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:

Pharmacokinetic Study of FK949E -A Pharmacokinetic Study in Healthy Male Volunteers to Investigate the Effect of Food on the Pharmacokinetics of FK949E-

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

Investigator: [redacted]

Study Site: 1 site ([redacted])

Publication: Unpublished

Study Period: 0 years 2 months (duration from the starting day of the study to the day of study completion) **Study Initiation Date:** 17 June 2009 (the day when the first subject signed the written informed consent) **Study Completion Date:** 19 August 2009 [the day when the last subject was evaluated (the day of protocol-specified final assessments)]	**Phase of Development:** Phase 1 study

Study Objective:

To evaluate the effect of food on the pharmacokinetics of FK949E after the administration of 50 mg in healthy non-elderly adult male subjects using a 3-treatment, 6-sequence, 3-period crossover design, as well as to evaluate the safety.

Study Design and Methodology:

Randomized, open-label 3-treatment, 6-sequence, 3-period crossover design

Planned Sample Size: 24 subjects
[Rationale]

The sample size was set at a total of 24 subjects based on the number of subjects that is considered sufficient to evaluate the effect of food on the pharmacokinetics of the FK949E tablet, and also taking practicability into consideration.

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Diagnosis and Inclusion/Exclusion Criteria:

Non-elderly healthy adult male subjects are eligible for the study if all of the following inclusion criteria apply while none of the exclusion criteria are met:

1. Inclusion criteria

1. Sex. Male
2. Age (at informed consent acquisition): ≥20 years old, <45 years old
3. Body weight (at screening): ≥50.0 kg, <85.0 kg
4. BMI (at screening): ≥17.6, <26.4
5. Healthy, as judged by the investigator/subinvestigator based on the results of physical examinations (subjective symptoms and objective findings) and all tests obtained at screening and during the period from hospital admission in Period 1 to immediately before study medication.
6. Written informed consent has been obtained.

2. Exclusion criteria

1. Subjects with the following history.
   (1) Hepatic disease (e.g. viral hepatitis, drug-induced liver injury).
   (2) Heart disease (e.g. congestive heart failure, angina pectoris, arrhythmia requiring treatment).
   (3) Respiratory disease (e.g. serious bronchial asthma, chronic bronchitis)
   (4) Gastrointestinal disease (e.g. serious peptic ulcer, gastroesophageal reflux esophagitis; diseases requiring several selections except for appendicitis)
   (5) Renal disease (e.g. acute renal failure, glomerulonephritis, interstitial nephritis).
   (6) Cerebrovascular disorder (e.g. cerebral infarction).
   (7) Malignant tumor.
   (8) Drug allergies. Allergic disorders (except for hay fever)
   (9) Any use of drugs abuse. Alcohol abuse.

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2. Any concurrent illness (except for caries)
3. A deviation from the normal reference range of blood pressure, pulse rate, body temperature, or 12-lead ECG at screening or upon admission in Period 1 (day preceding the day of study medication).
4. Any deviation of the following criteria for clinical laboratory tests at screening or upon admission in Period 1 (day preceding the day of study medication). The normal reference ranges specified at the study site will be used as the normal reference ranges in the present study.

   (1) Hematology:

   - A deviation of ±20% from the upper or lower limit of the normal range

   (2) Blood biochemistry:

   - A deviation from the normal range for AST, ALT, creatinine (Cre), or serum electrolytes.
   - A deviation of ±20% from the upper or lower limit of the normal range for other items than the above.
   - However, the lower limit of the normal range will not be established for items for which a deviation from the lower limit is not considered clinically significant [AST, ALT, total bilirubin (T-Bil), ALP, γ-GTP, LDH, CK, Cre, uric acid (UA) and total cholesterol (T-Cho)].

   (3) Urinalysis:

   - U-Glu, U-Pro ≥+1
   - U-Uro ≥+2

   (4) Urinary drug test:

   A positive result for phencyclidine, benzodiazepine, cocaine, amphetamines, cannabis, opiates, barbiturates or tricyclic antidepressants

   (5) Immunological test:

   A positive result for HBs antigen, HCV antibody, syphilis, or HIV antigen/antibody.

