SYNOPSIS

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: FK949E (quetiapine fumarate)		

Title of Study:
Phase I Study of FK949E - Multiple Dose Study of Non-Elderly Adult Patients with Major Depressive Disorder (MDD) -

Responsible Officer or Designee: [redacted] Astellas Pharma Inc.

Investigators: [redacted] and others

Study Sites: [redacted], and two other sites.

Publication: Unpublished

Study Period: 0 years and 10 months (duration from the starting day of the study to the day of study completion) Study Initiation Date: 21 May 2009 (the day when the first subject signed the written informed consent) Study Completion Date: 23 March 2010 [the day when the last subject was evaluated (the day of protocol-specified final assessments)]	**Phase of Development:** Phase 1 study

Study Objectives:
The objective of the study was to evaluate the safety and PK of multiple oral doses of FK949E (extended-release formulation of quetiapine) of 300 mg/day and 600 mg/day in patients with major depressive disorder (MDD).

Study Design and Methodology:
Multicenter, open-label design

Planned Sample Size: 300 mg treatment group: 8 subjects
600 mg treatment group: 8 subjects

[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.

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Diagnosis and Inclusion/Exclusion Criteria:

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.

1. Inclusion criteria

1. Provision of written informed consent.
2. Aged 20 to 64 years, inclusive, at the time of providing written informed consent
3. Diagnosis of major depressive disorder according to the DSM-IV-TR*

   * For patients not on antidepressant medication: diagnosis of major depressive disorder within 6 months prior to provision of written informed consent.
   For patients on antidepressant medication: use of antidepressant medication at the time of providing written informed consent.
4. Female patients of childbearing potential with a negative serum pregnancy test result and who were willing and able to use a reliable method of birth control during the study.
5. Patients who could understand and comply with the requirements of the study, as judged by the investigator/sub-investigator.

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. Diagnosis of a DSM-IV-TR Axis II disorder that was considered to have 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 prior to the start of study drug administration and 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, and ethotoin.

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5. Pregnant or lactating women
6. 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).
7. A clinical finding that in the opinion of the investigator/sub-investigator could be negatively affected by the study or that would affect the study results (e.g., hypertension, unstable angina).
8. Conditions that could affect absorption and metabolism of the study medication (e.g., malabsorption syndrome, liver disease).
9. A current diagnosis of malignant tumor unless in remission for at least 5 years (except basal or squamous cell skin carcinoma).
10. A current or past diagnosis of transient ischemic attack (TIA).
11. A history of seizure disorder, except for febrile convulsions.
12. Application of electroconvulsive therapy within 90 days prior to the start of 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 the start of study drug administration and throughout the study period.
14. Patients could require psychotherapy (other than supportive psychotherapy) during the study period, unless psychotherapy had been ongoing for a minimum of 90 days prior to the start of study drug administration.
15. A score of ≥ 3 on the HAM-D_{17} Item (suicide) or a suicide attempt within the past 6 months, and those 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

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Reactions to Pharmaceutical Products" (Pharmaceutical Affairs Bureau Safety Division's Notification No. 80 issued on 29 June 1992)).

18. A white blood cell count (WBC) of $\leq 3{,}000/mm^3$ at screening assessment.
19. A thyroid stimulating hormone (TSH) concentration of > 10% above the upper limit of the normal range at screening assessment, regardless of whether 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's Notification No. 80 issued on 29 June 1992)).
21. Treatment with epinephrine at the time of providing written informed consent.
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 (mania) 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 (applies to both Astellas staff and staff at the study site).
26. Previous randomization in a clinical study of quetiapine.
27. Participation in another clinical study or post-marketing study within 12 weeks prior to the start of study drug administration.
28. Patients who were judged to be inappropriate as subjects of this study by the investigator/sub-investigator.

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Test Drug, Dose, and Mode of Administration

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.	[redacted] (Manufacturer: AstraZeneca)

2. Dosage and mode of administration

[Dose]

1. 300 mg treatment group: 300 mg/day on Day 5 and subsequent days.
2. 600 mg treatment group: 600 mg/day on Day 7 and subsequent days.

[Dose regimen and administration period]

A prescribed number of tablets was taken orally once daily after breakfast (within 10 minutes after completion of breakfast).

1. 300 mg treatment group: Started with an initial dose of 50 mg on the first day of administration, increased to 150 mg on Day 3, and to 300 mg on Day 5.
2. 600 mg treatment group: Started with an initial dose of 50 mg on the first day of administration, increased to 150 mg on Day 3, to 300 mg on Day 5, and to 600 mg on Day 7.

Number of tablets administered

Treatment group	Study drug	Hospitalization (or ambulatory treatment)												
		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
300 mg	50 mg tablet	1	1											
	150 mg tablet			1	1	2	2	2	2	2	2	2		
600 mg	50 mg tablet	1	1											
	150 mg tablet			1	1	2	2	4	4	4	4	4	4	4

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

Based on the results of the overseas clinical studies, a dose-escalation method was used in the present study to confirm the safety.

In six of the eight overseas clinical studies of quetiapine XR in patients with major depressive disorder, improvement of depressive symptoms was demonstrated by administering 50 mg to 300 mg of quetiapine XR once daily, indicating the usefulness of quetiapine XR for the treatment of major depressive disorder. In addition, in two studies using quetiapine XR concomitantly for subjects showing an insufficient response to antidepressant agents (Study No. D1448C00006 and D1448C00007), an improvement in depressive symptoms was demonstrated by administering 150 mg and 300 mg quetiapine XR once daily, which indicated the usefulness of quetiapine XR also in combination therapy with other antidepressants. Based on these results, the study in Japanese subjects was first conducted in the 300 mg treatment group to confirm that there were no clinically critical findings nor any increase in the incidence or in the severity of adverse events associated with the dose increase during the escalation period. In addition, taking into consideration the differences between individuals, the safety and tolerability of FK949E at a dose of up to 600 mg was investigated. A study of quetiapine up to a dose of 600 mg was conducted also because quetiapine is likely to be used in combination with other antidepressant drugs that inhibit the enzyme CYP3A4, resulting in an increased effect of quetiapine.

No placebo treatment group was included in the present study: a placebo-controlled study was considered not necessary because the safety of quetiapine had been sufficiently studied in healthy adults and patients with depression in overseas studies, and because in Japan, it is difficult to find subjects to participate in a phase 1 study from among patients with depression that requires hospitalization for a long period of time (2 to 3 weeks) and involves administration of placebo.

The dose escalation schedule was established based on the results of overseas clinical studies (Study No. D1448C00001 to D1448C00007). The overseas studies (Study No. D1448C00001 to D1448C00007) employed a dose-escalation schedule in which the target dose, once it was reached, was maintained as a fixed dose or was further increased during the study, while the method of escalation was the same in all studies, i.e., the dose was increased every 2 days to reach 300 mg on Day 5. Since no major differences in the incidence of adverse events were observed between the studies using different regimens, a dose escalation schedule to increase the dose every 2 days was used in the present study.

