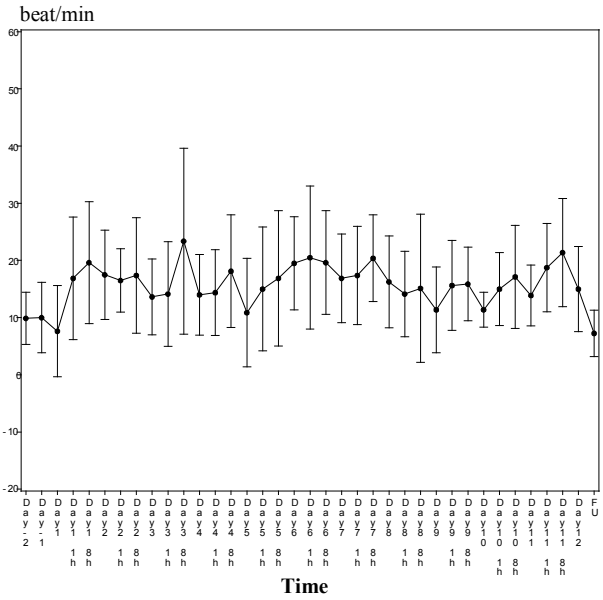
Treatment group = Group 2

Diastolic blood pressure (1 Minute after Standing Up – Supine)



Time points of measurement: 1 h, 1 hour post-dose; 8 h, 8 hours post-dose; no description, before administration;
FU: Post-study visit

Figure 7 Changes in Pulse Rate (1 Minute after Standing Up – Supine) (Mean ± SD) (Group 2)



Time points of measurement: 1 h, 1 hour post-dose; 8 h, 8 hours post-dose; no description, before administration;
FU: Post-study visit

Electrocardiograms

No “clinically significant abnormal” ECG findings were observed in any of the subjects in either group. The ECG findings were “normal” before the start of study drug administration but were “not clinically significant abnormal” after the start of study drug administration in 1 subject in Group 1 ([redacted], sinus bradycardia on Day 18). However, the ECG findings at the post-study visit were “normal” in this subject.

Conclusions:

The present study was conducted as a multicenter open-label study to evaluate the safety and pharmacokinetics of FK949E (extended-release formulation of quetiapine) orally administered as multiple doses of 300 mg for 7 days in elderly patients with major depressive disorder. In Group 1, the study drug was orally administered once daily after breakfast for 17 days. Study drug administration was started at an initial dose of 50 mg/day and the dose was increased in increments of 50 mg/day every 2 days up to 300 mg/day (final dose) by Day 11. Administration at the final dose was repeated for 7 days. In Group 2, it was originally planned to administer the study drug after breakfast, as in Group 1. However, since the results of the food effect study (Study No. 6949-CL-0003) suggest an increase in plasma FK949E concentrations arising from food effects, the study drug was administered under fasting conditions in the phase I study in non-elderly patients with major depressive disorder (Study No. 6949-CL-0009), giving more careful consideration to safety, because an increase in the plasma

FK949E concentration may affect the occurrence of adverse events. In accordance with this dose regimen, the study design was changed for Group 2 and it was decided to administer the study drug under fasting conditions. Accordingly, the study drug was orally administered once daily in the morning under fasting conditions for 11 days. Study drug administration was started at an initial dose of 50 mg/day and the dose was increased to 150 mg/day on Day 3 and to 300 mg/day (final dose) on Day 5. Administration at the final dose was repeated for 7 days. Also in view of the results of the phase I study in non-elderly patients with major depressive disorder (Study No. 6949-CL-0001), which had been conducted before the present study, some arrangements including the addition of exclusion criteria and detailed assessments related to orthostatic hypotension were made to start the present study.

The target sample size was 8 subjects each in both groups and the study drug was administered to 11 subjects in Group 1 and 8 subjects in Group 2. All subjects who received the study drug were included in the SAF and the PKAS.

The results of pharmacokinetic evaluation showed that the C_{max} and AUC_{24h} (mean ± SD, the same hereinafter) of unchanged FK949E in plasma on the last day of the final dose period in Group 1 were 483.59 ± 169.94 ng/mL and 4091.09 ± 1510.34 ng·h/mL, respectively. The mean t_{max} at individual time points ranged from 5.1 to 5.8 hours. Similarly, the C_{max} and AUC_{24h} in Group 2 were 434.42 ± 184.20 ng/mL and 4912.00 ± 1996.19 ng·h/mL, respectively. The mean t_{max} ranged from 6.0 to 8.7 hours at each measurement time point. Both C_{max} and AUC_{24h} increased with increasing dose in both groups. The present study examined steady state in each group and accumulation following multiple-dose administration in an exploratory manner. When the steady state was examined based on C_{trough} as an indicator, the plasma unchanged FK949E concentration was considered to achieve the steady state immediately after the start of multiple-dose administration at the final dose. When accumulation following multiple-dose administration was examined based on the C_{max} and AUC_{24h} as indicators, the results of comparison between the first day and the last day of multiple-dose administration at the final dose suggested no great differences. Based on the above, interindividual and intraindividual changes in the plasma unchanged FK949E concentrations were great; however, the plasma unchanged FK949E concentration tended to increase with increasing dose. With the dose escalation method, the plasma unchanged FK949E concentration was considered to achieve the steady state immediately after the start of multiple-dose administration at the final dose.

The examination of safety results showed that adverse events and drug-related adverse events occurred in all the subjects consisting of 11 subjects in Group 1 and 8 subjects in Group 2. The number of adverse events was 60 in Group 1 and 52 in Group 2; the number of drug-related adverse events was 55 in Group 1 and 51 in Group 2. Adverse events resulting in death or leading to discontinuation of the study were not observed in either group. One serious adverse event (panic disorder) occurred in 1 subject in Group 2, but a causal relationship with study drug was ruled out.