5. Received medication within 14 days before hospital admission in Period 1 or is scheduled to receive medication.

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6. Received any investigational drugs in other clinical or post-marketing studies within 120 days before the screening assessment.
7. Previous treatment with FK949E.
8. Donated more than 400 mL of whole blood within 90 days, more than 200 mL of whole blood within 30 days, or blood components within 14 days before the screening assessment.
9. Excessive smoking or drinking habit (measure of "excessive": alcohol: 45 g/day [a 633 mL bottle of beer contains 25 g of alcohol, and 180 mL of Japanese sake contains 22 g of alcohol], smoking: 20 cigarettes/day).
10. Employees of the sponsor, or CROs or study sites related to the present study.
11. Other subjects concerned ineligible by the investigator/subinvestigator.

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Test Drug, Dose, and Mode of Administration:

1. Test drug and lot number

Test drug		Lot number
FK949E tablets: 50 mg	Oval, slightly yellowish, red film-coated tablet, containing 50 mg of quetiapine.	[redacted] (Manufacturer: AstraZeneca)

2. Dosage and mode of administration

[Dosage/mode of administration]

A 50 mg tablet of FK949E will be orally given as a single administration to each subject under fasted conditions or within 10 min after a meal (low or high fat meal). After a washout period, a similar single oral administration will be given under different meal conditions.

[Duration of treatment]

A single administration was given either under fasted conditions or after a meal during Period 1, Period 2, and Period 3.

	Period 1	Washout period	Period 2	Washout period	Period 3
A group (n=4)	Fasted	≥7 days	Low fat meal	≥7 days	High fat meal
B group (n=4)	Fasted		High fat meal		Low fat meal
C group (n=4)	Low fat meal		Fasted		High fat meal
D group (n=4)	Low fat meal		High fat meal		Fasted
E group (n=4)	High fat meal		Low fat meal		Fasted
F group (n=4)	High fat meal		Fasted		Low fat meal

Randomized to any 6 group (A to F) above, a 50 mg tablet of FK949E will be orally administered with 150 mL of water to 24 subjects at 09:00 (as a guide) on the day of administration. The washout period between study medications in Periods 1, 2 and 3 will be at least 7 days (following the day of study medication in Period 1 to the day preceding the day of

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study medication in Period 2 and following the day of study medication in Period 2 to the day preceding the day of study medication in Period 3).

The contents of the meal are as follows;

Fasted conditions: Oral administration after fasted overnight from after dinner on the day preceding the day of administration.

After meal: Oral administration within 10 min after a meal (the meal should be finished within 20 min after commencement).

A high fat meal (more than 900 kcal and more containing 35% lipid content: According to the "Guideline for Bioequivalence Studies of Generic Products") or a low fat meal (more than 700 kcal and less containing 20% lipid content: According to the "Guideline for Bioequivalence Studies of Generic Products") will be served immediately before administration for subjects administered under fed conditions.

[Rationale for Dose Setting]

A phase 1 multiple oral dosing of FK949E in non-elderly patients with depression (Study No. 6949-CL-0001) has been ongoing in Japan. Usually it is preferable to conduct a study at similar doses as the clinical dose. However, since the linearity has been confirmed for both C_{max} and AUC at doses between 50 and 400 mg, considering no impact on the evaluation of the effect of food, the dose was set at 50 mg, for which tolerability was established in the study conducted in healthy adults overseas (Study No. D1444C0003, Germany). In a clinical study conducted overseas (Study No. D1448C00013, USA), the onset of adverse events was observed at the assessment of an orthostatic change conducted the day after the dose was increased from 0 mg/day to 50 mg/day. Therefore, in order to assure the safety of the 50 mg dosing, the time to start administration, the time of the examination, contents of the examination, and items that subjects should have observed, were specified.

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Investigational Period:

Dose duration: Single dose

Duration of pharmacokinetic evaluation: 48 hours post-dose for each dosing time point

Duration of safety assessment: 7 days or longer after each dosing time point

Concomitant Medication (Drugs and Therapies):

Concomitant medication (use of other drugs or therapies than the study drug) during the study period were not allowed between the start of study drug administration in Period 1 and the post-study visit, except those applied as the treatment for adverse event(s).

