Synopsis

Sponsor: Janssen Pharmaceutical K.K.	Summary table of each study Relevant place in application dossiers Volume number: Page:	(For official use)
Brand name: Itrizole ® Oral Solution 1%		
Active Ingredient: Itraconazole		

Study Title:
A pharmacokinetic study of JK1211 in patients with systemic fungal infection (SFI) and patients with febrile neutropenia (FN) suspected of fungal infection.

Investigators:
A total of 10 investigators including Yasuhiro Yamazaki (see Appendix 16.1.4).

Investigator Sites:
A total of 10 investigator sites including Dohoku Hospital (see Appendix 16.1.4).

Published papers:
None

Study Period:	Clinical phase:
January 24, 2008 (Date of informed consent obtained from the first subject) May 8, 2009 (Date of the last observation in the last subject)	III
	Study type: Pharmacokinetic study

Objectives:
Primary objectives: To determine plasma drug concentrations in patients with systemic fungal infection (SFI) and patients with febrile neutropenia (FN) suspected of fungal infection to assess the pharmacokinetics of JK1211.
Secondary objectives: To assess the efficacy and safety of JK1211 in patients with SFI and patients with FN suspected of fungal infection.

Study methods:
This study was planned as a multicenter, open-label uncontrolled study. After obtaining informed consent from patients with SFI or patients with FN suspected of fungal infection, the subjects whose eligibility was confirmed in examinations and surveys during the screening period were registered at the Subject Registration Center, and then, treatment with the investigational product was started. The subjects with SFI were given "JK1211 alone" or "a switch treatment from ITCZ-IV to JK1211" according to the pathologic conditions at the discretion of the investigator or subinvestigator, and subjects with FN suspected of fungal infection were given "a switch treatment from ITCZ-IV to JK1211".
The SFI patients registered in JK1211 single-agent treatment were orally given JK1211 20 mL (ITCZ 200 mg) once daily in fasting conditions before breakfast. The dose of JK1211 could be increased or reduced in the range from 20 to 40 mL daily (20 mL, 30 mL or 40 mL) at the discretion of the investigator or subinvestigator. In the case of 30 mL per day, 15 mL was orally given to subjects in fasting conditions twice daily, before breakfast and before supper. In the case of 40 mL per day, 20 mL was orally given to subjects in fasting conditions in the same manner.
The SFI patients or FN patients suspected of fungal infection who were registered in "a switch treatment from ITCZ-IV to JK1211" received ITCZ-IV 200 mg twice daily for 2 days, followed by 200 mg intravenous infusion once daily for 1 to 12 days. In ITCZ-IV treatment, intravenous infusion was given to the subjects over 1 hour using a special filter set. Subsequently, as a switch treatment, JK1211 20 mL was orally given to the subjects in fasting conditions twice daily, before breakfast and before supper. The dose of JK1211 could be increased or reduced in the range from 20 to 40 mL daily (20 mL, 30 mL or 40 mL) at the discretion of the investigator or subinvestigator, in the same manner as JK1211 single-agent treatment.
Regarding the duration of treatment, JK1211 was administered to all the registered subjects for at least 7 days irrespective of the diagnostic category, in principle, and could be administered for up to 12 weeks (85 days). During the JK1211 treatment period, FN patients suspected of fungal infection were hospitalized, but SFI patients were allowed to receive treatment on the outpatient basis. During the ITCZ-IV treatment, subjects received treatment on the inpatient basis, irrespective of the diagnostic category.

