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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Diflucan®/Fluconazole

PROTOCOL NO.: A0561023

PROTOCOL TITLE: A multicenter open-label non-comparative study of fluconazole for the treatment of vulvovaginal candidiasis

Study Center(s): 10 centers in Japan

Study Initiation Date and Primary Completion or Final Completion Dates: 05 March 2013 and 22 November 2013
Phase of Development: Phase 3

Study Objective(s): Primary objective: To confirm the efficacy and safety of single oral administration of fluconazole 150 mg for the treatment of vulvovaginal candidiasis in Japanese patients.

Secondary objective: To measure the concentration of fluconazole in plasma and vaginal discharge in Japanese patients following single oral administration of fluconazole 150 mg and evaluate the drug disposition in Japanese patients.

METHODS

Study Design: This study was conducted as a multicenter, open-label, non-comparative study (Phase 3 study) in Japan. Three fluconazole 50 mg capsules were orally administered only once on the first day of the treatment of vulvovaginal candidiasis. Evaluation time points were as follows: Day 1 (the start of the treatment), Day 2, Day 3, Day 7, Day 14, Day 28.

Number of Subjects (Planned and Analyzed): Planned number of subjects and analyzed number of subjects were both 99 in modified-Intent to Treat (m-ITT) whose therapeutic responses were evaluated at Day 28 as effective or ineffective.

Diagnosis and Main Criteria for Inclusion: Female Japanese patients aged 18 years or older (<80 years as a general), who had clinical symptoms and signs of vulvovaginal candidiasis, who were positive for *Candida* by fungal culture.

Study Treatment: Fluconazole was supplied as 50 mg capsules. All subjects received a single oral dose of 150 mg of fluconazole (three 50 mg capsules) on Day 1.

Efficacy and Pharmacokinetic Endpoints:

Efficacy endpoints
Primary endpoint: Therapeutic outcome [7th day of treatment (Day 7), Day 14, Day 28]. Primary evaluation was the therapeutic outcome on Day 28. Secondary endpoints: Clinical efficacy (Day 7, Day 14, Day 28), mycological efficacy (Day 7, Day 14, Day 28), and clinical symptoms (Day 3, Day 7, Day 14, Day 28).

Pharmacokinetic endpoints
Pharmacokinetic parameters of fluconazole concentrations in plasma, potassium-corrected fluconazole concentrations in vaginal discharge, and weight-corrected fluconazole concentrations in vaginal discharge. Samples of plasma and vaginal discharge were collected before dosing and 2 hours (1.8-2.2 hours), 24 hours (20.4-27.6 hours), 48 hours (Day 3-Day 4), and 168 hours (Day 6-Day 8) after the dosing in order to analyze the concentration of fluconazole in plasma and vaginal discharge. A validated highly sensitive and specific high-performance liquid chromatography/tandem mass spectrometry method was used for analysis.

Safety Evaluations: Adverse events were recorded on the case report form from the time of the first treatment (Day 1) through the last subject visit, or including the 28 calendar days after the last administration of the investigational product, whichever is later. Serious adverse events were reported from the time that the signed informed consent was obtained through and including the 28 calendar days after the last administration of the investigational product. Clinical laboratory tests were performed and blood pressure (sitting systolic/diastolic) and heart rate were both measured prior to the first dose (Day 1), and on Day 7, Day 14, and Day 28.

Statistical Methods: The primary analysis population was m-ITT, which included subjects with vulvovaginal candidiasis who received the investigational products, who tested positive for *Candida* in the vulva and/or vagina at Day 1 (before dosing), and whose clinical efficacy was evaluated. The Per Protocol Set (PPS) included subjects in the above m-ITT who had incurred no major violation from the protocol, such as a violation of the inclusion criteria, and who underwent the evaluation specified for the observation time points defined in the protocol.

The plasma concentration analysis set was defined as those subjects who received the investigational products and whose plasma concentrations were measured at least once. The plasma parameter analysis set was defined as those subjects who were included in the plasma concentration analysis set and for whom at least one plasma concentration parameter was calculated. The vaginal discharge concentration analysis set and the vaginal discharge parameter analysis set were defined likewise.

For plasma concentration, weight-corrected vaginal discharge concentration, and potassium-corrected vaginal discharge concentration of fluconazole, and the pharmacokinetic parameters for fluconazole were estimated by using non-compartmental methods.

The safety analysis set was defined as all subjects who received the investigational products.