Variables and Schedule of Procedures:

1. Pharmacokinetics

- Plasma concentration of unchanged FK949E

  (The following parameters will be calculated: C_{max}, t_{max}, AUC_{inf}, AUC_{last}, k_{el}, $t_{1/2}$, CL/F and MRT etc.)

  Blood sampling time points for the plasma concentration of unchanged FK949E measurement: Pre-dose, and at 1, 2, 4, 6, 8, 10, 12, 14, 24, 36 and 48 h post-dose

2. Safety:

- Adverse events
- Vital signs (axillary body temperature, supine blood pressure, supine pulse rate)
- 12-lead ECG
- Clinical laboratory data (hematology, blood biochemistry, urinalysis)

Statistical Analysis

1. Population for analysis:

Pharmacokinetics analysis set (PKAS): It was defined as a subset of the subjects who received at least one dose of the FK949E tablet and for whom plasma unchanged FK949E concentration data are available (blood samples were collected) at least one time point after administration of the FK949E tablet.

Safety analysis set (SAF): It includes all the subjects who received the investigational drugs.

2. Demographics and other reference values:

The following analyses were performed on the SAF and PKAS.

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- Discrete data values were summarized.
- For continuous data, descriptive statistics were calculated.

3. Pharmacokinetics:

On the PKAS, descriptive statistics were calculated from plasma unchanged FK949E concentrations at each blood sampling time point by treatment regimen. Non-compartment model analysis on temporal changes in the unchanged FK949E concentration in the plasma by each subject to calculate C_{max}, t_{max}, AUC_{inf}, AUC_{last}, k_{el}, $t_{1/2}$, CL/F and MRT.

Among the calculated pharmacokinetic parameters, C_{max} and AUC_{last} were chosen as the primary variables for the examination of the effect of food, and the GMR of C_{max} and AUC_{last} after fed-state administration to those after fasted-state administration and its 90% CIs were calculated. GMR after fed-state administration either under high- or low fat meal conditions to those after fasted-state administration and its 90% CIs were calculated as the secondary variables on AUC_{inf}, $t_{1/2}$, CL/F, MRT_{inf}, and MRT_{last}. As for t_{max}, the difference of the least square mean between either these administrations under high or low fat meal conditions and those after fasted-state administration and its 90% CIs were estimated as the ratio to the least square mean of fasted-state administration. The secondary variables were considered as reference when examining the degree of the effect of food.

4. Safety:

The following analyses were performed on the SAF by food condition (fasted/low fat meal fed/high fat meal fed).

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

   Descriptive statistics were calculated for each time point, and a Spaghetti Plot was prepared.

2. 12-lead ECG

   The cross table for 12-lead ECGs on the day preceding the day of administration and at each time point were presented.

3. Clinical laboratory data

   Descriptive statistics for continuous data were calculated at each time point, and the scatter plots of continuous data on the day preceding the day of administration and at each time point were presented. The cross table for categorical data on the day preceding

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the day of administration and at each time point were presented.

4. Adverse events

The number and percentage of subjects with AEs and treatment-related AEs were calculated. The number and percentage of subjects with adverse events, as classified by MedDRA System Organ Class (SOC) and Preferred Term (PT), were summarized (ver. 12.0).

Results:

1. Disposition of subjects and analysis set:

Disposition of subjects are shown in Figure 1. The Informed consent was obtained from 33 subjects, and of those, 24 subjects were assigned to either one of 6 groups from group A to group F to receive the study drug. Details of the reasons for screening failure were 5 subjects of "Inclusion/Exclusion criteria not satisfied," 2 subjects with "Withdrawal of consent," and 2 subjects with "Others (fulfillment of subjects)". All subjects completed the administration from Period 1 to Period 3, and none discontinued the dosing.

All 24 subjects were included in PKAS and SAF.