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Investigational Period:

Pre-investigational period: No more than 28 days

Administration period: 300 mg treatment group: 11 days, 600 mg treatment group: 13 days.

Observation period after administration: 7 days

Concomitant Medications and Therapies:

[Concomitant drugs and therapies permitted with restrictions]

1. Antidepressant

   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, sertraline, milnacipran

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, rilmazafone hydrochloride, lormetazepam

3. Anticholinergics

   Anticholinergics could be used for the treatment of emergent extrapyramidal symptoms (only one of the following anticholinergics was permitted: trihexyphenidyl hydrochloride, profenamine, biperiden, metixene hydrochloride, piroheptine hydrochloride, and 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.

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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 not necessary (e.g., occurrence of adverse events, recovery of symptoms, etc.).

[Prohibited concomitant drugs and therapies]

For the drugs and therapies prohibited for concomitant use, except for those permitted with restrictions, the following drug washout periods prior to the start of study drug administration were to be observed.

1) Mood stabilizer: More than 5 times the $t_{1/2}$
2) Antipsychotics: More than 5 times the $t_{1/2}$
3) Anticholinergic agents: More than 5 times the $t_{1/2}$
4) Anxiolytics, antidepressants, and hypnotics: More than 5 times the $t_{1/2}$
5) Psychostimulants: More than 5 times the $t_{1/2}$
6) P450 (CYP3A4) inhibitors and inducers: 14 days
7) MAO inhibitors: 14 days
8) Depot antipsychotic injection: Twice the dosing interval
9) Electroconvulsive therapy: 90 days

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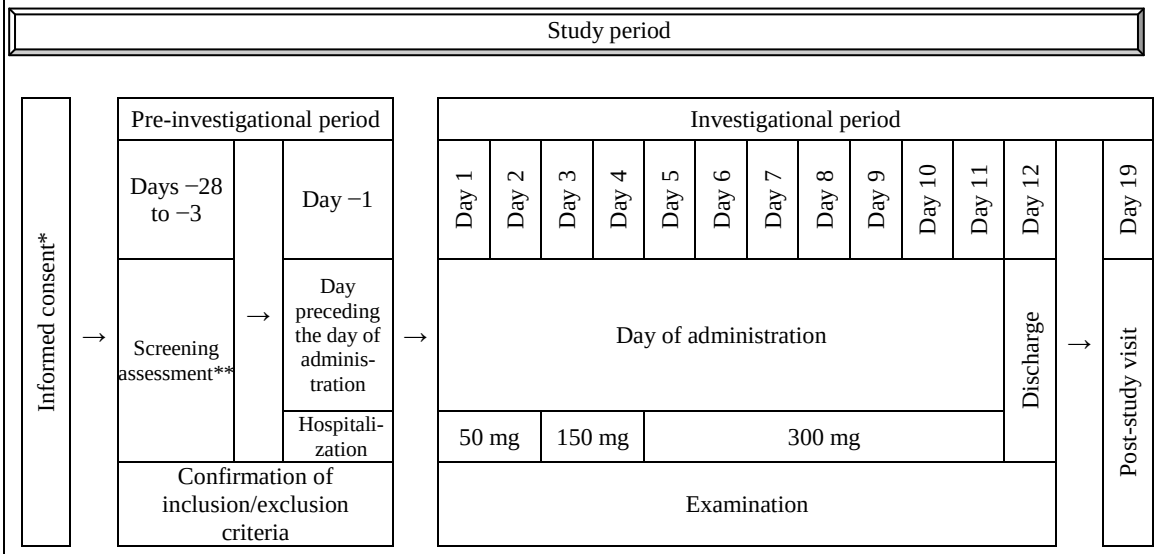
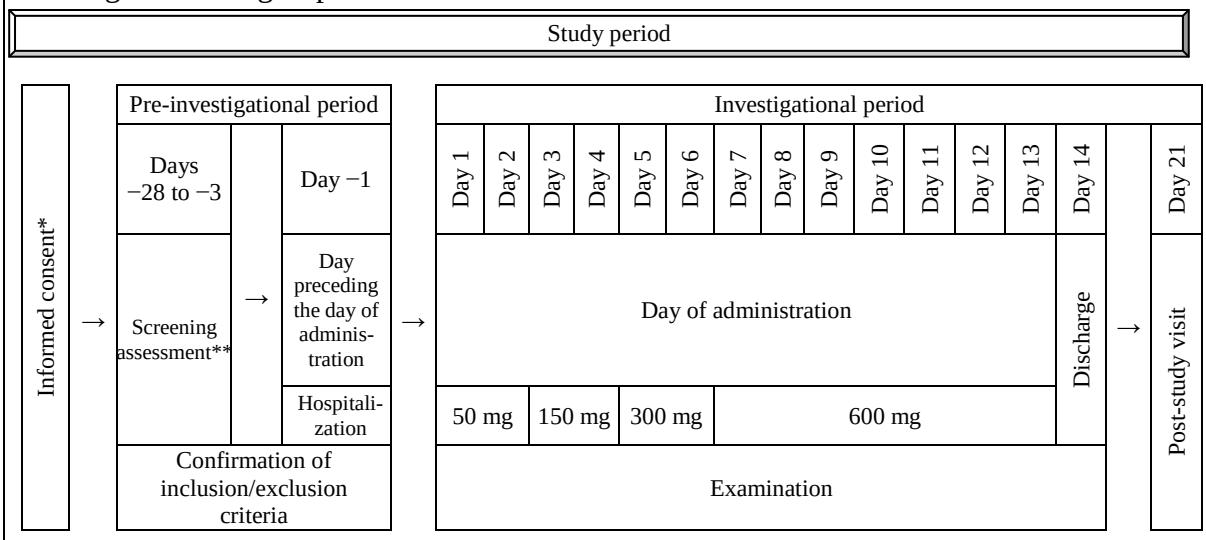
Schedule of Procedures:
Evaluation schedule

300 mg treatment group:



600 mg treatment group:



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.

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* 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}, k_{el}, $t_{1/2}$, CL/F, MRT_{inf}, C_{trough})

2. Safety:

- Adverse events
- Vital signs (axillary body temperature, supine blood pressure, standing blood pressure, supine pulse rate, standing pulse rate)
- 12-lead ECGs
- Laboratory assessments (hematology tests, blood biochemistry tests (including endocrine test), 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 (SAF): The safety analysis set included all subjects who received the study drug.

Pharmacokinetic Analysis Set (PKAS):

The pharmacokinetic analysis set included all subjects who received the study drug and who had values of plasma unchanged FK949E concentration (blood samples were 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.

- Summary 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}, k_{el}, $t_{1/2}$, CL/F, 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 was used for the calculation of the pharmacokinetic parameters.

For the calculated pharmacokinetic parameters, the descriptive statistics were calculated by 300 mg treatment group and 600 mg treatment group.