The point estimate of efficacy rate (rate of effectiveness) of the therapeutic outcome and the corresponding 95% confidence interval (CI) were calculated. The primary analysis of the primary endpoint was the efficacy rate of the therapeutic outcome in the m-ITT on Day 28, and efficacy in this study would be confirmed if the lower bound of the 95% CI of the therapeutic outcome on Day 28 was greater than 38% (threshold value). For the clinical efficacy, the point estimate of cure rate and cure or improvement rate and the corresponding 95% CIs were calculated, respectively. For the mycological efficacy, the point estimate of eradication rate and the corresponding 95% CI were calculated. For the clinical symptoms, the frequency and proportion for each category were summarized.

Major safety analyses were summarized according to algorithms and forms specified in the Pfizer Data Standards (PDS). Adverse events were coded by system organ class and preferred term from the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1.

RESULTS

Subject Disposition and Demography: Table 1 summarizes the subject disposition and analysis set. In this study, 157 subjects were assigned and all of them received fluconazole 150 mg. A total of 99 subjects completed the study, and 58 subjects discontinued the study. The reasons for discontinuation of the study were "does not meet the inclusion criteria" (56 subjects), "no longer willing to participate in the study" (1 subject), and "adverse events not related to the study drug" (1 subject). Of the 56 subjects who did not meet the inclusion criteria, 55 subjects were negative for *Candida* by fungal culture, and the remaining 1 subject had abnormal liver function test, which met the exclusion criteria. For efficacy, among all 157 subjects who received the investigational products, 102 subjects were included in the m-ITT, and 100 subjects were included in the PPS. A total of 55 subjects were excluded from the m-ITT for efficacy because they were negative for *Candida* by fungal test. A total of 57 subjects including the above 55 and 2 subjects (1 subject who discontinued the study because of abnormal liver function test values before the administration of the investigational product and did not undergo evaluation on Day 28 and the other subject who was no longer willing to participate in the study) were excluded from the PPS. For the pharmacokinetics population, all 157 subjects were included in the plasma pharmacokinetics concentration, the plasma pharmacokinetics parameters, the vaginal discharge pharmacokinetics concentration, and the vaginal discharge pharmacokinetics parameters analysis sets. For the safety analysis set, all 157 subjects who took the investigational products were included.

Table 1. Subject Disposition and Analysis Set

	Number (%) of Subjects
Assigned to study treatment	157
Treated	157
Completed	99 (63.1)
Discontinued	58 (36.9)
Does not meet the inclusion criteria	56 (35.7)
No longer willing to participate in the study	1 (0.6)
Adverse events not related to the study drug	1 (0.6)
Analyzed for efficacy:	
m-ITT	102 (65.0)
PPS	100 (63.7)
Analyzed for pharmacokinetics:	
Plasma concentration analysis set	157 (100.0)
Plasma parameter analysis set	157 (100.0)
Vaginal discharge concentration analysis	157 (100.0)
Vaginal discharge parameter analysis set	157 (100.0)
Analyzed for safety:	
Adverse events	157 (100.0)
Laboratory data	157 (100.0)

m-ITT = modified-Intent to Treat, PPS = Per Protocol Set

For all of the 157 subjects who received the investigational products, the mean age was 31.8 years (range: 18 to 57 years), the mean weight was 54.0 kg (range: 39.8 to 136.8 kg), and the mean body mass index was 21.3 kg/m^2 (range: 15.9 to 47.4 kg/m^2). There were no apparent differences in demographic characteristics among the analysis populations (Table 2).

Table 2. Demographic Characteristics

Number (%) of Subjects	ALL Treated N=157	m-ITT N=102	PPS N=100
Gender			
Female	157 (100.0)	102 (100.0)	100 (100.0)
Race			
Asian	157 (100.0)	102 (100.0)	100 (100.0)
Age (years)			
<18	0	0	0
18 - 44	141 (89.8)	91 (89.2)	89 (89.0)
45 - 64	16 (10.2)	11 (10.8)	11 (11.0)
≥65	0	0	0
Mean ± Standard Deviation	31.8±8.5	31.9±8.2	32.1±8.1
Range	18～57	18～55	18～55
Weight (kg)			
<40	1 (0.6)	0	0
40 - <50	55 (35.0)	37 (36.3)	36 (36.0)
50- <60	74 (47.1)	48 (47.1)	47 (47.0)
≥60	27 (17.2)	17 (16.7)	17 (17.0)
Mean ± Standard Deviation	54.0±10.9	53.9±11.5	53.9±11.6
Range	39.8～136.8	40.0～136.8	40.0～136.8
BMI (kg/m^2)			
Mean ± Standard Deviation	21.3±3.7	21.2±3.9	21.2±3.9
Range	15.9～47.4	15.9～47.4	15.9～47.4
Height (cm)			
Mean ± Standard Deviation	159.2±5.5	159.2±5.3	159.2±5.3
Range	145.0～173.0	145.0～172.0	145.0～172.0

m-ITT = modified-Intent to Treat, PPS = Per Protocol Set, BMI = body mass index
BMI = Weight / (Height × 0.01)^2

Among all of the 157 subjects who received the investigational products, 102 subjects tested positive for *Candida* by fungal culture at baseline: *Candida* detected included *Candida albicans* (100 strains), *C.parapsilosis* (2 strains), *C.glabrata* (1 strain), and *Candida species* (1 strain). The remaining 55 subjects were negative for *Candida*.

