Name of Sponsor: Astellas Pharma Inc.	**Individual Study Table** **Referring to Part of the Dossier** **Volume:** Not determined **Page:** Not determined	(For National Authority Use Only)
Product Name: Not determined		
Name of Active Ingredient: Quetiapine fumarate		

SYNOPSIS

Title of Study:

Phase I Study of FK949E - A Study of Drug-drug Interactions between FK949E and Fluvoxamine in Healthy Male Adults -

Responsible Officer or Designee:

[redacted], Astellas Pharma Inc.

Investigators:

[redacted]

Study Sites:

[redacted], one site

Publication Based on the Study:

Unpublished

Study Period:

1 month (duration from the starting day of the study to the day of study completion)

Study Initiation Date:

15 July 2011 (the day when the first subject signed the written informed consent)

Study Completion Date:

22 August 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 assess the effect of multiple-dose fluvoxamine on the pharmacokinetics of quetiapine in healthy adult male subjects. The safety of FK949E in the population was also evaluated.

Study Design and Methodology:

Type of blinding: Open-label design

Randomization: Not applicable

FK949E was administered as a single dose followed by washout in non-elderly, healthy adult male subjects confirmed to be eligible for the study. FK949E was again administered as a single dose in combination with multiple-dose fluvoxamine.

Planned Sample Size:

24 subjects

[Rationale]

The total number of subjects was set at 24 as a sample size that is adequate to assess drug interactions between FK949E and fluvoxamine, taking the feasibility of the study into consideration.

Diagnosis and Inclusion/Exclusion Criteria:

Adult males who volunteered to participate in the study (prospective study subjects) were eligible for the study if they met all the inclusion criteria and did not meet any exclusion criteria listed below:

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1. Inclusion criteria

1) Sex; male
2) Age (at informed consent): 20 (inclusive) to 45 (exclusive) years
3) Body weight (at the screening assessment): 50.0 (inclusive) to 80.0 kg (exclusive)
4) BMI (at the screening assessment): 17.6 (inclusive) to 26.4 kg/m^2 (exclusive)
5) Subjects who were considered to be healthy by the investigator/sub-investigator based on the results of the screening assessments and all examinations performed immediately before the study drug administration, including a physical examination (subjective symptoms and objective findings).
6) Written informed consent obtained from the subject himself.

2. Exclusion criteria

1) Medical history of any of the following conditions:
   [1] Hepatic disease (e.g., hepatitis viral, drug-induced liver disorder)
   [2] Heart disorder (e.g., congestive cardiac failure, angina pectoris, arrhythmia requiring treatment)
   [3] Respiratory disease (e.g., serious bronchial asthma, chronic bronchitis; except a history of non-serious childhood asthma)
   [4] Gastrointestinal disease (e.g., serious peptic ulcer, reflux oesophagitis, diseases requiring various kinds of surgical resection; except appendicitis)
   [5] Renal disease (e.g., acute renal failure, glomerulonephritis, interstitial nephritis; except a history of calculus)
   [6] Cerebrovascular disorder (e.g., cerebral infarction)
   [7] Convulsion disorder (e.g., epilepsy)
   [8] Hemorrhagic disease
   [9] Malignant tumor
   [10] Drug allergy, allergic diseases, except pollinosis
   [11] Drug dependence, alcohol dependence
   [12] Suicide attempt

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2) Any disease (except dental caries) found at the time of informed consent.

3) Deviation from the reference range for supine blood pressure, supine pulse rate, axillary body temperature, or 12-lead electrocardiogram (ECG) at the screening assessment (Table 1)

4) Deviation from the following criteria at the screening assessment or in laboratory tests on the day preceding the day of study drug administration:

   [1] Hematology:

   - 20% deviation from the upper or lower limit of the reference range of the site.

   [2] Blood biochemistry:

   - For AST, ALT, Cre, HbA1c, and serum electrolytes, deviation from the reference range of the site.
   - For the other blood biochemistry parameters, 20% deviation from the upper or lower limit of the reference range of the site.

     No lower limit is specified for parameters for which deviation from the lower limit of normal is not considered clinically significant (T-Bil, ALP, AST, ALT, γ-GTP, LDH, CK, UA, T-Cho, Cre, BUN).

   [3] Urinalysis:

   - U-Glc and/or U-Pro results of (±) or worse.
   - U-Uro results of (+) or worse.

   [4] Urine drug test:

   Positive results for phencyclidines, benzodiazepines, cocaine narcotics, stimulants, cannabis, morphine narcotics, barbiturates, or tricyclic antidepressants.

   [5] Immunological test:

   Positive results for hepatitis B, hepatitis C, syphilis, or HIV.

5) History of treatment, including medication, within 14 days before the start of study drug administration.

6) Consumption of food or beverages containing St. John's Wort within 14 days before the start of study drug administration, or consumption of grapefruit (or food or beverages containing it) within 7 days before the start of study drug administration.

7) Previous participation in a pre- or post-marketing clinical study of another prescription drug or a medical device within 120 days before the screening assessment, or current participation in such a study.

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8) History of administration of quetiapine.

9) History of administration of fluvoxamine.

10) Whole blood sampling of 400 mL or more within 90 days before the screening assessment, whole blood sampling of 200 mL or more within 30 days before the screening assessment, or blood component donation within 14 days before the screening assessment.

11) Routine excessive alcohol consumption ("excessive alcohol" is roughly defined as an average of 45 g of alcohol per day [cf., a large bottle of beer containing 25 g of alcohol, 180 mL of sake containing 22 g of alcohol]).

12) Subjects with a smoking habit (except those who quit smoking at least 90 days before the screening assessment).

13) Persons involved in the study (e.g., the sponsor, persons concerned in study-related CROs or the study site).

14) Individuals considered ineligible for participation in the study by the investigator/sub-investigator.

Table 1 Requirements for Eligibility Related to Exclusion Criterion 3

Variable	Acceptable range
Axillary body temperature	≥35.0°C to < 37.0°C
Supine blood pressure	Systolic blood pressure: ≥100 mmHg to <140 mmHg
	Diastolic blood pressure: ≥40 mmHg to <90 mmHg
Supine pulse rate	≥40 bpm to ≤ 90 bpm
12-lead electrocardiogram	Normal findings, or abnormal, but clinically insignificant, findings

Test Drug, Dose, and Dose Regimen:

1. Test drug and lot numbers

Test drug

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

Concomitant drug

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Test drug		Lot number
Luvox® Tablets 25 mg	A round, yellow-colored, film-coated tablet, containing 25 mg of fluvoxamine maleate.	[redacted] Manufacturer: Abbott Japan Co., Ltd. (former Abbott Pharmaceuticals)
Luvox® Tablets 50 mg	A round, yellow-colored, film-coated tablet, containing 50 mg of fluvoxamine maleate.	[redacted] Manufacturer: Abbott Japan Co., Ltd. (former Abbott Pharmaceuticals)

2. Dose and dose regimen

For morning dosing of FK949E alone or concomitantly with fluvoxamine, subjects were fasted from after the evening meal on the preceding day of study drug administration. On the day of administration, subjects skipped breakfast and received the study drug(s) orally with 150 mL water around 9:00 a.m.

For morning dosing of fluvoxamine alone, subjects took breakfast within 20 minutes from the specified time and received the study drug orally with 150 mL water within 10 minutes after finishing breakfast (breakfast had to start around 8:30 a.m.).

For evening dosing of FK949E concomitantly with fluvoxamine or fluvoxamine alone, subjects received the study drug(s) orally with 150 mL water 12 hours after the morning dose (around 21:00 p.m.).