4. Safety:

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

1. Vital signs (axillary body temperature, blood pressure, 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.
   - 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.
2. Laboratory assessments (hematology, blood biochemistry, 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

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of measurement was created.

3. 12-lead 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

   • The number and percentage of subjects with AEs and AEs considered to be drug related were summarized.

   • The number and percentage of subjects with AEs and AEs considered to be drug related, as classified by MedDRA System Organ Class (SOC) and Preferred Term (PT), were summarized.

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Results:

1. Disposition of subjects and analysis set:

Disposition of subjects in the present study is shown in Figure 1. Written informed consent was obtained from a total of 23 subjects, 13 in the 300 mg treatment group and 10 in the 600 mg treatment group, and these subjects were enrolled. Of the 13 subjects in the 300 mg treatment group who provided informed consent, 4 subjects were screening failures so that 9 subjects in this group received study drug. After the 300 mg treatment group was completed, the sponsor's responsible person, in consultation with the medical consultant and in consideration of the safety data obtained, made the decision that the study proceed with the 600 mg treatment group. In the 600 mg treatment group, 2 of the 10 subjects who provided informed consent were screening failures, so that 8 subjects received study drug. The reasons for the six screening failures were: "Not fulfill inclusion /exclusion criteria" in 2 subjects, "Untoward medical occurrences" in 1 subject, and "Others (worsening of the underlying disease)" in 3 subjects. All 9 subjects in the 300 mg treatment group completed the study treatment, whereas 1 subject in the 600 mg treatment group had to discontinue the study because the dose increase (from 50 mg to 150 mg) was judged to be inappropriate. This subject had insomnia as a symptom of the underlying disease that might have become worse if the study had continued; therefore, in overall consideration of the subject's safety, the dose increase was judged to be inappropriate.

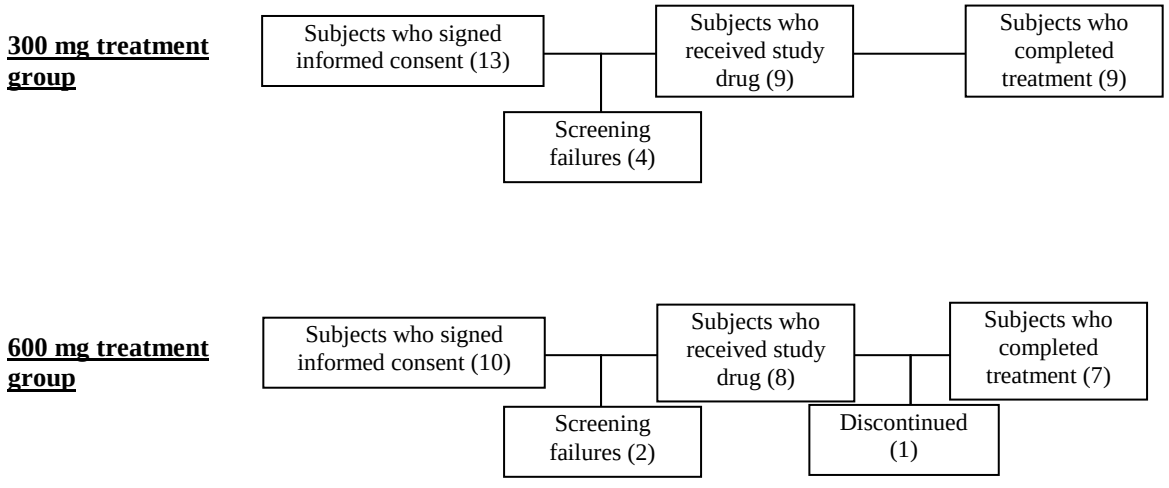

Figure 1: Disposition of Subjects

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The analysis set is presented in Table 1. All 9 subjects in the 300 mg treatment group who received study drug were included in the SAF and PKAS. In the 600 mg treatment group, 5 of the 8 subjects who received study drug were excluded from analyses due to GCP violation so the remaining 3 subjects were included in the SAF and PKAF. The deviations that were judged to be GCP violations in these 5 excluded subjects are described below in detail:

Adverse events (orthostatic hypotension) occurred in 5 of the 8 subjects on Day 5 of study drug administration, on which the dose increase to 300 mg was scheduled. These subjects received administration of a vasopressor (Metligine) for treatment of the adverse events, also in consideration of the dose increase up to 600 mg. In addition, 3 of the 5 subjects who had orthostatic hypotension were kept on vasopressor therapy when receiving the dose increase from 300 to 600 mg of the study drug in the continued study. For these 5 subjects, the vasopressor was administered not only for the treatment of the adverse event but also as a prophylaxis to prevent possible worsening of the adverse event, which was considered a deviation from the protocol. Because a safety evaluation could not be performed accurately due to the protocol deviation, these cases were considered GCP violations and excluded from the SAF and PKAS.

Because there were only 3 subjects left in the SAF of the 600 mg treatment group, no statistical analysis was performed in this group; however, additional analyses of demographics and other baseline characteristics (of all subjects in the 600 mg treatment group) and safety (separately for the SAF and excluded subjects, as well as for all subjects in the 600 mg treatment group) were conducted, and the results were included in this report in addition to the results of the planned analyses.

Table 1: Number of Subjects in Each Analysis Set

Analysis set	300 mg treatment group	600 mg treatment group	Total
Subjects who received study drug (n)	9	8	17
SAF (n)	9	3	12
PKAS (n)	9	3	12

2. Demographics and other baseline characteristics:

Table 2 shows the major demographics of the PKAS and SAF (9 subjects) of the 300 mg treatment group. For reference, the demographics of the 600 mg treatment group (all subjects who received study drug) are also shown. The two treatment groups were

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comparable in demographics, except for sex distribution, concurrent disease, and body weight.

Of the 9 subjects in the 300 mg treatment group, 4 subjects did not use any concomitant antidepressants with the study drug (monotherapy subjects) while the other 5 subjects used antidepressants. The antidepressants used were paroxetine (Paxil: 3 subjects) and sertraline (JZOLOFT: 2 subjects). Of the 8 subjects in the 600 mg treatment group, 5 were monotherapy subjects and 3 subjects used concomitant antidepressants. The antidepressants used were paroxetine (Paxil), sertraline (JZOLOFT), and milnacipran (Toledomin) (1 subject each).