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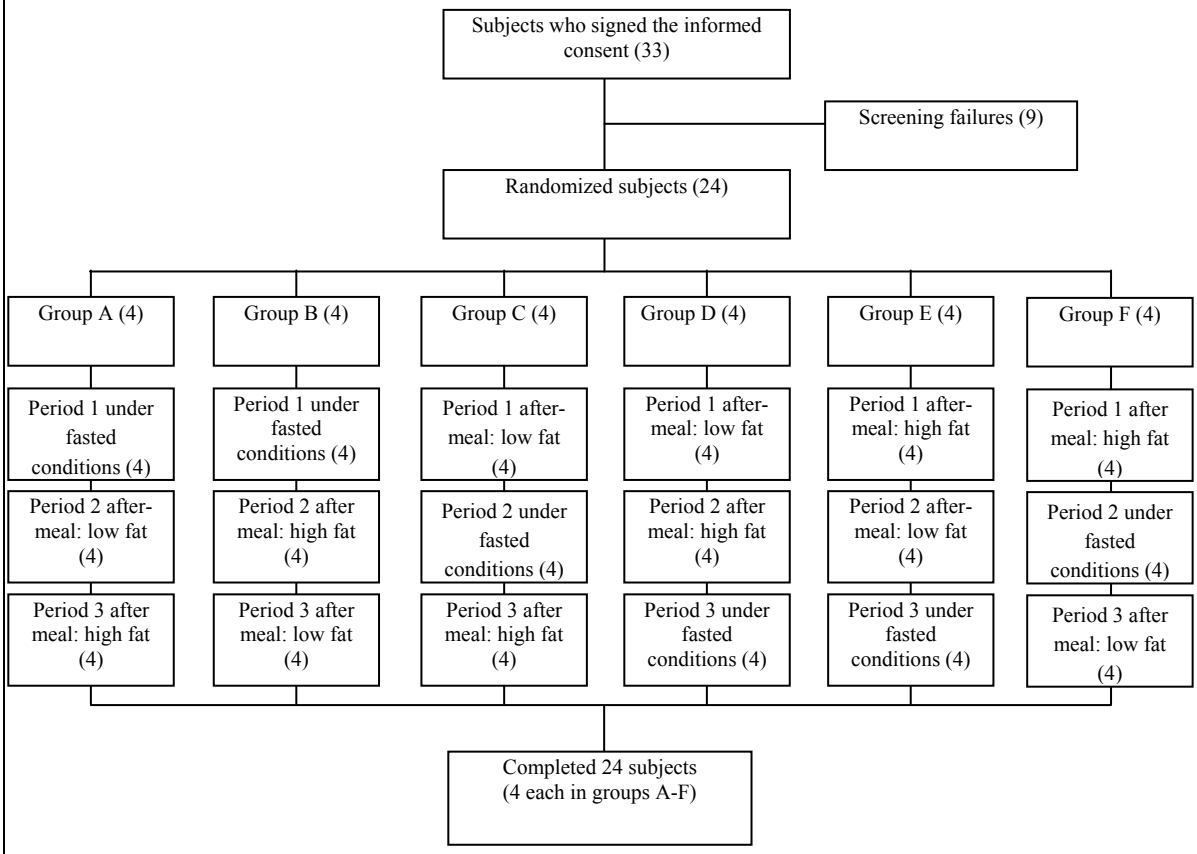
Figure 1 Disposition of subjects



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2. Demographics, other baseline characteristics:

Table 1 shows the major demographics of PKAS and SAF (24 subjects).

Table 1 Major demographics (24 subjects †)

Parameter	Mean±SD	Min to Max
Age (yrs) (at the time of Informed Consent)	26.8 ± 5.18	22-41
Height (cm)	170.48 ± 5.087	161.9-183.5
Body weight (kg) (at screening)	64.00 ± 7.482	50.2-77.7
BMI (kg/m^2)	22.01 ± 2.432	17.8-26.1

† PKAS and SAF

3. Study drug exposure:

In this study, administration of the study drug to each subject was witnessed by the investigator or subinvestigator and the study coordinator to ensure treatment compliance. The washout period between study medications (between Periods 1 and 2, and between Periods 2 and 3) were at least 7 days for each study subject.

4. Pharmacokinetics:
Pharmacokinetic parameter

Figure 2 shows the mean area under the plasma FK949E concentration - time curve. The mean unchanged FK949E concentration in plasma after a meal (low- and high fat food) was higher than that observed after administration under fasted conditions, and the plasma concentration of unchanged FK949E by subject was generally higher than that observed after a meal (low- and high fat food).