[Dose]

Administration of FK949E alone (Period 1):

Day 1: FK949E 50 mg once daily (a daily dose of 50 mg)

Co-administration (Period 2):

Days 1 to 2:	Fluvoxamine 25 mg twice daily (a daily dose of 50 mg)
Days3 to 7:	Fluvoxamine 50 mg twice daily (a daily dose of 100 mg)
Day 8:	Fluvoxamine 50 mg twice daily (a daily dose of 100 mg),
	FK949E 50 mg once daily (a daily dose of 50 mg)
Day 9:	Fluvoxamine 50 mg twice daily (a daily dose of 100 mg)

Number of tablets administered

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Study drug	Period 1			Period 2									
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
FK949E 50 mg tablet	1										1		
Fluvoxamine 25 mg tablet				2	2								
Fluvoxamine 50 mg tablet						2	2	2	2	2	2	2	

[Rationale for the dose and dose regimen]

In the United States, quetiapine XR was approved at a dose of 150 to 300 mg once daily for combination therapy in patients on existing antidepressants. In Japan, it is expected to use the same dose range of 150 to 300 mg as the clinical dose of FK949E. Overseas study data indicate that both C_{max} and AUC of FK949E administered under fasting conditions are linear in a dose range of 50 to 400 mg. A study in healthy adult subjects demonstrated the tolerability of 50 mg of FK949E, but the tolerability of 150 or 300 mg of the drug has not been evaluated. In Japanese patients, dose correlation was observed between two doses of 50 and 300 mg of FK949E. In view of these findings, drug interactions at the expected clinical dose could be estimated by assessing the drug interactions at a dose of 50 mg of FK949E in healthy adult subjects. Regarding the regimen, the drug had to be administered under fasting conditions in the present study, as well as in the planned phase II and subsequent studies.

In the present study, plasma quetiapine concentrations may be increased due to the co-administration of fluvoxamine. Fluvoxamine is reported to increase AUC of midazolam (administered intravenously) and alprazolam, which are typical CYP3A4 substrates, by approximately 1.5 and 2 times, respectively, suggesting that fluvoxamine is a weak to moderate CYP3A4 inhibitor. It is also reported that the concomitant use of commercially available quetiapine products with erythromycin, which is known to be a moderate CYP3A4 inhibitor, results in an approximate 2-fold increase in the AUC of quetiapine. These reports suggest an approximate 2-fold increase in the AUC of quetiapine at the most when the drug is administered with fluvoxamine. A food effect study in Japanese healthy adult subjects (Study No. 6949-CL-0003) showed an approximate 2-fold increase in the C_{max} of quetiapine after administration under fed conditions compared with administration under fasted conditions. No major safety concerns were seen after a single 50 mg dose of FK949E under fed conditions. Overseas clinical studies in healthy adult subjects (Study Nos. D1448C00008 and D1448C00013) failed to demonstrate the tolerability of FK949E based on the protocol-specified assessment of intolerability rates, but the studies showed no serious adverse events or deaths among healthy adult subjects

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receiving 150 or 300 mg of FK949E. These findings indicate that an approximate 2-fold increase in the blood quetiapine concentrations after co-administration of fluvoxamine would cause no major safety problems.

The dose of fluvoxamine used in the present study was set at 100 mg/day (50 mg twice daily), which is the clinical dose that is widely used in Japanese patients with major depressive disorder. While the maximum dose of fluvoxamine approved in Japan is 150 mg/day, multiple-dose administration of the drug for a total of 9 days in healthy adult subjects was planned in the present study, in which gastrointestinal symptoms, and neurological and psychiatric disorders were expected to occur frequently as adverse reactions in view of the pharmacological action of the drug. It was also planned to co-administer the drug with quetiapine, resulting in the selection of 100 mg/day of fluvoxamine from the viewpoints of subject safety and ethics.

In an overseas drug interaction study of alprazolam and fluvoxamine (multiple-dose administration at a dose of 100 mg once daily for 7 days) in healthy adult male subjects, it was possible to assess CYP3A4 inhibition. It was thus concluded that the effect of fluvoxamine on the pharmacokinetics of quetiapine could be assessed in the present study.

The administration period was determined as the number of days it takes for the plasma fluvoxamine concentration to reach the steady state, and to ensure adequate assessment of CYP3A4 inhibition, in reference to the information listed in the package insert of fluvoxamine (Luvox® Tablets); the information shows that a steady state concentration was reached by 3 days after the start of multiple-dose administration of fluvoxamine at a dose of 75 mg once daily in a Japanese study in healthy adult male subjects.

[Rationale for the dosing interval]

Washout was set to be at least 5 times the elimination half-life of quetiapine based on the “Guideline for Bioequivalence Studies of Generic Products (amended on 24 November 2006).” A food effect study in Japan (Study No. 6949-CL-0003) demonstrated that the mean elimination half-life of FK949E was 6.8 hours after a single 50 mg dose under fasting conditions. This suggests the need for washout of at least 34 hours, and 72-hour washout was thus selected. While no data on metabolites in the Japanese population are available, a study assessing the effect of food (approximately 300 kcal light meal) on the pharmacokinetics (Study No. D1444C00003; Germany) showed that, among the quetiapine metabolites, the elimination half-life of M4 and M2 were comparable to that of quetiapine under fasting conditions, although M1 was not assessed and the elimination half-life of M5 was not available due to a lack of data.

Investigational period:

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Pre-investigational period: No more than 30 days

Administration period: 12 days (including 2-day washout)

Observation period after administration: 8 days

Concomitant Medications and Therapies:

Concomitant treatments (use of other medications or therapies than the study drugs) were prohibited from the start of study drug administration through the completion of the post-study visit, except for treatments for adverse events. When a concomitant treatment was unavoidable, the investigator/sub-investigator had to determine whether to continue the study using the treatment in the subject.

Assessments, Schedule of Procedures, and Evaluation Criteria:

Evaluation schedule

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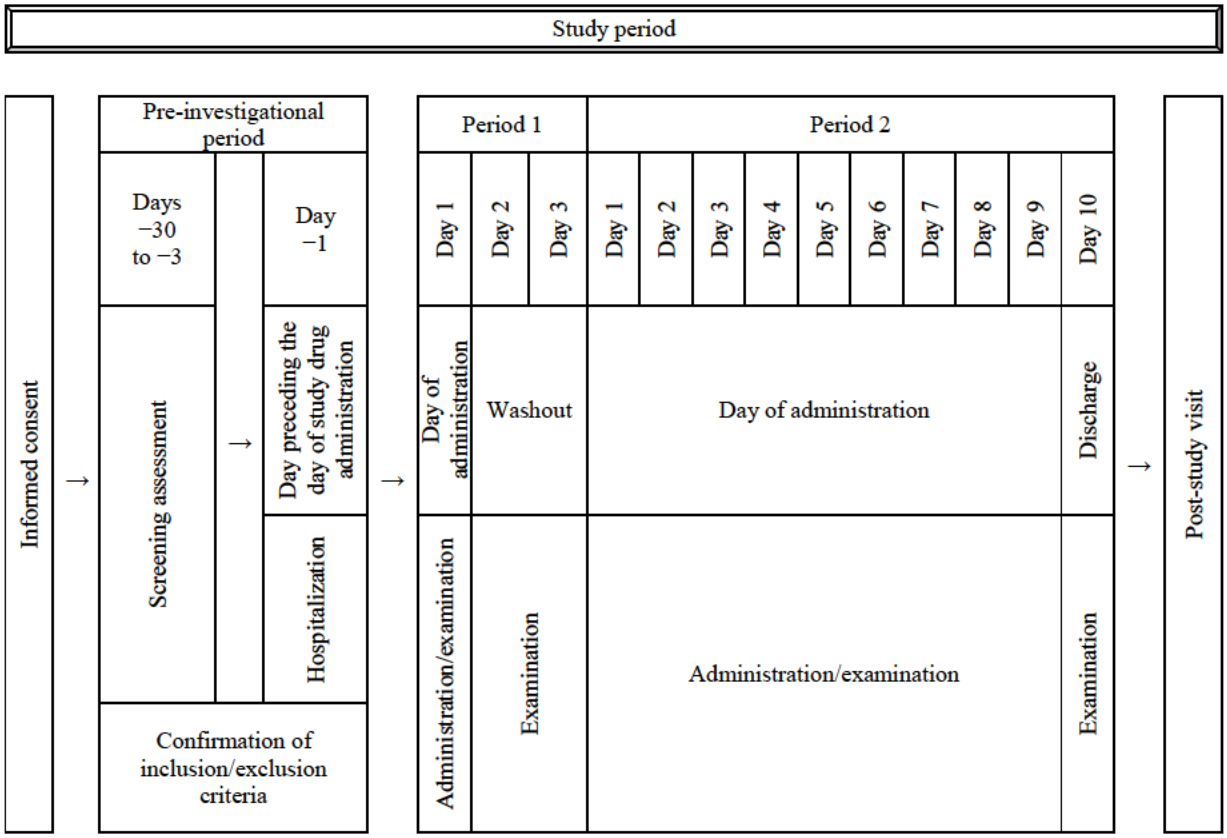