Table 2: Major Demographics

Variable		300 mg treatment group N = 9[†]	600 mg treatment group N = 8[‡]
Sex	Male	8 (88.9%)	3 (3 7.5%)
	Female	1 (11.1%)	5 (62.5%)
	Total	9	8
Past disease	No	8 (88.9%)	7 (87.5%)
	Yes	1 (11.1%)	1 (12.5%)
	Total	9	8
Concurrent disease	No	4 (44.4%)	1 (12.5%)
	Yes	5 (55.6%)	7 (87.5%)
	Total	9	8
Age (yrs) (at the time of informed consent)	Mean ± SD Median Min - Max	37.7 ± 12.35 40.0 23 - 60	41.8 ± 15.76 49.0 22 - 61
Height (cm)	Mean ± SD Median Min - Max	169.08 ± 5.068 168.40 160.4 - 177.6	161.10 ± 8.415 161.40 150.7 - 173.5
Body weight (kg) (day preceding the day of study drug administration)	Mean ± SD Median Min - Max	69.19 ± 15.822 75.60 47.9 - 88.0	56.64 ± 7.361 55.50 48.7 - 67.4

[†]SAF and PKAS

[‡]All subjects who received study drug (for reference)

Number of subjects (%)

3. Study drug exposure:

Except for 1 subject in the 600 mg treatment group (Subject No. [redacted]), in whom study treatment was discontinued with the dose on Day 2, all subjects in the 300 mg and 600 mg treatment groups completed the study treatment.

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4. Pharmacokinetics:
300 mg treatment group

Table 3 shows the pharmacokinetic parameters of plasma concentrations of unchanged FK949E in the 300 mg treatment group at each measurement time point (the first day of the 50 mg dose period, the first day of the 300 mg dose period, and the seventh day of the 300 mg dose period). Figure 2 shows the mean area under the plasma FK949E concentration-time curves.

The C_{max} values of unchanged FK949E (mean ± SD) in plasma were 58.69 ± 30.87 ng/mL on the first day of the 50 mg dose period, 293.04 ± 95.66 ng/mL on the first day of the 300 mg dose period, and 335.50 ± 171.00 ng/mL on the seventh day of the 300 mg dose period; likewise, the AUC_{inf} values were 519.43 ± 323.72 ng·h/mL, 4016.42 ± 2343.36 ng·h/mL, and 4087.72 ± 2335.71 ng·h/mL, respectively. Both C_{max} and AUC_{inf} increased with increasing dose of FK949E. C_{max} and AUC_{inf} were both slightly higher on the seventh day compared to the values on the first day of the 300 mg dose period. Mean t_{max} values were 5.3 h both on the first days of the 50 mg and 300 mg dose periods, whereas on the seventh day of the 300 mg dose period it was 6.0 h.

Table 3: Pharmacokinetic Parameters of Plasma Concentrations of Unchanged FK949E (Mean ± SD) (300 mg Treatment Group)

Pharmacokinetic parameter	First day of the 50 mg dose period N = 9	First day of the 300 mg dose period N = 9	Seventh day of the 300 mg dose period N = 9
C_{max} (ng/mL)	58.69 ± 30.87	293.04 ± 95.66	335.50 ± 171.00
t_{max} (h)	5.3 ± 1.0	5.3 ± 1.0	6.0 ± 1.0
AUC_{24h} (ng·h/mL)	475.59 ± 256.98	3124.56 ± 1507.75	3464.85 ± 1811.28
AUC_{inf} (ng·h/mL)	519.43 ± 323.72	4016.42 ± 2343.36	4087.72 ± 2335.71
$t_{1/2}$ (h)	5.2 ± 2.2	10.1 ± 9.6	7.2 ± 2.1
k_{el} (1/h)	0.1559 ± 0.0625	0.1056 ± 0.0508	0.1041 ± 0.0323
CL/F (L/h)	132.52 ± 72.77	96.09 ± 47.62	93.77 ± 44.21
MRT_{inf} (h)	10.8 ± 2.8	16.8 ± 12.6	13.2 ± 2.8

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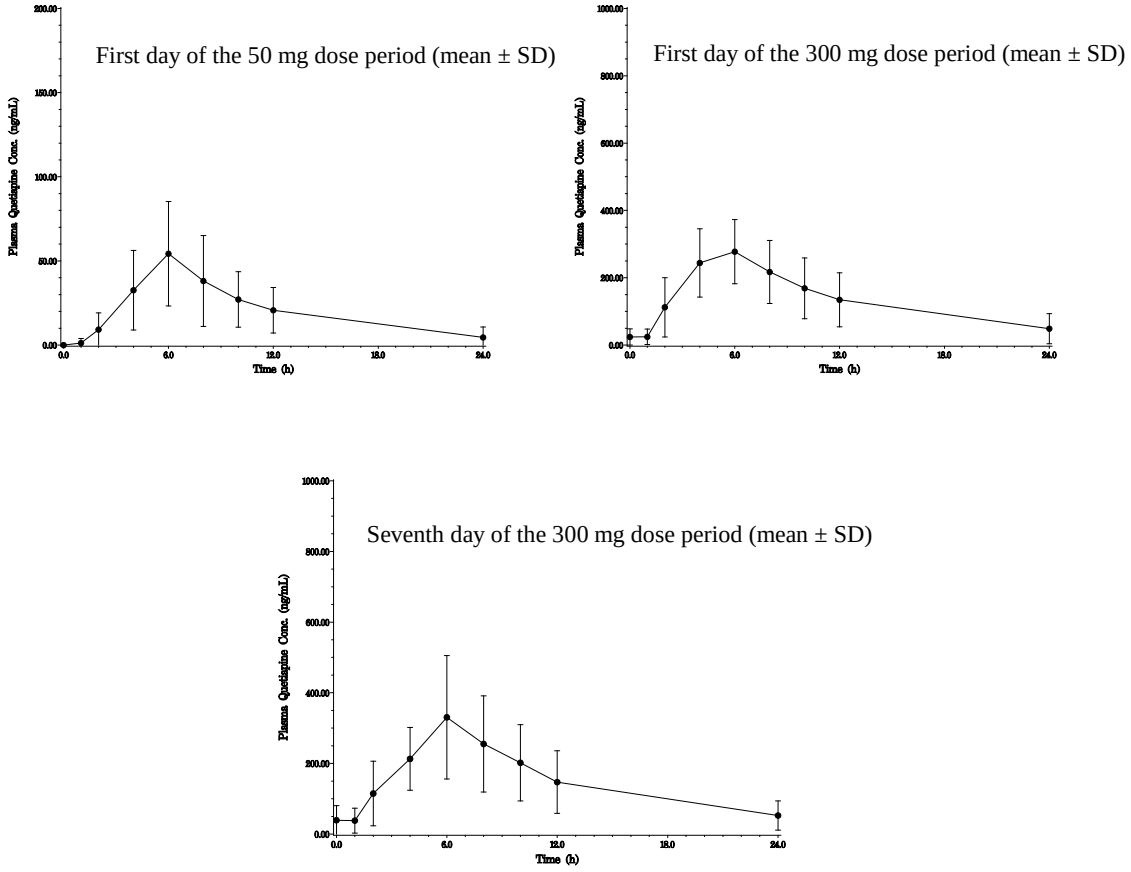

Figure 2: Mean Area under the Plasma FK949E Concentration-Time Curve (300 mg Treatment Group)

600 mg treatment group

Table 4 shows the pharmacokinetic parameters of plasma concentrations of unchanged FK949E in the 600 mg treatment group at each measurement time point (the first day of the 150 mg dose period, the first day of the 600 mg dose period, and the seventh day of the 600 mg dose period). Figure 3 shows the mean area under the plasma FK949E concentration-time curves. In the 600 mg treatment group, there were 3 subjects in the PKAS in 1 of whom the study was discontinued on Day 3 so that the values of plasma unchanged FK949E concentration could be obtained from only 2 subjects. Accurate

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evaluation of pharmacokinetics in the 600 mg treatment group was therefore not possible, and the data are presented only for reference purposes.