Table 2 shows the pharmacokinetic parameters of unchanged FK949E concentration in plasma after administration under fasted conditions and after a meal (low- and high fat food). The C_{max} values of the unchanged FK949E concentration in plasma under each meal condition (under fasted conditions, and after low- and high-fat food) (mean ± SD) were 33.03 ± 17.72 ng/mL, 62.39 ± 38.17 ng/mL, and 70.18 ± 32.56 ng/mL, respectively; likewise, AUC_{last} values were 423.64 ± 283.23 ng·h/mL, 455.47 ± 308.97 ng·h/mL, and 496.78 ± 334.14 ng·h/mL, respectively. Both C_{max} and AUC_{last} showed the highest values after a high fat meal compared

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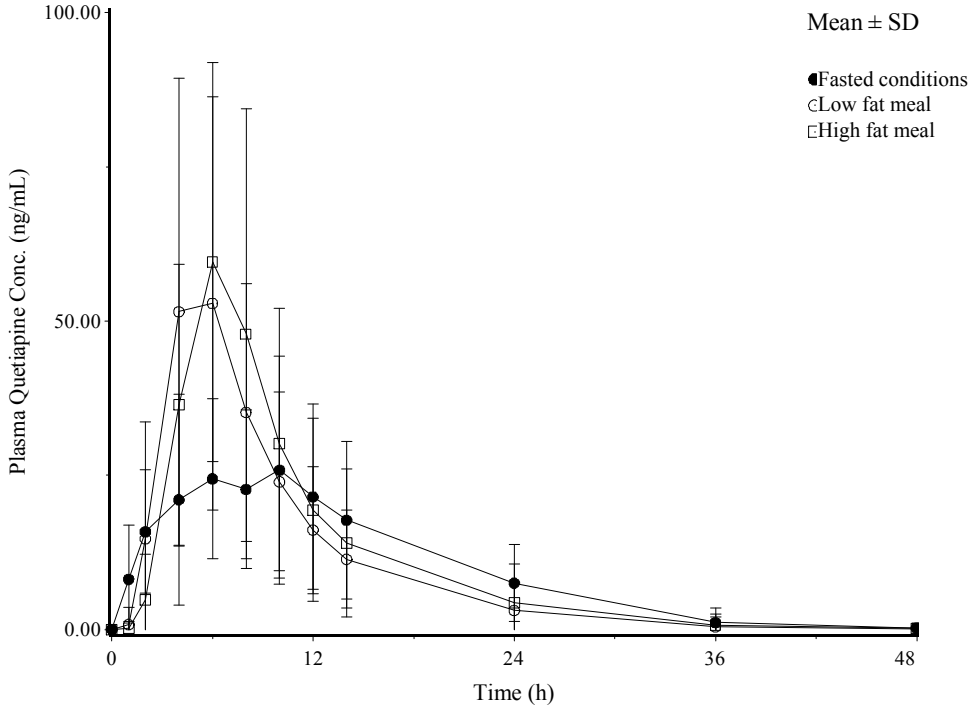
to the administration under fasted conditions, followed by low fat meal conditions. Compared to administration under fasted conditions, t_{max} was slightly decreased under low- and high fat food conditions, and $t_{1/2}$ was slightly decreased.

Figure 2 Mean area under the plasma FK949E concentration - time curve



●: Administered under fasted conditions (N=24), ○: Administered after a low fat meal (N=24), □: Administered after a high fat meal (N=24)

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Table 2 Pharmacokinetic parameters of plasma concentrations of unchanged FK949E (mean ± SD)

Pharmacokinetic parameter	Fasted N=24 †	Low fat meal N=24	High fat meal N=24
C_{max} (ng/mL)	33.03 ± 17.72	62.39 ± 38.17	70.18 ± 32.56
t_{max} (h)	8.0 ± 4.9	5.2 ± 2.0	6.0 ± 1.4
AUC_{inf} (ng·h/mL)	465.50 ± 291.69	485.36 ± 312.45	528.26 ± 339.10
AUC_{last} (ng·h/mL)	423.64 ± 283.23	455.47 ± 308.97	496.78 ± 334.14
k_{el} (1/h)	0.1108 ± 0.0362	0.1631 ± 0.0623	0.1530 ± 0.0509
$t_{1/2}$ (h)	6.8 ± 1.7	4.8 ± 1.7	5.0 ± 1.7
CL/F (L/h)	140.12 ± 65.11	140.18 ± 78.84	124.18 ± 62.49
MRT_{inf} (h)	13.8 ± 2.8	9.4 ± 1.8	10.3 ± 2.3
MRT_{last} (h)	11.3 ± 3.0	8.1 ± 1.7	8.9 ± 2.2

† Except 2 subjects (V30101, V30603) who were not evaluable for the terminal phase with data at this time, AUC_{inf}, k_{el}, $t_{1/2}$, CL/F, and MRT_{inf} were calculated in 22 subjects.