Efficacy, Pharmacokinetic Research Results:

Efficacy results

Table 3 summarizes the therapeutic outcomes in the m-ITT. The therapeutic outcome was considered as effective when the clinical efficacy was cure and the mycological efficacy was eradication. The efficacy rate for the therapeutic outcome on Day 28 in the m-ITT (primary analysis population) was 74.7% [95% CI: 65.0% to 82.9%]. Efficacy was confirmed since the lower bound of the 95% CI of the efficacy rate of the therapeutic outcome on Day 28 was greater than 38% (pre-specified threshold value). The same result was also obtained in the PPS.

Table 3. Therapeutic Outcome (m-ITT, Day 28: Primary Analysis of Primary endpoint)

	Number of Evaluated Subjects	Therapeutic Outcome				
		Effective Number (%) of Subjects	Ineffective Number (%) of Subjects	Indeterminate Number (%) of Subjects	Efficacy Rate[a] %	95%CI
Day 7	95	31 (32.6)	61 (64.2)	3 (3.2)	33.7	24.2 - 44.3
Day 14	100	52 (52.0)	44 (44.0)	4 (4.0)	54.2	43.7 - 64.4
Day 28	102	74 (72.5)	25 (24.5)	3 (2.9)	74.7	65.0 - 82.9

m-ITT = modified-Intent to Treat, CI = confidence interval
a. Efficacy Rate (%) = Number of Subjects with Effective result/ Number of Evaluated Subjects excluding Number of Subjects with Indeterminate result × 100

Table 4 summarizes the clinical efficacy in the m-ITT. Subjects with complete disappearance of clinical symptoms were considered as cure, and those with improved clinical symptoms were considered as improvement. The cure rate was 34.8% on Day 7, 57.3% on Day 14, and 81.6% on Day 28. The cure and improvement rate was 100.0% on Day 7, 99.0% on Day 14, and 95.9% on Day 28. The results were also the same in the PPS.

Table 4. Clinical Efficacy (m-ITT)

	Number of Evaluated Subjects	Clinical Efficacy							
		Cure Number (%) of Subjects	Improvement Number (%) of Subjects	Failure Number (%) of Subjects	Indeterminate Number (%) of Subjects	Cure Rate[a]		Cure and Improvement Rate[b]	
						%	95%CI	%	95%CI
Day 7	99	32 (32.3)	60 (60.6)	0	7 (7.1)	34.8	25.1 - 45.4	100.0	96.1 - 100.0
Day 14	101	55 (54.5)	40 (39.6)	1 (1.0)	5 (5.0)	57.3	46.8 - 67.3	99.0	94.3 - 100.0
Day 28	102	80 (78.4)	14 (13.7)	4 (3.9)	4 (3.9)	81.6	72.5 - 88.7	95.9	89.9 - 98.9

m-ITT = modified-Intent to Treat, CI = confidence interval
a. Cure Rate (%) = Number of Subjects with Cure/ Number of Evaluated Subjects excluding Number of Subjects with Indeterminate result × 100
b. Cure and Improvement Rate (%) = Number of Subjects with Cure and Improvement/ Number of Evaluated Subjects excluding Number of Subjects with Indeterminate result × 100

Table 5 summarizes the mycological efficacy in the m-ITT. The eradication rate was 95.7% on Day 7, 89.8% on Day 14, and 85.9% on Day 28. The results were also the same in the PPS.

Table 5. Mycological Efficacy (m-ITT)

	Number of Evaluated Subjects	Mycological Efficacy				
		Eradication Number (%) of Subjects	Persistence Number (%) of Subjects	Indeterminate Number (%) of Subjects	Eradication Rate[a] %	95%CI
Day 7	95	90 (94.7)	4 (4.2)	1 (1.1)	95.7	89.5 - 98.8
Day 14	100	88 (88.0)	10 (10.0)	2 (2.0)	89.8	82.0 - 95.0
Day 28	102	85 (83.3)	14 (13.7)	3 (2.9)	85.9	77.4 - 92.0

m-ITT = modified-Intent to Treat, CI = confidence interval
a Eradication Rate (%) = Number of Subjects with Eradication/ Number of Evaluated Subjects excluding Number of Subjects with Indeterminate result ×100

For clinical symptoms, the total scores for clinical symptoms for each subject in the m-ITT improved from Day 3. The mean total scores were 4.5 at Day 3, 0.8 at Day 14, and 0.4 at Day 28 (Table 6).