The mean C_{max} values of unchanged FK949E in plasma were 239.74 ng/mL on the first day of the 150 mg dose period, 1523.27 ng/mL on the first day of the 600 mg dose period, and 1034.57 ng/mL on the seventh day of the 600 mg dose period; likewise, the AUC_{24h} values were 1936.36 ng·h/mL, 14767.21 ng·h/mL, and 12504.10 ng·h/mL, respectively. Both C_{max} and AUC_{24h} increased with increasing dose of FK949E. C_{max} and AUC_{24h} were both slightly lower on the seventh day compared to the values on the first day of the 600 mg dose period. Mean t_{max} values were 7.0 h both on the first day of the 150 mg period and seventh day of the 600 mg dose period, whereas on the first day of the 600 mg dose period it was 9.0 h.

Table 4: Pharmacokinetic Parameters of Plasma Concentrations of Unchanged FK949E (Mean) (600 mg Treatment Group; for Reference)

Pharmacokinetic parameter	First day of the 150 mg dose period N = 2	First day of the 600 mg dose period N = 2†	Seventh day of the 600 mg dose period N = 2
C_{max} (ng/mL)	239.74	1523.27	1034.57
t_{max} (h)	7.0	9.0	7.0
AUC_{24h} (ng·h/mL)	1936.36	14767.21	12504.10
AUC_{inf} (ng·h/mL)	2021.28	-	13804.97
$t_{1/2}$ (h)	4.2	-	5.5
k_{el} (1/h)	0.1652	-	0.1268
CL/F (L/h)	74.97	-	45.04
MRT_{inf} (h)	10.3	-	12.5

Standard deviation was not calculated due to the small number of subjects (n = 2).

†Since the terminal elimination half-life could not be determined in 1 of the 2 subjects, pharmacokinetic parameters other than C_{max}, t_{max}, and AUC_{24h} were not calculated.

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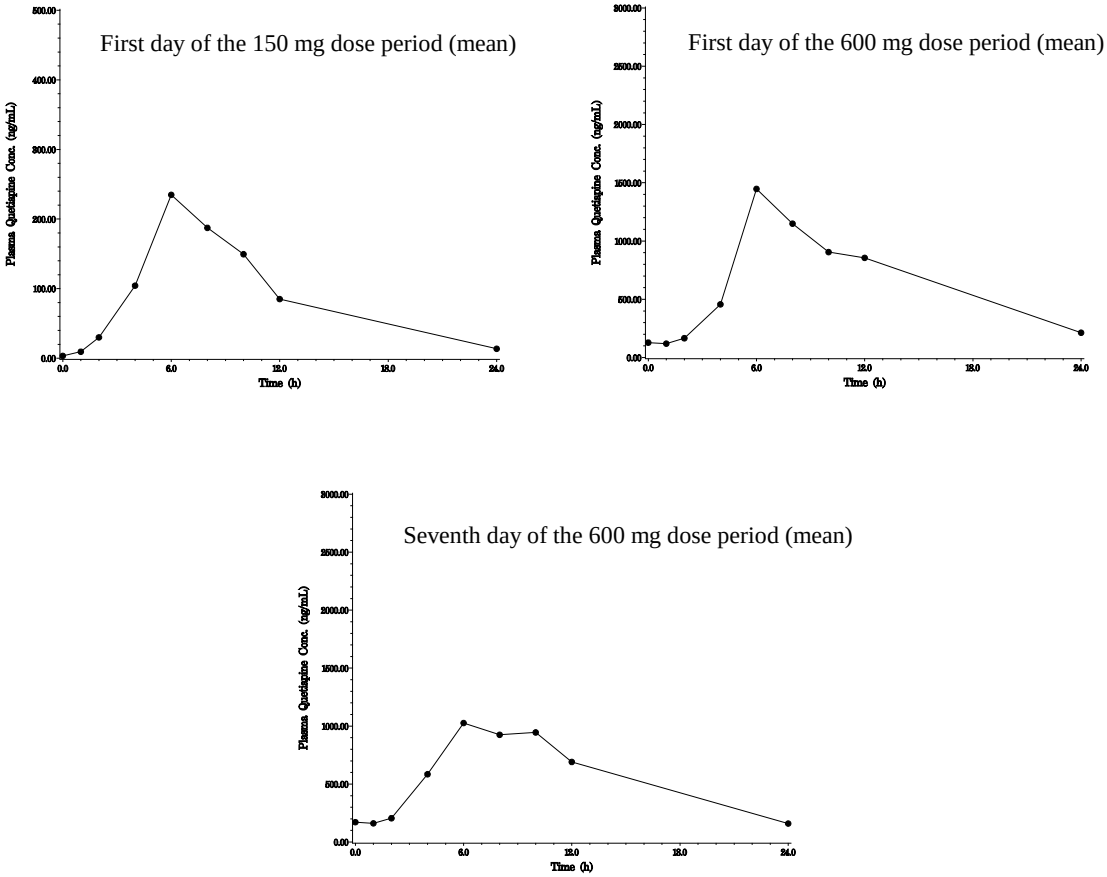

Figure 3: Mean Area under the Plasma FK949E Concentration-Time Curve (600 mg Treatment Group)

5. Safety:

Adverse events

A summary of adverse events in the 300 mg treatment group is shown in Table 5. A total of 20 adverse events were observed in 8 (88.9%) of the 9 subjects. Of these, 15 adverse events were considered to be drug related. A summary of adverse events in the 600 mg treatment group is shown in Table 6. There were 3 subjects in the SAF; however, the results obtained for subjects excluded from the analysis and the results obtained for all subjects who received

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study drug are also presented for reference. With regard to the 3 subjects in the SAF, 6 adverse events were observed in 2 (66.7%) subjects. Of these, 5 adverse events were considered to be drug related. With regard to all subjects in the 600 mg treatment group, a total of 34 adverse events were observed in 7 (87.5%) of the 8 subjects. Of these, 29 adverse events were considered to be drug related.

Death, other serious adverse events, or adverse events resulting in discontinuation of the study did not occur in either the 300 mg or 600 mg treatment group.