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Number of subjects (planned and analyzed):
Planned:
Target number of subjects: 50 (as subjects for JK1211 treatment)
- ≥20 subjects with SFI
- ≥20 subjects with febrile neutropenia suspected of fungal infection

Of the target number of subjects, the number of subjects assessed for pharmacokinetics: 40
- 20 subjects with SFI
- 20 subjects with febrile neutropenia suspected of fungal infection

Analyzed:
Number of registered subjects: 55
- 32 subjects with SFI
- 23 subjects with FN suspected of fungal infection

Pharmacokinetic analysis set: 51 subjects
- 29 subjects with SFI
- 22 subjects with FN suspected of fungal infection

Full analysis set (FAS): 53 subjects
- 31 subjects with SFI
- 22 subjects with FN suspected of fungal infection

Safety population (SP): 55 subjects
- 32 subjects with SFI
- 23 subjects with FN suspected of fungal infection

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Diagnosis and Inclusion Criteria:

[Systemic fungal infection (SFI)]

1. Patients who are at least 18 years of age and younger than 80 years of age at the time of informed consent.
2. Patients who meet either of the following in the examination or diagnosis prior to the start of investigational treatment.

· Clinically suspected case: Patients whose fungal infection is clinically suspected from clinical symptoms, routine laboratory examination findings, auxiliary diagnosis (diagnostic imaging, serodiagnosis, genetic diagnosis) and risk factors (see "Diagnostic Criteria for Systemic Fungal Infection [Appendix 16.1.1, Protocol, Appendix 2)"])

· Proven case: Patients whose pathogenic fungus is proved in mycological examinations (direct microscopy, histopathological examination, culture test) (see "Diagnostic Criteria for Systemic Fungal Infection [Appendix 16.1.1, Protocol, Appendix 2)"])

3. Both inpatients and outpatients are acceptable. However, all subjects had to be hospitalized during the ITCZ-IV treatment period.
4. Prior to the study, patients who have given his/her own consent or his/her representative's consent to participate in the study in writing after being given a sufficient explanation about the investigational product and this study. For minors who can give their own consent, the patient's own consent and his/her representative's consent in writing were to be obtained.

[Febrile neutropenia suspected (FN) of fungal infection]

1. Patients who are at least 18 years of age and younger than 80 years of age at the time of informed consent.
2. Patients who met the following two conditions in pretreatment examinations.

· Fever persisting for ≥3 days which is refractory to broad-spectrum antimicrobial agents (axillary temperature ≥37.5 °C, use of broad-spectrum antimicrobial agent ≥3 days)

· If neutrophil count is less than 500/mm^3, or it is less than 1,000/mm^3 and is expected to decrease to less than 500/mm^3.

3. Inpatients
4. Prior to the study, patients who have given his/her own consent or his/her representative's consent to participate in the study in writing after being given a sufficient explanation about the investigational product and this study. For minors who can give their own consent, the patient's own consent and his/her representative's consent in writing were to be obtained.

Investigational Product, Dosage and Treatment Methods, Lot Number:

1. ITCZ oral solution (JK1211)

Investigational product and lot number: A syrup product containing ITCZ 10 mg per mL (lot numbers: 61B4600, 8CB2Z00)

Dosage and treatment methods:

In JK1211 single-agent treatment, JK1211 20 mL (ITCZ 200 mg) was orally given once daily, and in a switch treatment from ITCZ-IV to JK1211, JK1211 20 mL was orally given twice daily. The dosage of JK1211 could be increased or reduced in the range from 20 mL to 40 mL daily (20 mL, 30 mL or 40 mL) at the discretion of the investigator or subinvestigator. In the case of 20 mL/day, 20 mL was orally given to the subjects in fasting conditions before breakfast. In the case of 30 mL/day, 15 mL was orally given to the subjects in fasting conditions twice daily before breakfast and before supper, and in the case of 40 mL/day, 20 mL was orally given in the same manner.

2. ITCZ injection (ITCZ-IV)

Investigational product and lot number: An injection containing ITCZ 10 mg per mL (lot number: 6KB3600)

Dosage and treatment methods:

ITCZ-IV 200 mg was administered twice daily for 2 days, followed by 200 mg once daily for 1-12 days by intravenous infusion over 1 hour using a special filter set.