Examination of the effect of food

Table 3 shows the geometric mean ratio of C_{max} and AUC_{last} after the 2 fed-state administrations (low- and high fat meals) to those after fasted-state administration and the 90% confidence interval (CI). The geometric mean ratio of C_{max} was 1.817 and 2.140 for low- and high fat meals, respectively, and likewise, AUC_{last} was 1.062 and 1.179, respectively. The effect of food on the pharmacokinetics of the unchanged FK949E concentration in plasma after FK949E administration was observed, because the 90%CIs did not fall within the range of 0.8-1.25 except for the AUC_{last} of low fat meal.

Table 3 Examination of the effect of food (primary variables)

Variable	Comparison	Geometric mean ratio †	90%CI Lower limit	90%CI Upper limit
C_{max}	Low fat meal vs. fasted	1.817	1.598	2.066
	High fat meal vs. fasted	2.140	1.882	2.434
AUC_{last}	Low fat meal vs. fasted	1.062	0.938	1.203
	High fat meal vs. fasted	1.179	1.041	1.336

† Administered after meal/Administered under fasted conditions, N=24 (MRT_{last}: N=24)

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Table 4 shows the geometric mean ratio (GMR) of pharmacokinetic parameters other than C_{max} and AUC_{last} after the 2 fed-state administrations (low- and high fat meals) to those after fasted-state administration and its 90% confidence interval (CI). The effect of food (low- and high fat meals) was also observed on $t_{1/2}$, MRT_{inf}, and MRT_{last}. On the other hand, 90%CIs of GMR of AUC_{inf} and CL/F were all within the range of 0.8-1.25 of those with low- and high fat meal conditions. As for t_{max}, Table 5 shows the rate of change after the 2 fed-state administrations (low- and high fat meals) to those after fasted-state administration and its 90%CI. Compared to the administration under fasted conditions, t_{max} was decreased approximately 35% and 25% under low- and high fat food conditions, respectively.

Table 4 Examination of the effect of food (secondary variables, other than t_{max})

Variable	Comparison	Geometric mean ratio	90%CI Lower limit	90%CI Upper limit
AUC_{inf}	Low fat meal vs. fasted	1.002	0.887	1.131
	High fat meal vs. fasted	1.106	0.980	1.249
$t_{1/2}$	Low fat meal vs. fasted	0.696	0.606	0.799
	High fat meal vs. fasted	0.731	0.637	0.840
CL/F	Low fat meal vs. fasted	0.998	0.884	1.127
	High fat meal vs. fasted	0.904	0.801	1.020
MRT_{inf}	Low fat meal vs. fasted	0.691	0.630	0.758
	High fat meal vs. fasted	0.748	0.681	0.820
MRT_{last}	Low fat meal vs. fasted	0.725	0.657	0.799
	High fat meal vs. fasted	0.794	0.720	0.876

Administered after meal/Administered under fasted conditions, N=22

Table 5 Examination of the effect of food (secondary variable, t_{max})

Variable	Comparison	Rate of change of least square mean	90%CI Lower limit	90%CI Upper limit
t_{max} †	(Low fat meal - fasted)/fasted	-0.354	-0.542	-0.166
	(High- fat meal - fasted)/fasted	-0.250	-0.438	-0.062

† Estimated difference of mean , N=24

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5. Safety:

Adverse events

A summary of the food conditions at the onset of adverse events is shown in Table 6 below.

Adverse events were observed in 6 of 24 subjects in total (25.0%); 3 events in 3 subjects (12.5%) under fasted conditions, 1 event in 1 subject (4.2%) after a low fat meal, and 2 events in 2 subjects (8.3%)after a high fat meal. Of these adverse events, 1 event (skin tear) that occurred under fasted conditions was considered as being not related to the study drug by the investigator, and other events were considered to be treatment-related. As for adverse events, all of the subjects who experienced events had only 1 event per subject, and none had multiple events under different administration conditions.