Table 5: Summary of Adverse Events (300 mg Treatment Group)

	300 mg treatment group N = 9	
	Number of subjects with an AE†	Number of AEs
Subjects who received study drug	9	
SAF	9	
Adverse events	8 (88.9%)	20
Adverse events considered to be drug related	8 (88.9%)	15
Death	0	0
Serious adverse events	0	0
Adverse events resulting in discontinuation	0	0

†Number of subjects (incidence)

Table 6: Summary of Adverse Events (600 mg Treatment Group; for Reference)

	600 mg treatment group (SAF) N = 3		600 mg treatment group (subjects excluded from SAF) N = 5		600 mg treatment group (all subjects) N = 8	
	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
Subjects who received study drug	3		5		8	
SAF	3		-		-	
Adverse events	2 (66.7%)	6	5 (100.0%)	28	7 (87.5%)	34
Adverse events considered to be drug related	2 (66.7%)	5	5 (100.0%)	24	7 (87.5%)	29
Death	0	0	0	0	0	0
Serious adverse events	0	0	0	0	0	0
Adverse events resulting in discontinuation	0	0	0	0	0	0

†Number of subjects (incidence)

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The incidence of adverse events and incidence of adverse events considered to be drug related in the 300 mg treatment group are shown in Tables 7 and 8, respectively. The most commonly observed adverse event was orthostatic hypotension (8 events in 6 subjects [66.7%]). Other events observed in more than 1 subject were nasopharyngitis in 3 subjects (33.3%) and thirst and nasal congestion in 2 subjects each (22.2%). All of the adverse events observed in more than 1 subject, except for nasopharyngitis in the 3 subjects, were considered to be drug related. All adverse events were non-serious, and were mild or moderate in severity. Except for one case of nasopharyngitis, all adverse events resolved without any treatment or with appropriate treatment. The one case of nasopharyngitis that did not improve was considered to not be related to the study treatment because it had occurred after last dose of study drug.

Table 7: Incidence of Adverse Events (300 mg Treatment Group)

System Organ Class/Preferred Term[†]	300 mg treatment group N = 9
Cardiac disorders	1 (11.1%)
Palpitations	1 (11.1%)
General disorders and administration site conditions	2 (22.2%)
Thirst	2 (22.2%)
Infections and infestations	3 (33.3%)
Nasopharyngitis	3 (33.3%)
Nervous system disorders	3 (33.3%)
Akathisia	1 (11.1%)
Headache	1 (11.1%)
Somnolence	1 (11.1%)
Respiratory, thoracic and mediastinal disorders	2 (22.2%)
Nasal congestion	2 (22.2%)
Skin and subcutaneous tissue disorders	1 (11.1%)
Heat rash	1 (11.1%)
Vascular disorders	6 (66.7%)
Orthostatic hypotension	6 (66.7%)

Number of subjects (incidence)

[†] MedDRA ver.12.0 (SOC / PT)

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Table 8: Incidence of Adverse Events Considered to Be Drug Related (300 mg Treatment Group)

System Organ Class/Preferred Term[†]	300 mg treatment group N = 9
General disorders and administration site conditions	2 (22.2%)
Thirst	2 (22.2%)
Nervous system disorders	3 (33.3%)
Akathisia	1 (11.1%)
Headache	1 (11.1%)
Somnolence	1 (11.1%)
Respiratory, thoracic and mediastinal disorders	2 (22.2%)
Nasal congestion	2 (22.2%)
Vascular disorders	6 (66.7%)
Orthostatic hypotension	6 (66.7%)

Number of subjects (incidence)

[†] MedDRA ver.12.0 (SOC / PT)

The incidence of adverse events and incidence of adverse events considered to be drug related in the 600 mg treatment group are shown in Table 9 and Table 10, respectively. There were 3 subjects in the SAF; however, the results obtained for subjects excluded from the SAF and those obtained for all subjects who received study drug are also presented for reference. The adverse events most commonly observed in the 3 subjects in the SAF were dizziness postural and somnolence; 2 events occurred in 2 subjects each (66.7%). In addition, nasopharyngitis and alanine aminotransferase abnormal occurred in 1 subject each (33.3%). The one case of nasopharyngitis was considered not related to the study drug. The most commonly observed adverse event in all subjects in the 600 mg treatment group was somnolence (8 events in 7 subjects [87.5%]), followed by orthostatic hypotension (6 events in 5 subjects [62.5%]). Somnolence and orthostatic hypotension were considered to be drug related. All adverse events were non-serious, and were mild or moderate in severity. All adverse events resolved without any treatment or with appropriate treatment.

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Table 9: Incidence of Adverse Events (600 mg Treatment Group; for Reference)

System Organ Class/Preferred Term[†]	600 mg treatment group (SAF) N = 3	600 mg treatment group (Exclusions from SAF) N = 5	600 mg treatment group (All subjects) N = 8
Gastrointestinal disorders	0 (0.0%)	1 (20.0%)	1 (12.5%)
Abdominal pain upper	0 (0.0%)	1 (20.0%)	1 (12.5%)
Diarrhoea	0 (0.0%)	1 (20.0%)	1 (12.5%)
General disorders and administration site conditions	0 (0.0%)	4 (80.0%)	4 (50.0%)
Feeling abnormal	0 (0.0%)	1 (20.0%)	1 (12.5%)
Thirst	0 (0.0%)	3 (60.0%)	3 (37.5%)
Infections and infestations	1 (33.3%)	2 (40.0%)	3 (37.5%)
Nasopharyngitis	1 (33.3%)	2 (40.0%)	3 (37.5%)
Investigations	1 (33.3%)	0 (0.0%)	1 (12.5%)
Alanine aminotransferase abnormal	1 (33.3%)	0 (0.0%)	1 (12.5%)
Nervous system disorders	2 (66.7%)	5 (100.0%)	7 (87.5%)
Akathisia	0 (0.0%)	3 (60.0%)	3 (37.5%)
Dizziness	0 (0.0%)	1 (20.0%)	1 (12.5%)
Dizziness postural	2 (66.7%)	0 (0.0%)	2 (25.0%)
Dysgeusia	0 (0.0%)	2 (40.0%)	2 (25.0%)
Dyskinesia	0 (0.0%)	1 (20.0%)	1 (12.5%)
Somnolence	2 (66.7%)	5 (100.0%)	7 (87.5%)
Skin and subcutaneous tissue disorders	0 (0.0%)	1 (20.0%)	1 (12.5%)
Acne	0 (0.0%)	1 (20.0%)	1 (12.5%)
Vascular disorders	0 (0.0%)	5 (100.0%)	5 (62.5%)
Orthostatic hypotension	0 (0.0%)	5 (100.0%)	5 (62.5%)

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

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Table 10: Incidence of Adverse Events Considered to Be Drug Related (600 mg Treatment Group; for Reference)