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Study period:
[Screening period]
The duration from obtaining informed consent to the start of investigational treatment. The duration to confirm the subject's eligibility was to be for up to 7 days prior to the start of investigational treatment.
[Treatment period]
1. Systemic fungal infection (SFI)
· JK1211 single-agent treatment: for up to 85 days
· Switch treatment from ITCZ-IV to JK1211:
For up to 99 days (ITCZ-IV+JK1211). Of the duration, the ITCZ-IV treatment period was for 3-14 days, and the JK1211 treatment period was for up to 85 days.
2. Febrile neutropenia (FN) suspected of fungal infection
· Switch treatment from ITCZ-IV to JK1211:
For up to 99 days (ITCZ-IV+JK1211). Of the duration, the ITCZ-IV treatment period was for 3-14 days, and the JK1211 treatment period was for up to 85 days.
[Follow-up period]
For 30 days after the end of investigational treatment

Evaluation criteria:
Pharmacokinetics (primary endpoint):
1. Descriptive statistics of plasma drug concentrations of ITCZ and hydroxy-itraconazole (OH-ITCZ)
2. Evaluation of pharmacokinetic parameters of ITCZ
3. Assessment of the relationship of pharmacokinetic parameters of ITCZ with the efficacy and safety.
Efficacy (secondary endpoints):
1. Improvement of clinical symptoms
2. Mycological effects
3. Serologic effect on fungi
4. Improvement in endoscopy and diagnostic imaging
5. Overall response
Safety:
1. Subjective symptoms and objective findings
2. Blood pressure and pulse rate
3. ECG examination
4. Laboratory examinations (hematology, blood chemistry, urinalysis)
5. Ccr

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Statistical methods:
Demographic data and other baseline characteristics:
In FAS, demographic data and other baseline characteristics were totaled overall and by subject disease (systemic fungal infection and febrile neutropenia suspected of fungal infection).
For continuous data, descriptive statistics (number of subjects, mean, standard deviation, minimum, median, maximum) were calculated, and for categorical data, the frequency tabulation was conducted.
Pharmacokinetics:
In pharmacokinetic analysis set, descriptive statistics of plasma drug concentrations [plasma ITCZ and OH-ITCZ concentrations] were calculated for each blood sampling time. As an assessment of pharmacokinetic parameters, a population pharmacokinetic analysis was conducted using measurement values of plasma ITCZ concentration obtained at each blood sampling time to calculate pharmacokinetic parameters of plasma ITCZ in each subject by Bayes procedures. Descriptive statistics of pharmacokinetic parameters of plasma ITCZ were calculated for each subject. In addition, the relationship of plasma ITCZ and OH-ITCZ concentrations or pharmacokinetic parameters with the efficacy and safety in each subject was assessed.
Efficacy:
FAS was used as a main analysis set for efficacy, and the following analyses were conducted in the whole analysis set and by subject disease. For the overall response, the treatment success rate at the end (or discontinuation) of investigational treatment and the efficacy rate, and the 95% confidence intervals were calculated. For the improvement of clinical symptoms, mycological effect, serologic effect on fungi, and improvement of endoscopy and diagnostic imaging, the composition by assessment result over time was calculated. For the improvement of clinical symptoms and serologic effect on fungi, changes in measurement value over time were calculated.
In addition, for overall response examined totally and by subject disease, a subgroup analysis of factors, etc. that may affect the therapeutic effect was conducted.
Safety:
In SP, the following analysis for the whole analysis set and by therapy (switch treatment from ITCZ-IV to JK1211, and JK1211 single-agent treatment) were conducted. In addition, for subjects given a switch treatment from ITCZ-IV to JK1211, another analysis was also conducted by dividing the treatment period into the ITCZ-IV treatment period and JK1211 treatment period.
For adverse events and adverse reactions, the number of events, the number of subjects with events and the incidence were calculated and totaled for the seriousness, severity, outcome and causal relationship with the investigational product, respectively. For quantitative laboratory examination items (hematology, blood chemistry, urinalysis), Ccr, blood pressure (systolic/diastolic), pulse rate and ECG examination, descriptive statistics of the test value in each test time and the difference from baseline were calculated. For “deviation from baseline” in quantitative laboratory test values, deviations from the reference value of each test value or those from the threshold value specified in the statistical analysis plan were totaled. As for a qualitative laboratory test item (urinalysis), the difference from baseline in each test time was totaled as a shift table.