Variables

1. Pharmacokinetics:

- Plasma concentration of the unchanged drug (quetiapine)

  The following parameters were calculated: C_{max}, t_{max}, AUC_{inf}, AUC_{last}, k_{el}, $t_{1/2}$, CL/F and MRT_{inf}

- Plasma concentrations of metabolites* (quetiapine)

  The following parameters were calculated: C_{max}, t_{max}, AUC_{inf}, AUC_{last}, k_{el}, $t_{1/2}$ and MRT_{inf}

  *: 7-hydroxy N-desalkyl quetiapine (M1), 7-hydroxy quetiapine (M2), quetiapine sulfoxide (M4), N-desalkyl quetiapine (M5)

- Plasma concentration of the unchanged drug (fluvoxamine)

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The following parameters were calculated:C_{max}, t_{max}, AUC_{last}, $t_{1/2}$ and C_{trough}

2. Safety:

- Adverse events
- Vital signs (axillary body temperature, blood pressure, and pulse rate)
- 12-lead ECG
- 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 FK949E and in which samples for pharmacokinetic assessment were measured (collected) for at least one time point after administration.

2. Demographics and other baseline characteristics:

The following analyses were performed 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 concentrations of quetiapine and its metabolites, and the descriptive statistics were summarized. If the measured values were below the quantitation limit, the concentrations were treated as zero. The same analyses were performed on fluvoxamine.

Non-compartment model analysis was performed on the time course of the plasma concentrations of unchanged quetiapine and its metabolites for each subject on each day of assessment to estimate the parameters listed

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below. Similarly, another non-compartment model analysis was performed on the time course of plasma concentrations of unchanged fluvoxamine for each subject to estimate the parameters listed below.

Parameter values were only calculated when adequate data were available to estimate values correctly. The actual time course after administration (time elapsed after the last study drug administration) was used for the calculation of the pharmacokinetic parameters.

- Quetiapine

Plasma concentration of the unchanged drug: C_{max}, t_{max}, AUC_{inf}, AUC_{last}, k_{el}, $t_{1/2}$, CL/F and MRT_{inf}

Plasma concentrations of metabolites (M1, M2, M4, M5): C_{max}, t_{max}, AUC_{inf}, AUC_{last}, k_{el}, $t_{1/2}$ and MRT_{inf}

- Fluvoxamine

Plasma concentration of the unchanged drug: C_{max}, t_{max}, AUC_{last}, $t_{1/2}$ and C_{trough}

Data from subjects with pharmacokinetic parameter values that were calculated both in Period 1 (administration of quetiapine alone) and Period 2 (co-administration of quetiapine and fluvoxamine) were used to assess drug interactions. The primary analysis of drug interactions was performed on natural log-transformed C_{max} and AUC_{last} of plasma unchanged quetiapine in a linear mixed effect model with regimen as the fixed effect and subject as a random effect. To assess the effect of the regimen, this model was used to calculate the geometric mean ratio of values for co-administration of quetiapine and fluvoxamine versus values for administration of quetiapine alone and its 90% confidence interval (CI). As the secondary analysis, the same analysis as above was performed on natural log-transformed C_{max} and AUC_{last} of quetiapine metabolites. Specifically, to assess the effect of regimen, the same model was used to calculate the geometric mean ratio of values for co-administration of quetiapine and fluvoxamine versus values for administration of quetiapine alone and its 90% CI. Results of this analysis were used as reference for assessing the extent of interactions, etc.

4. Safety:

The following analyses were performed on the SAF. Analysis by the condition of administration was also performed on the adverse events.

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.
- For each item, spaghetti plot were created.

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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, frequencies were tabulated for each time point.
- For discrete data, cross tables of the measured values were created.

3) Adverse events

Adverse events were counted as described below for the entire study period, administration of FK949E alone in Period 1, administration of fluvoxamine alone in Period 2, and co-administration of fluvoxamine and FK949E in Period 2. The duration of counting by regimen was as shown below. Subjects who did not receive administration of fluvoxamine alone in Period 2 were excluded from the analysis of adverse events for administration of fluvoxamine alone in Period 2. Subjects who did not receive co-administration of fluvoxamine and FK949E in Period 2 were excluded from the analysis of adverse events for co-administration of fluvoxamine and FK949E in Period 2.

Administration of FK949E alone in period 1:

Adverse events occurred after the start of administration of FK949E in Period 1 up to immediately before administration of fluvoxamine in Period 2.

Administration of fluvoxamine alone in period 2:

Adverse events occurred after the start of administration of fluvoxamine in Period 2 up to immediately before co-administration of fluvoxamine and FK949E in Period 2.

Co-administration of fluvoxamine and FK949E in period 2:

Adverse events occurred after the start of co-administration of fluvoxamine and FK949E in Period 2 up to the post-study visit.

- Frequencies of adverse events and drug-related adverse events were tabulated.
- The numbers of adverse events and drug-related adverse events were tabulated.
- Frequencies of adverse events and drug-related adverse events were tabulated by system organ class (SOC) and preferred term (PT).

4) 12-lead ECG

- Frequencies were tabulated for each time point.
- Cross tables of discrete data were created.

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 45 subjects, of whom 24 received the study drug. Among the other 21 subjects handled as screening failures, the reason was reported as "not meeting the inclusion criteria, or meeting any exclusion criteria" in 11 subjects, "withdrawal of consent" in 1 subject, and "others (sufficient subject enrollment)" in 9 subjects. Of subjects receiving the study drug, 2 were withdrawn from the study drug administration. The reason for discontinuation was adverse events in both cases; one subject was withdrawn on Day 2 of Period 1 due to blood creatine phosphokinase increased, and the other was withdrawn on Day 8 of Period 2 due to syncope.

Table 2 shows the number of subjects in each analysis set. All subjects who received the study drug were included in the SAF and PKAS.

Figure 1 Disposition of Subjects

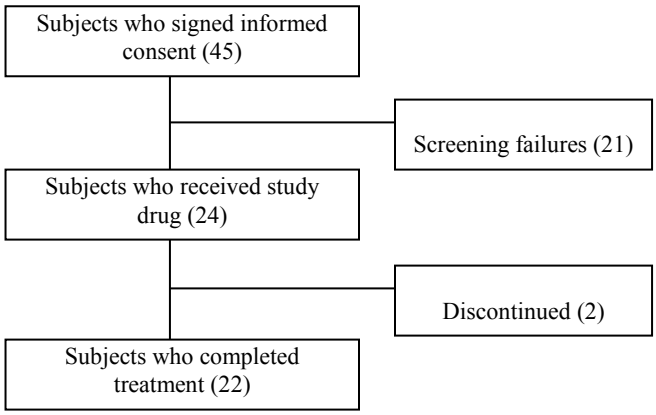

Table 2 Number of Subjects in Analysis Sets

Analysis set	Number of subjects
SAF (n)	24
PKAS (n)	24

2. Demographics and Other Baseline Characteristics:

Table 3 shows the major demographics of the SAF and PKAS (both consisting of 24 subjects). No subjects had any past or concurrent diseases. The mean age ± SD was 30.4 ± 5.49 years, and the mean BMI ± SD was 22.23 ± 2.198 kg/m^2.

Table 3 Major Demographics and Other Baseline Characteristics

Variable		All subjects N=24 †
Sex	Male	24 (100.0%)
	Female	0 (0.0%)
	Total	24
Past disease	No	24 (100.0%)
	Yes	0 (0.0%)
	Total	24
Concurrent disease	No	24 (100.0%)
	Yes	0 (0.0%)
	Total	24
Age (yrs) (at the time of informed consent)	Mean ± SD Median Min - Max	30.4 ± 5.49 30.5 21 to 38
Body weight (kg) (on the day preceding the day of study drug administration)	Mean ± SD Median Min - Max	63.73 ± 7.494 63.90 51.6 to 78.3
BMI (kg/m^2) (at the time of screening assessment)	Mean ± SD Median Min - Max	22.23 ± 2.198 22.05 18.4 to 25.9

†SAF and PKAS
Number of subjects (%)

3. Study drug exposure:

Among the 24 subjects who received the study drug, 2 were withdrawn from the study drug administration. One (Subject No. [redacted]) was withdrawn after receiving the study drug only on Day 1 of Period 1, while the other (Subject No. [redacted]) was withdrawn after receiving the morning dose on Day 8 of Period 2.