System Organ Class/Preferred Term†	600 mg treatment group (SAF) N = 3	600 mg treatment group (Exclusions from SAF) N = 5	600 mg treatment group (All subjects) N = 8
General disorders and administration site conditions	0 (0.0%)	4 (80.0%)	4 (50.0%)
Feeling abnormal	0 (0.0%)	1 (20.0%)	1 (12.5%)
Thirst	0 (0.0%)	3 (60.0%)	3 (37.5%)
Investigations	1 (33.3%)	0 (0.0%)	1 (12.5%)
Alanine aminotransferase abnormal	1 (33.3%)	0 (0.0%)	1 (12.5%)
Nervous system disorders	2 (66.7%)	5 (100.0%)	7 (87.5%)
Akathisia	0 (0.0%)	3 (60.0%)	3 (37.5%)
Dizziness	0 (0.0%)	1 (20.0%)	1 (12.5%)
Dizziness postural	2 (66.7%)	0 (0.0%)	2 (25.0%)
Dysgeusia	0 (0.0%)	2 (40.0%)	2 (25.0%)
Dyskinesia	0 (0.0%)	1 (20.0%)	1 (12.5%)
Somnolence	2 (66.7%)	5 (100.0%)	7 (87.5%)
Skin and subcutaneous tissue disorders	0 (0.0%)	1 (20.0%)	1 (12.5%)
Acne	0 (0.0%)	1 (20.0%)	1 (12.5%)
Vascular disorders	0 (0.0%)	5 (100.0%)	5 (62.5%)
Orthostatic hypotension	0 (0.0%)	5 (100.0%)	5 (62.5%)

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

Orthostatic hypotension, the most common adverse event in the 300 mg treatment group, was further investigated. In the 300 mg treatment group, 8 cases of orthostatic hypotension were observed in 6 of the 9 subjects, 1 case each during the 50 mg and 150 mg dose periods and 6 cases during the 300 mg dose period. All of the events occurred on the first day of the first dose (50 mg) or of the increased doses (150 mg and 300 mg). All cases of orthostatic hypotension observed in the 300 mg treatment groups resolved without dose reduction or discontinuation of the study drug or any other symptomatic treatment. All cases of orthostatic hypotension were mild to moderate in severity and "probably related" to the study drug. Although only for reference, the results of the 600 mg treatment group were as follows: 6 cases of orthostatic hypotension were observed in 5 out of 8 subjects (i.e., all subjects in the 600 mg treatment group), 1 case during the 50 mg and 5 cases during the 300 mg dose periods. All of the events occurred on the first day of the first dose (50 mg) or of the increased dose (300 mg); 5 cases of orthostatic hypotension that occurred on the first day of the 300 mg dose period persisted until 1 day after last dose of study drug. One of the 6 cases resolved without dose reduction or discontinuation of the study drug or any other symptomatic treatment, whereas the other 5 cases were resolved through medical treatment

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(administration of vasopressor agents). All cases of orthostatic hypotension were moderate in severity and were judged to be "possibly related" or "probably related" to the study drug.

Clinical laboratory evaluations

In hematology and biochemistry of the 300 mg treatment group, the mean values of chloride, HDL cholesterol, and triglyceride during study drug administration were each outside the normal reference range. However, the mean values of all these parameters were found to be within the normal reference range at the post-study visit; and in the opinion of the investigator, none of the findings were considered to represent an abnormal change or be clinically significant. In urinalysis, none of the test results was found to be outside the normal reference range.

In the 600 mg treatment group, 1 subject (Subject No. [redacted]) had alanine aminotransferase abnormal on Day 14, which, however, was found to be within the normal reference range at the post-study visit.

Vital signs

In the 300 mg treatment group, the mean values of systolic and diastolic blood pressure showed a tendency to decrease after administration, and correspond to decrease in blood pressure decrease, the mean pulse rate showed a tendency to increase. Overall, the variations in blood pressure and pulse rate were more pronounced in the standing position compared to those in the supine position. The differences between the supine and standing values of blood pressure and pulse rate (standing minus supine values) are presented in Figure 4 and Figure 5, respectively. On Days 1, 3, and 5, which were the first days of the 50 mg, 150 mg, and 300 mg dose periods, respectively, blood pressure and pulse rate were measured before administration and at 1 and 6 hours post-dose to follow the time course of these parameters. Generally, the differences between the standing and supine values of blood pressure and pulse rate were the largest at 6 hours post-dose, and resolved before administration on the following day. The differences between the standing and supine values of blood pressure and pulse rate were larger after administration of 300 mg than after that of 50 mg or 150 mg. No particular tendency was observed in the time course of mean body temperature.

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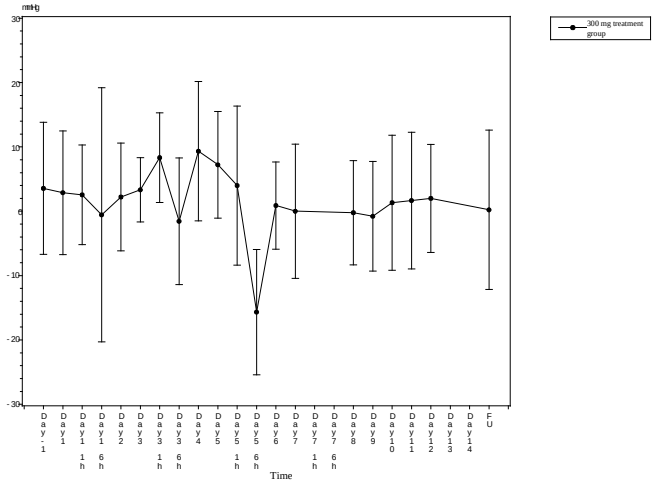
Systolic blood pressure (standing- supine)



Diastolic blood pressure (standing- supine)

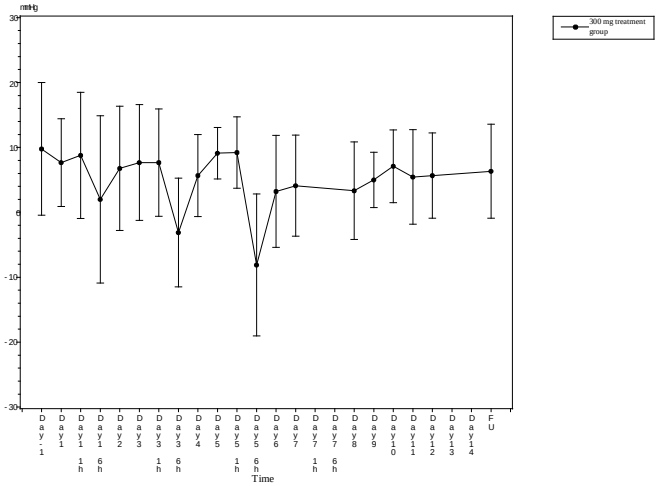


Figure 4: Changes in the Difference between Systolic and Diastolic Blood Pressure (Standing - Supine) (Mean ± SD) (300 mg Treatment Group)