The most common adverse event was somnolence, which was reported in all the subjects in both groups. Adverse events with incidences of at least 20% in Group 1 were somnolence (100%), dry mouth (63.6%), malaise (45.5%), orthostatic hypotension (45.5%), and blood creatinine increased (27.3%). Adverse events with incidences of at least 20% in Group 2 were somnolence (100%), orthostatic hypotension (75.0%), dry mouth

(50.0%), constipation (25.0%), asthenia (25.0%), thirst (25.0%), tri-iodothyronine free decreased (25.0%), and headache (25.0%). The status of the occurrence of drug-related adverse events was similar to that of adverse events in both groups. All adverse events were mild in severity. Eleven events of orthostatic hypotension occurred in 6 of 8 subjects (75.0%) in Group 2. There were no orthostatic hypotension-related events that the investigator/sub-investigator considered uncontrollable or unpredictable events, and all of them were controllable or predictable. Among subjects with orthostatic hypotension, some experienced a decrease in standing systolic blood pressure to below 80 mmHg, but all of these events recovered promptly without intervention and were assessed to be mild in severity. Evaluation of orthostatic hypotension-related events was conducted in Group 2, but was not carried out in Group 1, in which 5 events of orthostatic hypotension were observed in 5 of 11 subjects (45.5%). All of these events recovered without intervention and were assessed to be mild in severity. Orthostatic hypotension is a characteristic adverse event that has been reported in Japanese clinical studies in non-elderly patients with major depressive disorder and in overseas clinical studies, as well as with the use of the existing formulation of quetiapine, and it also occurred with a high incidence in the present study. In the evaluation of adverse events by the time of onset, somnolence occurred in the early phases of study drug administration (Day 1 to Day 3) in Group 1, whereas in Group 2, it occurred in all 8 patients on the day of the first dose (Day 1) but there was no tendency indicating that the number of somnolence events increased with increasing dose.

On clinical laboratory evaluations of hematology and blood biochemistry after the start of study drug administration, mean values deviating from the reference range include low tri-iodothyronine free in Group 1 and high LDL cholesterol, high triglyceride, high total cholesterol, and low tri-iodothyronine free in Group 2. However, mean values of triglyceride and total cholesterol were already at high levels before the start of study drug administration and no aggravation was noted after the start of study drug administration. Mean values of LDL cholesterol and tri-iodothyronine free (Group 1 and Group 2) returned to within the reference range at the post-study visit. In urinalysis, 1 subject in Group 1 tested positive (+) for protein urine at the post-study visit; however, none of the other subjects showed any laboratory data deviating from the reference range after the start of study drug administration. All of these laboratory-related adverse events were mild in severity. In the evaluation of the differences arising from a postural change, the differences in blood pressure and pulse rate measured in the supine position and 1 minute after standing up (1 minute after standing up – supine) became the greatest at 6 or 8 hours post-dose and the parameters tended to recover by the time of study drug administration on the following day.

In the present study, adverse events such as somnolence, orthostatic hypotension, dry mouth, and malaise were reported with relatively high incidences; however, these adverse events were known from the phase I studies in non-elderly patients with major depressive disorder (Study No. 6949-CL-0001, 6949-CL-0009) and overseas clinical studies, as well as with the use of the existing formulation of quetiapine. In Group 2, there were no orthostatic hypotension-related events that the investigator/sub-investigator considered uncontrollable or unpredictable events, and all of them were controllable or predictable. All were mild in severity and recovered without intervention. Based on these results, although adverse events were reported with high incidences in elderly patients with major depressive disorder in the present study, these adverse events were already known and therefore considered to be tolerable.

The status of the occurrence of adverse events in Group 2 of the present study was compared with the status of the occurrence of adverse events in the 300 mg group of the phase I study in non-elderly patients (Study No. 6949-CL-0009), in which the same dose regimen as that in Group 2 of the present study was used. The most

common adverse event in the 300 mg group (10 subjects) in the phase I study in non-elderly patients (Study No. 6949-CL-0009) was somnolence (100.0%), followed by dry mouth (70.0%), nasal congestion (50.0%), orthostatic hypotension (40.0%), diarrhoea (40.0%), blood prolactin increased (40.0%), dizziness postural (20.0%), back pain (20.0%), and upper respiratory tract inflammation (20.0%). Somnolence (100%), orthostatic hypotension (75.0%), and dry mouth (50.0%), which occurred with high incidences in Group 2 (8 subjects) of the present study, had also been reported with high incidences in the 300 mg group of the phase I study in non-elderly patients (Study No. 6949-CL-0009) and no great differences in the tendency of the occurrence of these characteristic adverse events were noted. All the adverse events reported in the 300 mg group of the phase I study in non-elderly patients (Study No. 6949-CL-0009) and in Group 2 of the present study were mild in severity. The incidence of orthostatic hypotension in Group 2 of the present study (75.0%) was higher than that in the 300 mg group of the phase I study in non-elderly patients (40%) (Study No. 6949-CL-0009); however, all were controllable and predictable. All of these orthostatic hypotension events were mild in severity and recovered without intervention. In the evaluation of adverse events by the time of onset, somnolence and orthostatic hypotension generally tended to occur on the day of the first dose (Day 1) and on the day of dose escalation of the study drug (Day 3 and Day 5) in both studies. Based on the above results, administration of FK949E at the same dose regimen to elderly and non-elderly patients was considered to make no great differences in the status of the occurrence or severity of characteristic adverse events. However, it is considered necessary to take adequate safety measures for such as orthostatic hypotension when the study drug is administered to elderly patients in the subsequent studies.

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