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Summary – Conclusion

Pharmacokinetic results:

From 51 subjects in the pharmacokinetic analysis set (29 SFI patients, 22 FN patients), measurement values of plasma ITCZ and OH-ITCZ concentrations were obtained. In SFI patients given JK1211 alone, 400 mg/day was administered to only 1 subject, and it was not possible to assess the relationship of the dosage with plasma ITCZ and OH-ITCZ concentrations and pharmacokinetic parameters. In SFI patients given a switch treatment and FN patients given a switch treatment, ITCZ-IV 400 mg/day was administered for 2 days followed by 200 mg/day for 1-12 days. Subsequently, the treatment was switched to repeated oral dose treatment with JK1211 200, 300 or 400 mg/day. Plasma ITCZ and OH-ITCZ concentrations after switching to JK1211 200 mg/day showed almost constant concentration changes, whereas the concentrations in 300 mg/day and 400 mg/day treatments showed changes at higher levels than in the switch treatment. This suggests that plasma ITCZ and OH-ITCZ concentrations after ITCZ-IV treatment are considered to be maintainable at the dose of 200 mg/day in the switch treatment to JK1211.

The population pharmacokinetic analysis was conducted using combined data of plasma ITCZ concentration obtained from this study and Japanese phase 1 studies of JK1211 (JK1211-1 study and JK1211-2 study). As a result, Ccr, ALT, total bilirubin and albumin were identified as significant covariates on bioavailability, the distribution volume of central compartment, the maximum metabolic rate, and Michaelis constant for the metabolism enzyme of ITCZ, respectively. Therefore it was suggested to significantly affect the pharmacokinetics of ITCZ by changes in hepatic function.

The relationship of pharmacokinetic parameters of plasma ITCZ (C_{max}, AUC_{24}, C_{max}/MIC, AUC_{24}/MIC and T>MIC) with the efficacy and safety in each subject was examined, and as a result, C_{max} and AUC_{24} did not show a relationship with the efficacy and safety in any therapy. Although the number of examined subjects was small – 9 subjects, C_{max}/MIC, AUC_{24}/MIC and T>MIC did not show a relationship with the efficacy and safety.

Efficacy results:

[Results in systemic fungal infection (SFI) patients]

In the overall response evaluated by the Efficacy and Safety Monitoring Committee (central judgment), the treatment success rate [effective cases / (effective cases + ineffective cases + unevaluable cases) ×100] was 58.1% (18/31), and the effective rate [effective cases / (effective cases + ineffective cases) ×100] was 62.1% (18/29). The success rates by diagnostic name were 100% (1/1) in candidaemia, 100% (3/3) in oesophageal candidiasis, 62.5% (5/8) in chronic necrotic pulmonary aspergillosis, 60.0% (3/5) in invasive (bronchopulmonary) aspergillosis, 50.0% (2/4) in pulmonary cryptococcosis, and 40.0% (4/10) in pulmonary aspergilloma. The efficacy rates by diagnostic name were 100% (1/1) in candidaemia, 100% (3/3) in oesophageal candidiasis, 62.5% (5/8) in chronic necrotic pulmonary aspergillosis, 60.0% (3/5) in invasive aspergillosis, 50.0% (2/4) in pulmonary cryptococcosis, and 50.0% (4/8) in pulmonary aspergilloma.