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

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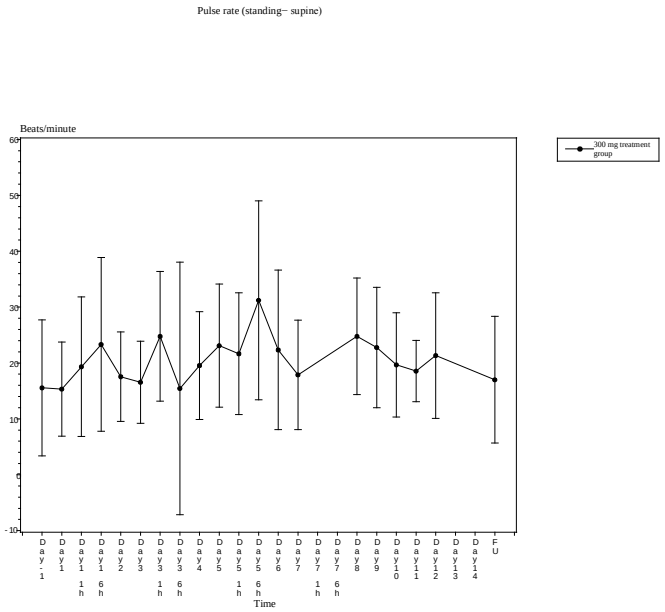

Figure 5: Changes in the Difference between Standing and Supine Pulse Rates (Standing - Supine) (Mean ± SD) (300 mg Treatment Group)

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

Electrocardiograms

Three of 9 subjects in the SAF of the 300 mg treatment group and 1 of 3 subjects in the SAF of the 600 mg treatment group were found to have “abnormal - not clinically significant” 12-lead ECG findings after administration, however, all of them had been observed already before administration. No “abnormal - clinically significant” findings were observed either before or after administration.

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Conclusions:

In order to evaluate the safety and pharmacokinetics of multiple oral doses of FK949E (extended-release formulation of quetiapine) 300 mg/day and 600 mg/day after breakfast, the multicenter, open-label clinical study was conducted in patients with major depressive disorder using oral administration of FK949E, beginning with the initial dose of 50 mg followed by dose escalation of up to 300 mg or 600 mg.

Eight subjects were planned for each treatment group, and 9 subjects in the 300 mg treatment group and 8 subjects in the 600 mg treatment group received the study drug. In the 300 mg treatment group, all 9 subjects were included in the SAF and PKAS. In the 600 mg treatment group, 5 of the 8 subjects who received study drug were excluded from the safety analysis due to deviation from the protocol (use of medical treatment for adverse events that occurred at the time of the dose increase to 300 mg); thus 3 subjects were included in the SAF and PKAS. Due to the small number of subjects in the analysis sets, accurate evaluation was not possible in the 600 mg treatment group.

Twenty adverse events were observed in 8 (88.9%) of the 9 subjects in the 300 mg treatment group. Of these, 15 adverse events were considered to be drug related. In the 600 mg treatment group, 6 adverse events were observed in 2 (66.7%) of the 3 subjects of the SAF. Of these, 5 adverse events were considered to be drug related. Although only for reference purposes, data on all subjects in the 600 mg treatment group showed 34 adverse events in 7 (87.5%) of the 8 subjects. Of these, 29 adverse events were considered to be drug related. No deaths, other serious adverse events, or adverse events resulting in discontinuation of the study were observed in the 300 mg or 600 mg treatment group.

The most commonly observed adverse event in the 300 mg treatment group was orthostatic hypotension (8 events in 6 subjects [66.7%]). Other events observed in more than 1 subject were nasopharyngitis in 3 subjects (33.3%) and thirst and nasal congestion in 2 subjects each (22.2%). The adverse events most commonly observed in the 3 subjects of the SAF of the 600 mg treatment group were dizziness postural and somnolence; 2 events occurred in 2 subjects each (66.7%). In addition, nasopharyngitis and alanine aminotransferase abnormal occurred in 1 subject each (33.3%). Although only for reference purposes, data on all subjects in the 600 mg treatment group show that the most commonly observed adverse event in this group was somnolence (8 events in 7 subjects [87.5%]), followed by orthostatic hypotension (6 events in 5 subjects [62.5%]).

All adverse events observed in the present study were of mild or moderate severity. Except for the 1 case of nasopharyngitis (300 mg treatment group), all events resolved without any

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treatment or with appropriate treatment. The adverse events found in the present study were consistent with the known safety profile of quetiapine as confirmed in overseas clinical studies or observed with the existing formulation of quetiapine. An analysis of time of onset of adverse events by dose in the 300 mg treatment group showed no tendency for the incidence of adverse events to be higher in the early stage after the start of study drug administration.

With regard to clinical laboratory data, the mean values of chloride, HDL cholesterol, and triglyceride during study drug administration were each outside the normal reference range in the 300 mg treatment group; however, the mean values of all these parameters were found to be within the normal reference range at the post-study visit. With regard to vital signs, the mean values of systolic and diastolic blood pressure in the 300 mg treatment group showed a tendency to decrease after administration, and correspond to decrease in blood pressure, the mean pulse rate showed a tendency to increase. Generally, the variations in blood pressure and pulse rate were the largest at 6 hours post-dose, and resolved before administration on the following day. Orthostatic hypotension is a characteristic vital change that has been reported in overseas clinical studies or observed with the existing formulation of quetiapine.

The pharmacokinetic analysis of FK949E 300 mg following oral administration after breakfast with dose escalation revealed the C_{max} values of unchanged FK949E in plasma (mean ± SD) of 58.69 ± 30.87 ng/mL on the first day of the 50 mg dose period, 293.04 ± 95.66 ng/mL on the first day of the 300 mg dose period, and 335.50 ± 171.00 ng/mL on the seventh day of the 300 mg dose period; likewise, the AUC_{inf} values were 519.43 ± 323.72 ng·h/mL, 4016.42 ± 2343.36 ng·h/mL, and 4087.72 ± 2335.71 ng·h/mL, respectively. Both C_{max} and AUC_{inf} increased with increasing dose of FK949E. An accurate evaluation of the pharmacokinetics was not possible in the 600 mg treatment group because the number of subjects in the PKAS was too small to estimate the pharmacokinetics of FK949E following an oral dose of 600 mg after breakfast with dose escalation; nevertheless, both C_{max} and AUC_{24h} increased with increasing dose of FK949E.

In the present study, the safety and pharmacokinetics of FK949E were studied in patients with major depressive disorder using 50 mg of FK949E as the initial dose, which was gradually escalated up to 300 mg or 600 mg. As a result of the evaluation of safety in the 300 mg treatment group, it was considered appropriate to proceed to the study of the 600 mg treatment group. However, because of the medical treatment to the subjects in the 600 mg treatment group for an adverse event (orthostatic hypotension) during the 300 mg dose period, precise evaluation of safety during the 300 mg and 600 mg dose periods became

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<tr><td>Name of Active Ingredient:
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<tr><td colspan="3">impossible. Further studies are therefore considered necessary.</td></tr>
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