No deaths, other serious adverse events, or adverse events that led to discontinuation of the study were observed.

Table 6 Summary of adverse events

	Total	Fasted	Low fat meal	High fat meal
Safety analysis set	24	24	24	24
Adverse events	6/24 (25.0%)	3/24 (12.5%)	1/24 (4.2%)	2/24 (8.3%)
Adverse event considered to be treatment-related	5/24 (20.8%)	2/24 (8.3%)	1/24 (4.2%)	2/24 (8.3%)
Deaths	0	0	0	0
Serious adverse events	0	0	0	0
Adverse events leading to study discontinuation	0	0	0	0

N (incidence)

The incidences of adverse events are shown in Table 7. The most commonly observed adverse event was somnolence in 3 subjects in total; 2 subjects under fasted conditions and in 1 after a low fat meal. Other events observed were; skin tear in 1 subject under fasted conditions, and 1 subject each of feeling abnormal and gamma-glutamyltransferase increased after a high fat meal. The severity of adverse events were either mild (4 subjects) or moderate (2 subjects), and recovered with or without appropriate procedures. None were serious. Of 2 moderate events, an event of skin tear was considered an incidental injury and considered as being not related to the study drug. The other event was feeling abnormal, complaining of a bad feeling, that recovered

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15 minutes after the onset without any treatment. In the subject who experienced gamma-glutamyltransferase increased, no abnormal values were observed in other liver function variables.

Table 7 The incidences of adverse events

System Organ Class/Preferred Term †	Total	Fasted	Low fat meal	High fat meal
General disorders and administration site conditions	1(4.2%)	0	0	1(4.2%)
Feeling abnormal	1(4.2%)	0	0	1(4.2%)
Injury, poisoning, and procedural complications	1(4.2%)	1(4.2%)	0	0
Skin tear	1(4.2%)	1(4.2%)	0	0
Investigations	1(4.2%)	0	0	1(4.2%)
Gamma-glutamyltransferase increased	1(4.2%)	0	0	1(4.2%)
Nervous system disorders	3(12.5%)	2(8.3%)	1(4.2%)	0
Somnolence	3(12.5%)	2(8.3%)	1(4.2%)	0

N (incidence), † MedDRA ver. 12.0

Clinical laboratory evaluations

In hematology and biochemistry, total bilirubin and creatine kinase present changes exceeding 20% in mean 48 hours postdose values from those on the day preceding the day of administration. The mean total bilirubin was increased by 35.8% under fasted conditions, 27.9% after a low fat meal, and 22.5% after a high fat meal compared to those on the day preceding the day of administration. Mean creatine kinase was decreased by 26.9%, 26.2%, and 22.5%, under fasted conditions, after a low fat meal, and after a high fat meal, respectively, compared to those on the day preceding the day of administration. However, based on the investigator's evaluation, no subjects with abnormal changes in total bilirubin and creatine kinase were found. For other clinical laboratory data, no major changes between baseline and post-administration were observed; no clinically critical findings were recognized in clinical laboratory data in this clinical study.

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Vital signs and Electrocardiograms

The mean values of systolic and diastolic blood pressure showed a tendency to decrease after administration. Mean values at 6 hours postdose were the lowest, at 7.1%, 9.5%, and 9.7% decrease for systolic blood pressure under fasted conditions, after a low fat meal, and after a high fat meal, respectively, compared to those on the day preceding the day of administration; mean diastolic blood pressure values were decreased at 16.5%, 19.7%, and 19.9%, under fasted conditions, after a low fat meal, and after a high fat meal, respectively. Then, at 48 hours postdose, both systolic and diastolic blood pressure had recovered to the same levels as those observed on the day preceding the day of administration; there were no subjects who were determined to have had abnormal changes based on the investigator's evaluation. The time point showing the largest decrease in blood pressure (6 hours postdose) was almost the same timing as t_{max} under each administration condition (5.2-8.0 h). No definitive tendencies in the mean change of pulse rate and of body temperature were observed. As for 12-Lead ECG, there were no abnormal findings either before or after administration.