The subjects assessed as “Resolved” and “Improved” in the clinical symptom improvement (central evaluation) were 7/31 subjects (22.6%) and 12/31 subjects (38.7%), respectively, and the improvement was confirmed in more than a half subjects including “Resolved” and “Improved”. Changes in CRP (mean ±standard deviation) at baseline and at the end (or discontinuation) of treatment were 4.20 ±6.21 mg/dL and 2.64±5.18 mg/dL, respectively, and showed lower values at the end of treatment compared with baseline.

Although the serologic effect on fungi (central evaluation) was evaluated as “Negative” in only 1 subject; those evaluated as “Eradication” in the mycological effect (central evaluation) were 6 subjects (pulmonary aspergilloma in 3 subjects, and oesophageal candidiasis, chronic necrotic pulmonary aspergillosis, and pulmonary cryptococcosis in 1 subject each); and in the improvement of endoscopy/diagnostic imaging (central evaluation), those evaluated as “Resolved” were 3 subjects (all of whom had oesophageal candidiasis) and those evaluated as “Improved” were 12 subjects (invasive aspergillosis, chronic necrotic pulmonary aspergillosis, pulmonary aspergilloma, and pulmonary cryptococcosis 3 subjects each).

In the above items for which the central evaluation was conducted, the results of physician’s evaluation did not show a marked difference from the results of the central evaluation.

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[Results in systemic fungal infection (SFI) patients (continued)]
Changes of the proportion of subjects with "Fever present" at baseline, at the end of ITCZ-IV treatment, at 1 week after JK1211 treatment, and at the end (or discontinuation) of treatment were 38.7% (12/31), 23.1% (3/13), 18.5% (5/27), and 35.5% (11/31), respectively. The proportion of subjects who had fever at baseline was low and the proportions of "Fever present" at baseline and at the end of treatment were almost the same, but the proportion of "Fever present" during the ITCZ-IV or JK1211 treatment period was low compared with before and after treatment.
Regarding mycological effects of ITCZ against *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger* and *Cryptococcus neoformans* which were detected as pathogenic fungi, MICs were in the range from 0.06 to 1 μg/mL in "Eradication" cases and 1 μg/mL in "Persistence" cases. MICs of OH-ITCZ in "Eradication" cases were in the range from 0.12 to 1 μg/mL and 1 μg/mL in "Persistence" cases. Neither ITCZ nor OH-ITCZ showed a significant difference in MIC between the "Eradication" cases and "Persistence" cases.
The efficacy in FAS and the evaluable set (ES) showed no significant difference due to the analysis set.
In the overall effect by treatment (central evaluation) in the subgroup analysis, the treatment success rates in SFI patients given JK1211 alone and a switch treatment (except for those treated with ITCZ-IV only) were 66.7% (10/15) and 61.5% (8/13), respectively, and the effective rates were 76.9% (10/13) and 61.5% (8/13), respectively, and 3 subjects treated with ITCZ-IV only were ineffective. In the effective rates in SFI patients by treatment, the rate was slightly higher in SFI patients given JK1211 alone compared with a switch treatment (except for those treated with ITCZ-IV only), but there was no difference in the treatment success rate and almost the same results were obtained.
In the other subgroup analyses, the subgroup that showed a ≥20% difference in the treatment success rate or effective rate among subgroups of ≥10 subjects was age. The effective rate (central evaluation) was higher, 75.0% (9/12) in < 65 years of age, as compared with 52.9% (9/17) in ≥65 years of age.