4. Pharmacokinetics:

Plasma Quetiapine Concentration

Figure 2 depicts the mean plasma quetiapine concentration-time profile after administration of FK949E alone and after co-administration of fluvoxamine and FK949E. Table 4 presents the pharmacokinetic parameter of plasma quetiapine. The C_{max} of plasma quetiapine (mean ± SD, the same applies hereinafter) was 33.07 ± 14.50 ng/mL after administration of FK949E alone and 44.12 ± 18.89 ng/mL after co-administration of fluvoxamine and FK949E, and the AUC_{last} of plasma quetiapine was 398.96 ± 141.37 ng•h/mL after administration of FK949E alone and 541.18 ± 219.22 ng•h/mL after co-administration. Co-administration of fluvoxamine resulted in an increase in the mean plasma quetiapine concentration, but caused no major changes in the pattern of the concentration-time profile. Both the mean C_{max} and AUC_{last} values were higher after co-administration of fluvoxamine and FK949E than after administration of FK949E alone. The mean t_{max} and $t_{1/2}$ values after administration of FK949E alone and those after co-administration of fluvoxamine and FK949E did not differ markedly.

Figure 2 **Mean Plasma Quetiapine Concentration**

Period 1: Administration of FK949E alone

Period 2: Co-administration of fluvoxamine and FK949E

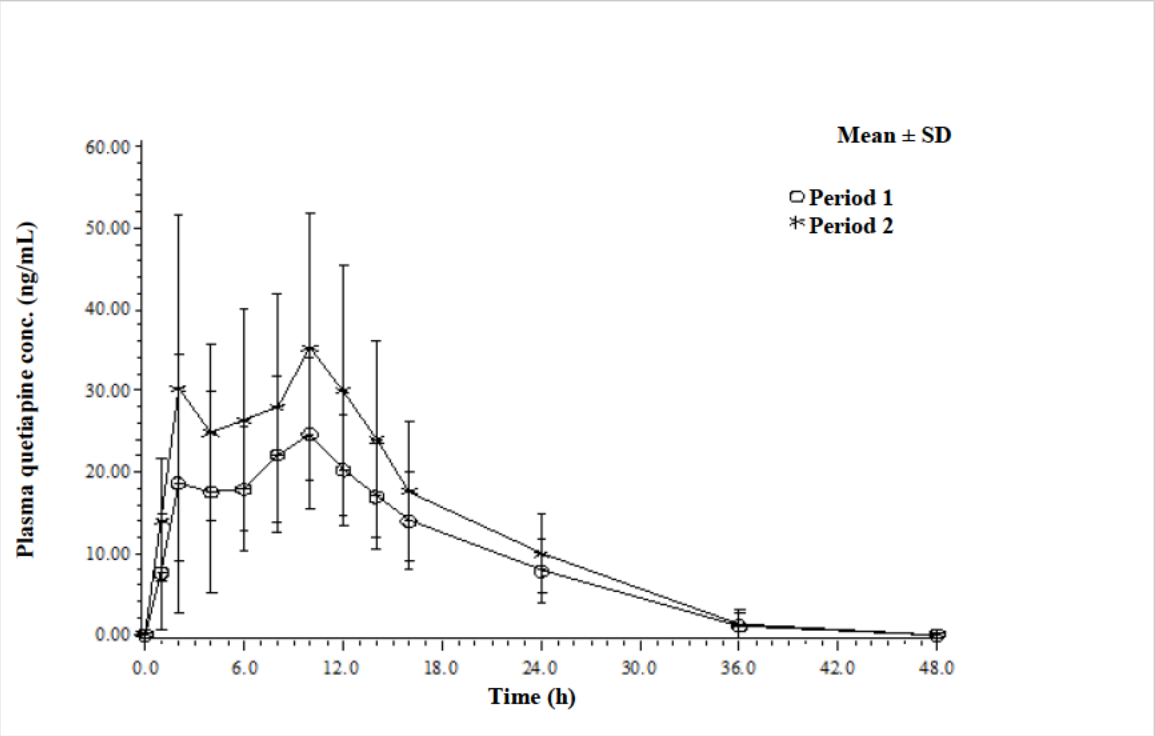

Table 4 **Pharmacokinetic Parameters of the Plasma Quetiapine Concentration (Mean ± SD)**

Pharmacokinetic parameter	Day 1 of Period 1 Administration of FK949E alone N=23	Day 8 of Period 2 Co-administration of fluvoxamine and FK949E N=22
C_{max} (ng/mL)	33.07 ± 14.50	44.12 ± 18.89
t_{max} (h)	7.3 ± 3.6	7.0 ± 3.8
AUC_{inf} (ng·h/mL)	481.01 ± 171.17	621.73 ± 232.14
AUC_{last} (ng·h/mL)	398.96 ± 141.37	541.18 ± 219.22
k_{el} (1/h)	0.090 ± 0.034	0.098 ± 0.030
$t_{1/2}$ (h)	8.9 ± 4.0	7.7 ± 2.4
CL/F (L/h)	118.83 ± 49.11	98.65 ± 61.28
MRT_{inf} (h)	16.7 ± 4.6	14.9 ± 3.7

Plasma Concentration of Quetiapine Metabolites

Figure 3, Figure 4, Figure 5, Figure 6 depict the mean plasma concentration-time profile of quetiapine metabolites M1, M2, M4, and M5, respectively, after administration of FK949E alone and after co-administration of fluvoxamine and FK949E. Table 5, Table 6, Table 7, Table 8 present pharmacokinetic parameter of plasma M1, M2, M4, and M5, respectively. The C_{max} (mean ± SD, the same applies hereinafter) of each metabolite after administration of FK949E alone and after co-administration of fluvoxamine and FK949E was 1.30 ± 0.35 ng/mL and 1.35 ± 0.39 ng/mL for M1, 2.10 ± 1.03 ng/mL and 1.95 ± 0.98 ng/mL for M2, 45.02 ± 21.76 ng/mL and 47.72 ± 17.98 ng/mL for M4, and 4.64 ± 1.47 ng/mL and 5.02 ± 1.71 ng/mL for M5, respectively. The AUC_{last} (mean ± SD, the same applies hereinafter) of each metabolite after administration of FK949E alone and after co-administration was 14.00 ± 4.44 ng•h/mL and 16.84 ± 6.52 ng•h/mL for M1, 23.82 ± 11.89 ng•h/mL and 22.71 ± 13.31 ng•h/mL for M2, 564.46 ± 142.70 ng•h/mL and 597.23 ± 169.08 ng•h/mL for M4, and 96.69 ± 22.42 ng•h/mL and 104.47 ± 32.14 ng•h/mL for M5, respectively. The pattern of the mean plasma concentration-time profile of quetiapine metabolites did not differ with and without concomitant fluvoxamine.

Regarding $t_{1/2}$, the concentrations of M1 and M2 were below the limit of quantification at many blood sampling points during the elimination phase, making it difficult to correctly assess the $t_{1/2}$. The $t_{1/2}$ values of M4 and M5 did not differ markedly after administration of FK949E alone and after co-administration of fluvoxamine and FK949E.