Conclusions:

In order to evaluate the effect of food on the pharmacokinetics of FK949E, the pharmacokinetics of unchanged FK949E concentration in plasma after administration of 50 mg of FK949E orally under fasted conditions or after a meal (low- and high fat food) in healthy non-elderly adult male subjects using a 3-treatment, 6-sequence, 3-period crossover design were examined.

The effect of food on the pharmacokinetics of the unchanged FK949E concentration in plasma after oral administration of 50 mg of FK949E was observed. Both C_{max} and AUC_{last} showed the highest values after a high fat meal compared to administration under fasted conditions, followed by low fat meal. Except for AUC_{last} after a low fat meal, the 90%CIs of geometric mean ratio did not fall within the range of 0.8-1.25. The effect of food (low- and high fat meals) was also observed on $t_{1/2}$, MRT_{inf}, and MRT_{last}. On the other hand, 90%CIs of GMR of AUC_{inf} and CL/F were all within a range of 0.8-1.25 of those under low- and high fat meal conditions. In addition, compared to administration under fasted conditions, t_{max} was approximately 35% and 25% decreased after low- and high fat meals, respectively.

Adverse events were observed in 6 of 24 subjects in total (25.0%); 3 events in 3 subjects (12.5%) under fasted conditions, 1 event in 1 subject (4.2%) after a low fat meal, and 2 events in 2 subjects (8.3%)after a high fat meal. Of these adverse events, 1 event (skin tear) that

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)		

occurred under fasted conditions was considered as being not related to the study drug by the investigator, and other events were considered to be treatment-related. The most commonly observed adverse event was somnolence in 3 subjects in total; 2 subjects under fasted conditions and in 1 after a low fat meal. Other events observed were; skin tear in 1 subject under fasted conditions, and 1 subject each of feeling abnormal and gamma-glutamyltransferase increased after a high fat meal. The severity of adverse events were either mild (4 subjects) or moderate (2 subjects), and recovered with or without appropriate procedures. No deaths, other serious adverse events, or adverse events that led to discontinuation of the study were observed.

As for mean value of clinical laboratory data, increased total bilirubin and decreased creatine kinase were recognized. Regarding vital signs, mean systolic and diastolic blood pressure showed a tendency to decrease after starting administration with the lowest values at 6 hours postdose. However, at 48 hours postdose, both had recovered to the same levels as those observed on the day preceding the day of administration. There were no subjects who were determined to have abnormal changes based on the investigator's evaluation. Decreased blood pressure is a distinctive change observed in foreign clinical studies of existing quetiapine pharmaceuticals, but orthostatic hypotension associated with clinically relevant findings was not identified in this clinical study.

Adverse events recognized in the study were not different from the safety profile observed in foreign clinical studies of existing quetiapine pharmaceuticals except for the event considered as being not related to the study drug (skin tear), and was determined as an incidental injury. Consequently, no major problems were observed in terms of the safety.

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Pharmacokinetic Study of FK949E

-A Pharmacokinetic Study in Healthy Male Volunteers to Investigate the Effect of Food on the Pharmacokinetics of FK949E-

Clinical Study Report

Synopsis

Amendment

Sponsor: Astellas Pharma Inc.

Amendment

Page	Item	Was	Is Amended To	Rationale
18	Conclusions	Regarding vital signs, mean systolic and diastolic blood pressure showed a tendency to decrease after starting administration with the lowest values at 6 hours postdose. However, at 48 hours postdose, both had recovered to the same levels as those observed on the day preceding the day of administration. There were no subjects who were determined to have abnormal changes based on the investigator's evaluation. Decreased blood pressure is a distinctive change observed in foreign clinical studies of existing quetiapine pharmaceuticals, but orthostatic hypotension associated with clinically relevant findings was not identified in this clinical study.	Regarding vital signs, mean systolic and diastolic blood pressure showed a tendency to decrease after starting administration with the lowest values at 6 hours postdose. However, at 48 hours postdose, both had recovered to the same levels as those observed on the day preceding the day of administration. There were no subjects who were determined to have abnormal changes based on the investigator's evaluation. Decreased blood pressure is a distinctive change observed in foreign clinical studies of existing quetiapine pharmaceuticals.	In this study, orthostatic blood pressure change was not observed. Therefore, it is unable to make clear evaluations on orthostatic hypotension.