[Results in febrile neutropenia (FN) patients suspected of fungal infection]
In the overall effect, the treatment success rate (central evaluation) was 72.7% (16/22) and the effective rate was 80.0% (16/20).
The subjects whose improvement in clinical symptoms (central evaluation) were evaluated as "Resolved" and "Improved" were 6/22 (27.3%) and 12/22 (54.5%), respectively, and the improvement was confirmed in more than 80% subjects including "Resolved" and "Improved". Body temperature values (mean ±standard deviation) at baseline and at the end (or discontinuation) of treatment were 38.19 ±0.75 °C and 37.19 ±0.76 °C, respectively, and showed lower values at the end of treatment compared with baseline. CRP values (mean ±standard deviation) at baseline and at the end (or discontinuation) of treatment were 7.42±5.78 mg/dL and 3.48±6.52 mg/dL, respectively, and showed lower values at the end of treatment compared with baseline.
In the mycological effect (central evaluation), improvement in endoscopy / diagnostic imaging (central evaluation) and serologic effect on fungi (central evaluation), the pathologic condition of FN was unknown in terms of the specific fungus or infection focus, and the assessment items were evaluated as "Unevaluable" in most subjects.
In the above items for which the central evaluation was conducted, the results of physician's evaluation showed no significant difference from the results in the central evaluation.
Changes in the proportion of subjects with "Fever present" at baseline, at the end of ITCZ-IV treatment, at 1 week after JK1211 treatment, and at the end (or discontinuation) of treatment were 95.5% (21/22), 77.3% (17/22), 57.1% (12/21), and 59.1% (13/22), respectively, and the temperature had decreased to < 37.0 °C in about 40% of the subjects at the end of treatment.
The efficacy results in FAS and ES showed no significant difference due to the analysis set.

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[Results in febrile neutropenia (FN) patients suspected of fungal infection (continued)]
In the overall effect (central evaluation) in subgroup analyses, the treatment success rate in subjects given a switch treatment (except for those treated with ITCZ-IV only) was 76.2% (16/21) and the effective rate was 84.2% (16/19), and 1 subjects treated with ITCZ-IV only was ineffective.
The other subgroup analyses suggested that the subgroup showing a ≥20% difference in the treatment success rate or effective rate among subgroups of ≥10 subjects evaluable was the most frequently used dosage of JK1211, and the treatment success rate (central evaluation) was high, 90% (9/10) at 400 mg/day, compared with 63.6% (7/11) at the most frequently used dosage of JK1211 – 200 mg/day.

From the above, the efficacy of JK1211 (200-400 mg/day) in the treatment of systemic fungal infection and febrile neutropenia suspected of fungal infection was confirmed.

Safety results:
The adverse events observed in this study were 402 events in 54/55 subjects (98.2%). The adverse events by therapy were 110 events in 16/16 (100%) in SFI patients given JK1211 alone, 118 events in 16/16 (100%) in SFI patients given a switch treatment, and 174 events in 22/23 (95.7%) in FN patients given a switch treatment. The number of subjects with adverse reactions and the incidence were the same as those in the adverse events. The number of adverse reactions was 283 events in total, 78 events in SFI patients given JK1211 alone, 93 events in SFI patients given a switch treatment, and 112 events in FN patients given a switch treatment.
The adverse events that occurred with a frequency of ≥20% were diarrhoea in 24/55 (43.6%), hypokalaemia in 21/55 (38.2%), liver disorder and urine beta 2 microglobulin in urine increased in 19/55 (34.5%) each, and beta-N-acetyl-D-glucosaminidase increased in 11/55 (20.0%), and most of the events were adverse reactions, defined as doubtfully, possibly, probably or very likely related to the study drug.
The adverse events evaluated as severe in severity were 18 events in 16/55 (29.1%) in total. The severe events by therapy were 4 events in 4/16 (25.0%) in SFI patients given JK1211 alone, 5 events in 4/16 (25.0%) in SFI patients given a switch treatment, and 9 events in 8/23 (34.8%) in FN patients given a switch treatment. Of the events, severe adverse reactions were 5 events in 5/55 (9.1%) in total. The severe adverse reactions by therapy were 2 events in 2/16 (12.5%) in SFI patients given JK1211 alone, 2 events in 2/16 (12.5%) in SFI patients given a switch treatment, and 1 event in 1/23 (4.3%) in FN patients given a switch treatment.
In the adverse events by onset time, the number of events was large “at 1 week” in all the following treatment groups: SFI patients given JK1211 alone and a switch treatment, and FN patients given a switch treatment. The adverse events with a frequency of ≥20% “at 1 week” were diarrhea in the SFI patients given JK1211 alone and a switch treatment, and malnutrition, liver disorder, hypokalaemia, and pancytopenia in FN patients given a switch treatment. “At 2 weeks” or later, alpha 1 microglobulin in urine increased was seen “at 12 weeks” in SFI patients given a switch treatment, and there were no other adverse events with a frequency of ≥20%. The incidence of adverse events did not show a tendency to increase with the passage of treatment period. The adverse reaction that occurred “at 12 weeks or later” was conjunctival oedema only in 1 SFI patient given a switch treatment.
In the adverse events by treatment period, the incidences of hypokalaemia, diarrhea, beta 2 microglobulin in urine increased and blood triglycerides increased were high in SFI patients and FN patients given a switch treatment in the JK1211 treatment period compared with the ITCZ-IV treatment period.
The incidences of adverse events by gender, age, and body weight were 96.4-100% in total. The incidences by therapy were 100% in SFI patients given JK1211 alone and a switch treatment, respectively, and 93.3-100% in FN patients given a switch treatment. There was no difference of the incidence in any therapy among the subject characteristics. In the incidences by event, although there were some adverse events with a ≥15% difference in the incidence, there were no significant differences in the number of subjects with events, except for rash by gender [males 7/39 (17.9%), females 0/16 (0%)] and renal disorder by body weight [< 45 kg 0/11 (0%), ≥45 kg 8/44 (18.2%)] because the number of subjects evaluated for each subject characteristic was small.