Figure 3 **Mean Plasma M1 Concentration**

Period 1: Administration of FK949E alone

Period 2: Co-administration of fluvoxamine and FK949E

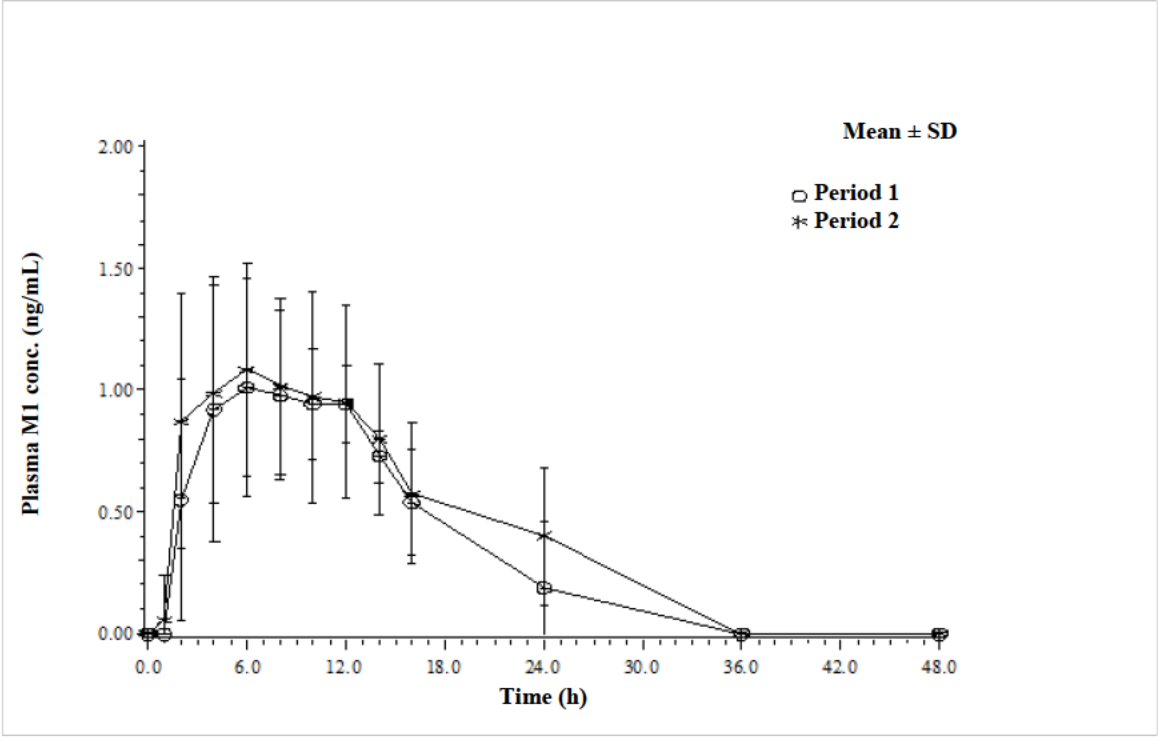

Table 5 **Pharmacokinetic Parameters of the Plasma M1 Concentration (Mean ± SD)**

Pharmacokinetic parameter	Day 1 of Period 1 Administration of FK949E alone N=23 †	Day 8 of Period 2 Co-administration of fluvoxamine and FK949E N=22 †
C_{max} (ng/mL)	1.30 ± 0.35	1.35 ± 0.39
t_{max} (h)	7.5 ± 3.3	7.1 ± 3.8
AUC_{inf} (ng·h/mL)	27.43 ± 11.71	34.03 ± 7.37
AUC_{last} (ng·h/mL)	14.00 ± 4.44	16.84 ± 6.52
k_{el} (1/h)	0.079 ± 0.049	0.048 ± 0.019
$t_{1/2}$ (h)	14.4 ± 12.8	17.0 ± 7.0
MRT_{inf} (h)	24.3 ± 16.7	27.2 ± 9.7

† N=17 for AUC_{inf}, k_{el}, $t_{1/2}$, MRT_{inf}

Figure 4 **Mean Plasma M2 Concentrations**

Period 1: Administration of FK949E alone

Period 2: Co-administration of fluvoxamine and FK949E

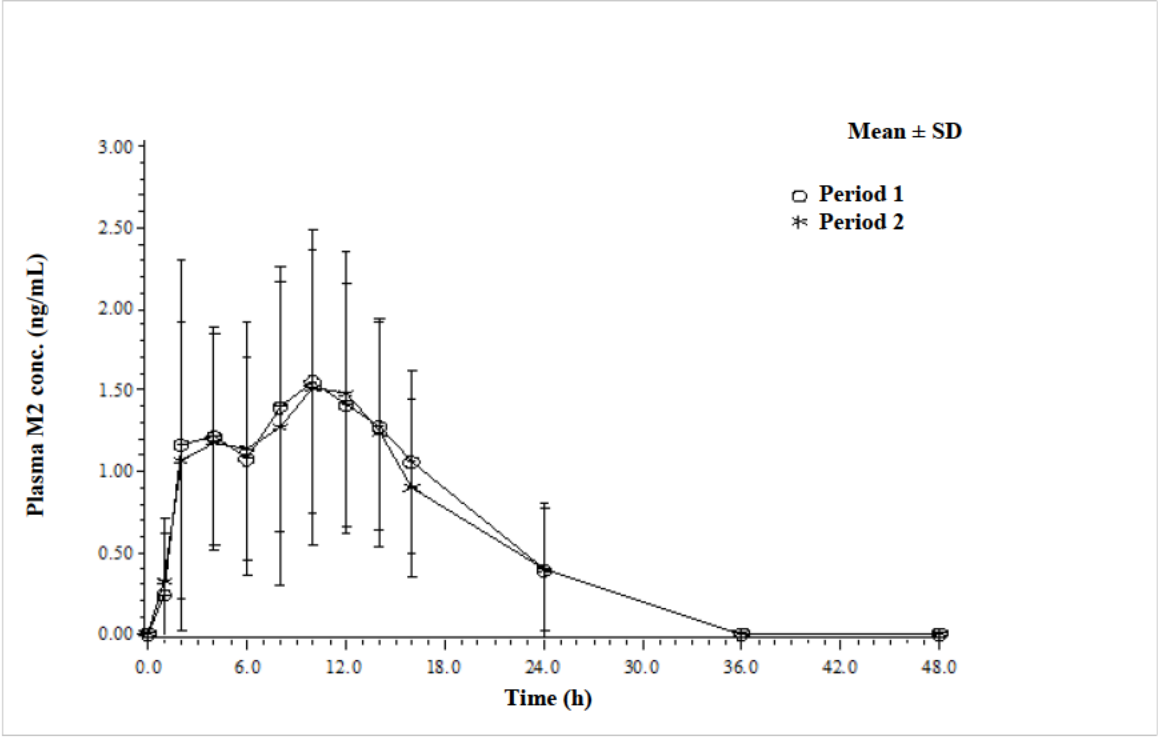

Table 6 **Pharmacokinetic Parameters of the Plasma M2 Concentration (Mean ± SD)**

Pharmacokinetic parameter	Day 1 of Period 1 Administration of FK949E alone N=23 †	Day 8 of Period 2 Co-administration of fluvoxamine and FK949E N=22 ††
C_{max} (ng/mL)	2.10 ± 1.03	1.95 ± 0.98
t_{max} (h)	7.5 ± 4.0	7.6 ± 4.3
AUC_{inf} (ng·h/mL)	33.47 ± 12.76	34.30 ± 13.76
AUC_{last} (ng·h/mL)	23.82 ± 11.89	22.71 ± 13.31
k_{el} (1/h)	0.091 ± 0.035	0.089 ± 0.039
$t_{1/2}$ (h)	9.1 ± 4.5	10.5 ± 7.4
MRT_{inf} (h)	17.7 ± 6.4	19.3 ± 10.5

† N=20 for AUC_{inf}, k_{el}, $t_{1/2}$, and MRT_{inf}
†† N=21 for t_{max}; N=19 for AUC_{inf}, k_{el}, $t_{1/2}$, and MRT_{inf}

Figure 5 **Mean Plasma M4 Concentration**

Period 1: Administration of FK949E alone

Period 2: Co-administration of fluvoxamine and FK949E

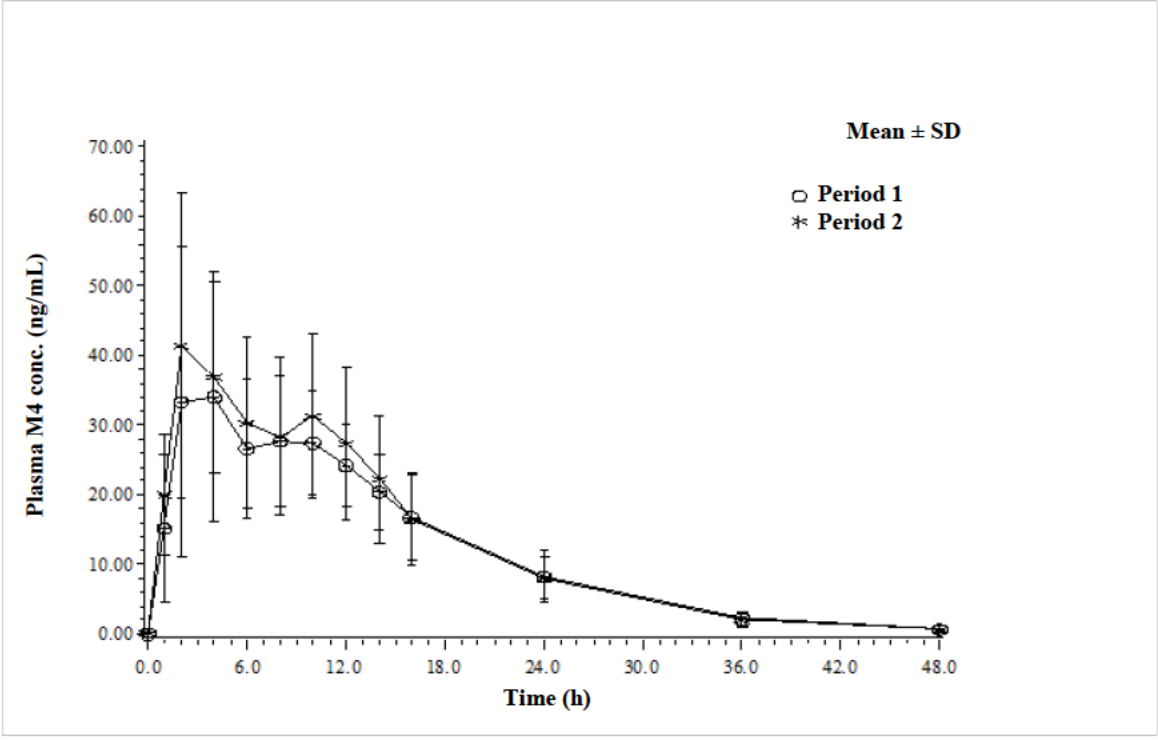

Table 7 **Pharmacokinetic Parameters of the Plasma M4 Concentration (Mean ± SD)**

Pharmacokinetic parameter	Day 1 of Period 1 Administration of FK949E alone N=23	Day 8 of Period 2 Co-administration of fluvoxamine and FK949E N=22
C_{max} (ng/mL)	45.02 ± 21.76	47.72 ± 17.98
t_{max} (h)	6.1 ± 3.5	6.0 ± 4.2
AUC_{inf} (ng·h/mL)	574.77 ± 142.29	608.91 ± 167.80
AUC_{last} (ng·h/mL)	564.46 ± 142.70	597.23 ± 169.08
k_{el} (1/h)	0.108 ± 0.023	0.106 ± 0.022
$t_{1/2}$ (h)	6.7 ± 1.4	6.9 ± 1.6
MRT_{inf} (h)	13.3 ± 1.9	12.6 ± 2.5

Figure 6 **Mean Plasma M5 Concentration**

Period 1: Administration of FK949E alone

Period 2: Co-administration of fluvoxamine and FK949E

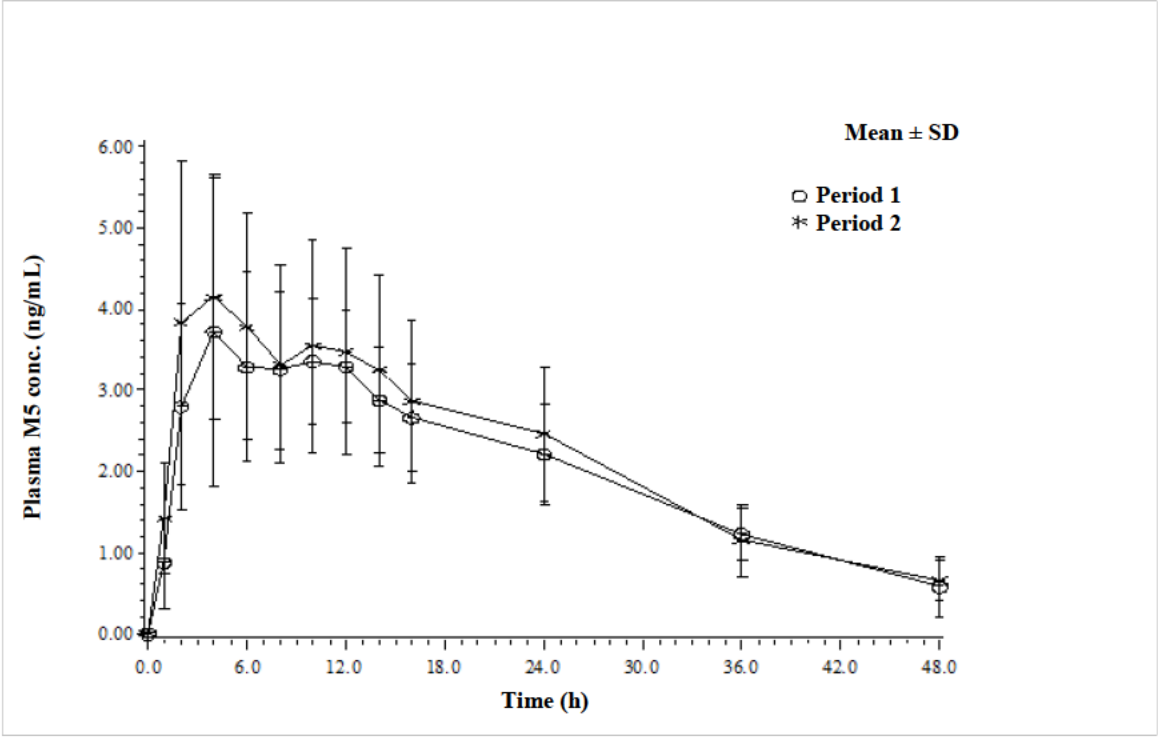

Table 8 **Pharmacokinetic Parameters of the Plasma M5 Concentration (Mean ± SD)**

Pharmacokinetic parameter	Day 1 of Period 1 Administration of FK949E alone N=23	Day 8 of Period 2 Co-administration of fluvoxamine and FK949E N=22
C_{max} (ng/mL)	4.64 ± 1.47	5.02 ± 1.71
t_{max} (h)	7.3 ± 3.6	6.3 ± 4.0
AUC_{inf} (ng·h/mL)	114.65 ± 22.81	120.41 ± 29.82
AUC_{last} (ng·h/mL)	96.69 ± 22.42	104.47 ± 32.14
k_{el} (1/h)	0.046 ± 0.008	0.050 ± 0.010
$t_{1/2}$ (h)	15.5 ± 3.1	15.2 ± 7.9
MRT_{inf} (h)	26.1 ± 3.3	25.6 ± 9.3

Plasma Fluvoxamine Concentration

Figure 7 depicts the mean plasma fluvoxamine concentration-time profile after co-administration of fluvoxamine and FK949E (on Day 8 of Period 2). Table 9 shows the pharmacokinetic parameters of plasma fluvoxamine after co-administration. For fluvoxamine, the C_{max} (mean ± SD, the same applies hereinafter) was 38.34 ± 19.81 ng/mL, the AUC_{last} was 377.22 ± 220.31 ng•h/mL, the t_{max} was 3.4 ± 1.3 h, and the $t_{1/2}$ was 13.2 ± 5.5 h.