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Safety results (continued):

There were a total of 5 fatal cases: 3 SFI patients given a switch treatment and 2 FN patients given a switch treatment. The causal relationship with the investigational product was ruled out in all of them, except 1 patient with pneumonia aspiration. The pneumonia aspiration (Subject Number SFI-06) was assessed as possibly related to oral solution form, not phramacological effect of itraconazole.

With regard to serious adverse events (SAE) including deaths, 15 SAEs occurred in 15/55 subjects (27.3%) in total. SAEs by therapy were 4 events in 4/16 SFI patients given JK1211 alone (25.0%), 8 events in 8/16 SFI patients given a switch treatment (50.0%), and 3 events in 3/23 FN patients given a switch treatment (13.0%). The other SAEs except death were 10 events in 10 subjects in total. The other SAEs by therapy were 4 events in 4 SFI patients given JK1211 alone, 5 events in 5 SFI patients given a switch treatment, and 1 event in 1 FN patients given a switch treatment. Of the other SAEs except death, all the events were recovered in 8-121 days from the onset by discontinuation of investigational treatment or a special treatment such as hospital care for drug therapy, except for 2 patients whose observation was completed with an outcome of "Not recovered".

The adverse events leading to discontinuation of investigational treatment were 23 events in 20/55 subjects (36.4%) in total. The adverse events by therapy were 8 events in 6/16 SFI patients given JK1211 alone (37.5%), 11 events in 10/16 SFI patients given a switch treatment (62.5%), and 4 events in 4/23 FN patients given a switch treatment (17.4%). Except for SAEs including death, the adverse events leading to discontinuation of investigational treatment were recovered in 3-113 days from the onset by discontinuation of investigational treatment or a special treatment, or without any treatment, with the exception of right ventricular failure and liver disorder with an outcome of "Not recovered".

The other significant adverse events were 166 events in 52/55 subjects (94.5%) in total. Such events by therapy were 50 events in 16/16 SFI patients given JK1211 alone (100.0%), 55 events in 15/16 SFI patients given a switch treatment (93.8%), and 61 events in 21/23 FN patients given a switch treatment (91.3%). Of the other significant adverse events, congestive heart failure and liver disorder, which are described as significant adverse reactions in the package insert of Itrizole® Oral Solution 1%, were observed in this study. Hypokalaemia and diarrhoea (probably induced by an additive of the product, HP-β-CD, as well as itraconazole) were frequently observed, but all of the events were recovered in 1-155 days by a special treatment or discontinuation of investigational treatment, or without any treatment, except for 1 subject with hypokalaemia whose outcome was "Not recovered".