Figure 7 Mean Plasma Fluvoxamine Concentration (Day 8 of Period 2)

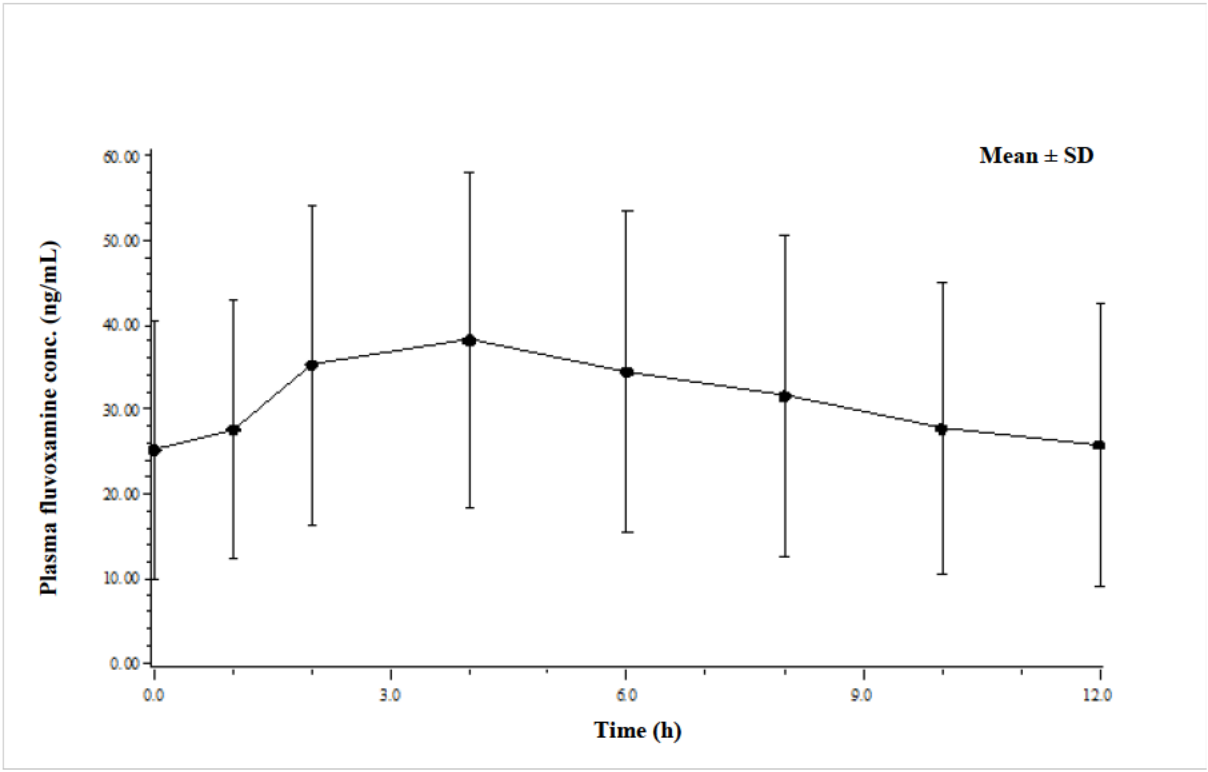

Table 9 Pharmacokinetic Parameters of the Plasma Fluvoxamine Concentration (Mean ± SD)

Pharmacokinetic parameter	Day 8 of Period 2 Co-administration of fluvoxamine and FK949E N=22 †
C_{max} (ng/mL)	38.34 ± 19.81
t_{max} (h)	3.4 ± 1.3
AUC_{last} (ng·h/mL)	377.22 ± 220.31
$t_{1/2}$ (h)	13.2 ± 5.5

† N=21 for $t_{1/2}$

Effect of Co-administration of Fluvoxamine on the Pharmacokinetics of Quetiapine and Its Metabolites

Table 10 shows the geometric mean ratios and their 90% CIs for the C_{max} and AUC_{last} of quetiapine after co-administration of fluvoxamine and FK949E versus those after administration of FK949E alone. The geometric

mean ratio was 1.324 for C_{max} and 1.341 for AUC_{last}. These ratios indicate the effect of co-administration of fluvoxamine on the pharmacokinetics of quetiapine, as represented by a 30% to 35% increase in C_{max} and AUC_{last} after co-administration compared with the values after administration of FK949E alone.

Table 10 Assessment of the Effect of Co-administration of Fluvoxamine on the Pharmacokinetics of Quetiapine

Parameter	Comparison†	Geometric mean ratio	Lower 90% CI	Upper 90% CI
C_{max}	Co-administration/FK949E alone	1.324	1.154	1.519
AUC_{last}	Co-administration/FK949E alone	1.341	1.174	1.532

† Co-administration: Co-administration of fluvoxamine and FK949E, FK949E alone: Administration of FK949E alone

Table 11 shows the geometric mean ratios and their 90% CIs for the C_{max} and AUC_{last} of quetiapine metabolites M1, M2, M4, and M5 after co-administration of fluvoxamine and FK949E versus those after administration of FK949E alone. The 90% CIs were within a range of 0.8 to 1.25 for C_{max} and AUC_{last} of all the metabolites, except for the AUC_{last} of M1 and the C_{max} of M4 of which the upper limit of the 90% CI exceeded 1.25, showing no major changes with co-administration of fluvoxamine and FK949E.

Table 11 Assessment of the Effect of Co-administration of Fluvoxamine on the Pharmacokinetics of Quetiapine Metabolites

Metabolite	Parameter	Comparison†	Geometric mean ratio††	Lower 90% CI	Upper 90% CI
M1	C_{max}	Co-administration/FK949E alone	1.024	0.910	1.152
	AUC_{last}	Co-administration/FK949E alone	1.151	0.924	1.433
M2	C_{max}	Co-administration/FK949E alone	0.923	0.830	1.026
	AUC_{last}	Co-administration/FK949E alone	0.899	0.820	0.986
M4	C_{max}	Co-administration/FK949E alone	1.095	0.930	1.289
	AUC_{last}	Co-administration/FK949E alone	1.061	0.952	1.182
M5	C_{max}	Co-administration/FK949E alone	1.072	0.935	1.230
	AUC_{last}	Co-administration/FK949E alone	1.060	0.918	1.224

† Co-administration: Co-administration of fluvoxamine and FK949E, FK949E alone: Administration of FK949E alone
†† N=22 for M1, M4 and M5; N=21 for M2

5. Safety:

Adverse Events

Table 12 shows a summary of the adverse events. Adverse events were evaluated in 24 subjects in Period 1 (administration of FK949E alone). Since one subject was withdrawn from the study during Period 1, adverse events were evaluated in 23 subjects in Period 2 (administration of fluvoxamine alone and co-administration of fluvoxamine and FK949E). In the entire study, adverse events occurred in all 24 subjects. FK949E-related adverse events were reported in all 24 subjects, and fluvoxamine-related adverse events were reported in all 23 subjects evaluated in Period 2.

For administration of FK949E alone in Period 1, both adverse events and FK949E-related adverse events occurred in 13 subjects (54.2%) each. For administration of fluvoxamine alone in Period 2, both adverse events and fluvoxamine-related adverse events occurred in 4 subjects (17.4%) each. For co-administration of fluvoxamine and FK949E in Period 2, adverse events occurred in all 23 subjects, and both FK949E-related adverse events and fluvoxamine-related adverse events were also reported in all 23 subjects.

No deaths occurred in the study. Two serious adverse events (blood creatine phosphokinase increased and syncope) were reported in 2 subjects, and both events resulted in discontinuation of the study.

Table 12 Summary of Adverse Events

	All subjects N=24 †		Period 1 Administration of FK949E alone N=24		Period 2 Administration of fluvoxamine alone N=23		Period 2 Co-administration of fluvoxamine and FK949E N=23	
	Number of subjects with an AE††	Number of AEs	Number of subjects with an AE††	Number of AEs	Number of subjects with an AE††	Number of AEs	Number of subjects with an AE††	Number of AEs
Adverse event	24 (100.0%)	49	13 (54.2%)	13	4 (17.4%)	6	23 (100.0%)	30
FK949E-related adverse events	24 (100.0%)	42	13 (54.2%)	13	0	0	23 (100.0%)	29
Fluvoxamine-related adverse events	23 (100.0%)	35	–	–	4 (17.4%)	6	23 (100.0%)	29
Death	0	0	0	0	0	0	0	0
Serious adverse events	2 (8.3%)	2	1 (4.2%)	1	0	0	1 (4.3%)	1
Adverse events resulting in discontinuation	2 (8.3%)	2	1 (4.2%)	1	0	0	1 (4.3%)	1

† N=23 for fluvoxamine-related adverse events.
†† Number of subjects (incidence)

Table 13 shows the incidence of adverse events. The incidences of FK949E-related and fluvoxamine-related adverse events are shown in Table 14 and Table 15, respectively.

In the entire study, the most common adverse event was somnolence, which occurred in 23 (95.8%) of 24 subjects. Other common adverse events reported in at least 5% of all subjects were feeling abnormal (12.5%) and alanine aminotransferase increased (8.3%). For administration of FK949E alone in Period 1, somnolence

(incidence, 50.0%) was the only adverse event reported in at least 5% of subjects. For administration of fluvoxamine alone in Period 2, adverse events reported in at least 5% of subjects were alanine aminotransferase increased (8.7%) and somnolence (8.7%). For co-administration of fluvoxamine and FK949E in Period 2, adverse events reported in at least 5% of subjects were somnolence (100.0%) and feeling abnormal (13.0%). The pattern of occurrence of FK949E-related and fluvoxamine-related adverse events was basically the same as the above.

The only adverse event classified as severe was syncope, which had occurred after co-administration of fluvoxamine and FK949E in Period 2. It was assessed as a serious adverse event and resulted in discontinuation of the study. All the other adverse events were mild in severity. The severe adverse event (syncope) was assessed as "probably related" to both FK949E and fluvoxamine.

Table 13 Incidence of Adverse Events

System Organ Class/Preferred Term†	All subjects N=24	Period 1 Administration of FK949E alone N=24	Period 2 Administration of fluvoxamine alone N=23	Period 2 Co-administration of fluvoxamine and FK949E N=23
Gastrointestinal disorders	**1 (4.2%)**	**0 (0.0%)**	**1 (4.3%)**	**0 (0.0%)**
Oropharyngeal pain	1 (4.2%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
General disorders and administration site conditions	**4 (16.7%)**	**0 (0.0%)**	**0 (0.0%)**	**4 (17.4%)**
Feeling abnormal	3 (12.5%)	0 (0.0%)	0 (0.0%)	3 (13.0%)
Gait disturbance	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Investigations	**4 (16.7%)**	**1 (4.2%)**	**2 (8.7%)**	**1 (4.3%)**
Alanine aminotransferase increased	2 (8.3%)	0 (0.0%)	2 (8.7%)	0 (0.0%)
Aspartate aminotransferase increased	1 (4.2%)	0 (0.0%)	1 (4.3%)	0 (0.0%)
Blood creatine phosphokinase increased	1 (4.2%)	1 (4.2%)	0 (0.0%)	0 (0.0%)
Blood uric acid increased	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Nervous system disorders	**23 (95.8%)**	**12 (50.0%)**	**2 (8.7%)**	**23 (100.0%)**
Somnolence	23 (95.8%)	12 (50.0%)	2 (8.7%)	23 (100.0%)
Syncope	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.3%)

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

Table 14 Incidence of FK949E-Related Adverse Events

System Organ Class/Preferred Term†	All subjects N=24	Period 1 Administration of FK949E alone N=24	Period 2 Co-administration of fluvoxamine and FK949E N=23
General disorders and administration site conditions	**4 (16.7%)**	**0 (0.0%)**	**4 (17.4%)**
Feeling abnormal	3 (12.5%)	0 (0.0%)	3 (13.0%)
Gait disturbance	1 (4.2%)	0 (0.0%)	1 (4.3%)
Investigations	**1 (4.2%)**	**1 (4.2%)**	**0 (0.0%)**
Blood creatine phosphokinase increased	1 (4.2%)	1 (4.2%)	0 (0.0%)
Nervous system disorders	**23 (95.8%)**	**12 (50.0%)**	**23 (100.0%)**
Somnolence	23 (95.8%)	12 (50.0%)	23 (100.0%)
Syncope	1 (4.2%)	0 (0.0%)	1 (4.3%)

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

Table 15 Incidence of Fluvoxamine-Related Adverse Events

System Organ Class/Preferred Term†	All subjects N=23	Period 2 Administration of fluvoxamine alone N=23	Period 2 Co-administration of fluvoxamine and FK949E N=23
Gastrointestinal disorders	**1 (4.3%)**	**1 (4.3%)**	**0 (0.0%)**
Oropharyngeal pain	1 (4.3%)	1 (4.3%)	0 (0.0%)
General disorders and administration site conditions	**4 (17.4%)**	**0 (0.0%)**	**4 (17.4%)**
Feeling abnormal	3 (13.0%)	0 (0.0%)	3 (13.0%)
Gait disturbance	1 (4.3%)	0 (0.0%)	1 (4.3%)
Investigations	**2 (8.7%)**	**2 (8.7%)**	**0 (0.0%)**
Alanine aminotransferase increased	2 (8.7%)	2 (8.7%)	0 (0.0%)
Aspartate aminotransferase increased	1 (4.3%)	1 (4.3%)	0 (0.0%)
Nervous system disorders	**23 (100.0%)**	**2 (8.7%)**	**23 (100.0%)**
Somnolence	23 (100.0%)	2 (8.7%)	23 (100.0%)
Syncope	1 (4.3%)	0 (0.0%)	1 (4.3%)

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

Deaths and Other Serious Adverse Events

No deaths occurred during the study. Table 16 presents the serious adverse events reported during the study period. Two serious adverse events were reported. One event (blood creatine phosphokinase increased) occurred after administration of FK949E alone in Period 1, and the other event (syncope) occurred after co-administration of fluvoxamine and FK949E in Period 2. Both events recovered.

[redacted]

[redacted]

Table 16 List of Serious Adverse Events

Subject No.	Sex Age (yrs)	Date and time of administration on Day 1 of Period 1 Date and time of administration on Day 1 of Period 2 Date and time of administration on Day 8 of Period 2	Adverse event†	Onset	Offset	Severity	Seriousness	Relationship to FK949E	Relationship to fluvoxamine	Action taken for study drug	Other treatment required	Outcome
[redacted]	[redacted]	[redacted] – –	Blood creatine phosphokinase increased	[redacted]	–††	Mild	Requires or prolongs hospitalization	Possible	Not related	Discontinuation	None	Not recovered ††
[redacted]	[redacted]	[redacted]	Syncope	[redacted]	[redacted]	Severe	Requires or prolongs hospitalization	Probable	Probable	Discontinuation	None	Recovered

† MedDRA/J ver.12.0
†† Normalization of creatine phosphokinase level was confirmed on [redacted], after discontinuation of the study.

Adverse Events Resulting in Discontinuation

Two serious adverse events resulted in discontinuation of the study. These events are detailed in "Serious Adverse Events Other Than Death."

Clinical Laboratory Evaluations

Among the hematology and blood biochemistry parameters, mean values deviating from the reference range after the start of study drug administration were observed for total protein (decreased) and creatine phosphokinase (decreased). Urinalysis revealed normal results at all measurement time points.

Laboratory-related adverse events reported in the present study were alanine aminotransferase increased in 2 subjects (8.3%), aspartate aminotransferase increased in 1 subject (4.2%), blood creatine phosphokinase increased in 1 subject (4.2%), and blood uric acid increased in 1 subject (4.2%). All the laboratory-related adverse events were mild in severity, but the blood creatine phosphokinase increased was assessed as a serious adverse event.

Vital Signs

No noteworthy changes were found in axillary body temperature, supine blood pressure, or supine pulse rate. In the present study, these vital signs were taken on the morning of each day of measurement (before study drug administration).

Electrocardiograms

All ECG findings were normal.

Conclusions:

To assess the effect of multiple-dose fluvoxamine on the pharmacokinetics of quetiapine, FK949E was administered as a single dose of 50 mg followed by 2-day washout in 24 non-elderly, healthy adult male subjects. FK949E was again administered as a single dose of 50 mg dose in combination with multiple-dose fluvoxamine (100 mg/day).

The geometric mean ratios of C_{max} and AUC_{last} of quetiapine after co-administration of fluvoxamine and FK949E versus those after administration of FK949E alone were 1.324 and 1.341, respectively. These ratios indicate the effect of co-administration of fluvoxamine on the pharmacokinetics of quetiapine, as represented by a 30% to 35% increase in C_{max} and AUC_{last} after co-administration compared with the values after administration of FK949E alone.

As for safety, adverse events occurred in all 24 subjects in the entire study. The incidence of adverse events was 54.2% for administration of FK949E alone, 17.4% for administration of fluvoxamine alone, and 100.0% for co-administration of fluvoxamine and FK949E. In the entire study, the most common adverse event was somnolence, which occurred in 23 (95.8%) of 24 subjects. Other common adverse events reported in at least 5% of all subjects were feeling abnormal (12.5%) and alanine aminotransferase increased (8.3%). Two serious adverse events (blood creatine phosphokinase increased and syncope) were reported, and both events were recovered. These adverse events have already been reported in previous Japanese phase I studies or overseas clinical studies of FK949E, or with the use of the existing quetiapine products.

Date of Document: 8 June 2012