There were no abnormal changes in laboratory data that were considered to be serious. The adverse event leading to discontinuation of investigational treatment due to abnormal changes in laboratory data was protein urine present in 1 subject, which was mild in severity and assessed as an adverse reaction. In vital signs, blood pressure increased and weight increased were observed in 1 FN patient given a switch treatment each. All the events were mild and assessed as adverse reactions. In electrocardiograms (ECG), electrocardiogram abnormal was observed in 1 SFI patient given JK1211 alone. The severity was mild and the causal relationship with the investigational product was assessed as "Doubtful".

In SFI patients given JK1211 alone and a switch treatment, no differences in the incidence of adverse events and the number of events were observed overall. Of adverse events that occurred in either SFI patients given JK1211 alone or a switch treatment with a frequency of ≥20%, the adverse events that showed a higher incidence in SFI patients given JK1211 alone compared with SFI patients given a switch treatment were renal disorder [JK1211 alone 25.0% (4/16), a switch treatment 12.5% (2/16)], β-N-acetyl-D-glucosaminidase increased [25.0% (4/16), 12.5% (2/16)], and C-reactive protein increased [25.0% (4/16), 6.3% (1/16)]. The adverse events that showed a higher incidence in SFI patients given a switch treatment compared with SFI patients given JK1211 alone were hypokalaemia [18.8% (3/16), 37.5% (6/16)] and oedema [0% (0/16), 25.0% (4/16)]. The incidences of severe adverse events in SFI patients given JK1211 alone and a switch treatment were similar, 25.0% (4/16), respectively. The incidences of SAE and adverse events leading to discontinuation of investigational treatment were higher in SFI patients given a switch treatment compared with SFI patients given JK1211 alone, but the difference in the number of events between them was 3-4 in any event.

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Active Ingredient: Itraconazole		

Safety results (continued):
As stated above, SFI patients and FN patients whose prognosis was poor were enrolled as subjects in this study. Although serious adverse events including death occurred in 15 subjects, the causal relationship with the investigational product could be ruled out in 8/15 subjects. Among the fatal cases, there was 1 subject with pneumonia aspiration of which the causal relationship with the investigational product could not be ruled out, but the relationship of the event with the pharmacological effect was ruled out. As for safety, there was no significant difference between the JK1211 alone treatment and the switch treatment from ITCZ-IV to JK1211.

Conclusion:
The pharmacokinetics of JK1211, the efficacy and safety in patients with systemic fungal infection and patients with febrile neutropenia suspected of fungal infection were assessed in this study.
As a result of the assessment of pharmacokinetic parameters of plasma ITCZ and the efficacy and safety in treatment with JK1211 200-400 mg/day, no relationship was observed in any pharmacokinetic parameter.
The JK1211 alone treatment or the switch treatment from ITCZ-IV to JK1211 was considered to be effective for the treatment of systemic fungal infection (58.1%), and the switch treatment from ITCZ-IV to JK1211 was considered to be effective for the treatment of febrile neutropenia suspected of fungal infection (72.7%).
Serious adverse events including death were observed in 15 patients in this study, but the causal relationship with the investigational product could be ruled out in a half of them – 8/15 patients (53.3%).

Based on the above, the JK1211 alone treatment and the switch treatment from ITCZ-IV to JK1211 will become a clinically useful therapy for patients with systemic fungal infection and patients with febrile neutropenia suspected of fungal infection by considering the risk-benefit ratio for each patient, by closely monitoring the patient's condition in the use of JK1211, and by giving an appropriate treatment as needed.