Table 6. Summary of Total Score for Clinical Symptoms (m-ITT)

	Number of Evaluated Subjects	Mean	Min	Max	Median
Day 1	102	11.0	4	19	11.0
Day 3	98	4.5	0	12	4.0
Day 7	93	1.8	0	10	1.0
Day 14	98	0.8	0	7	0.0
Day 28	99	0.4	0	9	0.0

m-ITT = modified-Intent to Treat

Individual clinical symptoms also improved from Day 3 (Table 7). The results were also the same in the PPS.

Table 7. Clinical Symptoms (m-ITT)

	N	Clinical Symptoms Number (%) of subjects				
		None (Score 0)	Mild (Score 1)	Moderate (Score 2)	Severe (Score 3)	NA
Vulvovaginal Itching						
Day 1	102	4 (3.9)	33 (32.4)	44 (43.1)	21 (20.6)	0
Day 3	99	27 (27.3)	62 (62.6)	9 (9.1)	1 (1.0)	0
Day 7	98	70 (71.4)	27 (27.6)	1 (1.0)	0	0
Day 14	99	83 (83.8)	16 (16.2)	0	0	0
Day 28	99	92 (92.9)	6 (6.1)	1 (1.0)	0	0
Vulvovaginal Burning Sensation						
Day 1	102	31 (30.4)	44 (43.1)	21 (20.6)	6 (5.9)	0
Day 3	99	77 (77.8)	16 (16.2)	6 (6.1)	0	0
Day 7	98	90 (91.8)	6 (6.1)	2 (2.0)	0	0
Day 14	99	95 (96.0)	4 (4.0)	0	0	0
Day 28	99	98 (99.0)	1 (1.0)	0	0	0
Vaginal Discharge						
Day 1	102	9 (8.8)	39 (38.2)	41 (40.2)	13 (12.7)	0
Day 3	99	51 (51.5)	38 (38.4)	10 (10.1)	0	0
Day 7	98	74 (75.5)	22 (22.4)	2 (2.0)	0	0
Day 14	99	91 (91.9)	7 (7.1)	1 (1.0)	0	0
Day 28	99	91 (91.9)	7 (7.1)	1 (1.0)	0	0
Excoriation						
Day 1	102	50 (49.0)	26 (25.5)	22 (21.6)	4 (3.9)	0
Day 3	99	70 (70.7)	26 (26.3)	2 (2.0)	0	1 (1.0)
Day 7	98	82 (83.7)	10 (10.2)	1 (1.0)	0	5 (5.1)
Day 14	99	97 (98.0)	1 (1.0)	0	0	1 (1.0)
Day 28	99	98 (99.0)	1 (1.0)	0	0	0
Vulval Oedema						
Day 1	102	58 (56.9)	27 (26.5)	17 (16.7)	0	0
Day 3	99	81 (81.8)	17 (17.2)	0	0	1 (1.0)
Day 7	98	92 (93.9)	1 (1.0)	0	0	5 (5.1)
Day 14	99	98 (99.0)	0	0	0	1 (1.0)
Day 28	99	99 (100.0)	0	0	0	0
Redness of Vulva						
Day 1	102	12 (11.8)	42 (41.2)	39 (38.2)	9 (8.8)	0
Day 3	99	40 (40.4)	53 (53.5)	5 (5.1)	0	1 (1.0)
Day 7	98	71 (72.4)	19 (19.4)	3 (3.1)	0	5 (5.1)
Day 14	99	91 (91.9)	7 (7.1)	0	0	1 (1.0)
Day 28	99	93 (93.9)	6 (6.1)	0	0	0
Vaginal Redness						
Day 1	102	23 (22.5)	39 (38.2)	32 (31.4)	8 (7.8)	0
Day 3	99	54 (54.5)	36 (36.4)	8 (8.1)	0	1 (1.0)
Day 7	98	74 (75.5)	18 (18.4)	1 (1.0)	0	5 (5.1)
Day 14	99	88 (88.9)	10 (10.1)	0	0	1 (1.0)
Day 28	99	98 (99.0)	0	1 (1.0)	0	0
Vaginal content character						
	N	**Normal (Score 0)**	**Mucoid (Score 1)**	**Paste-Like (Score 2)**	**Cottage Cheese-Like,Cheese-Like Or Granular (Score 3)**	**NA**
Day 1	102	1 (1.0)	3 (2.9)	41 (40.2)	57 (55.9)	0
Day 3	99	19 (19.2)	50 (50.5)	29 (29.3)	0	1 (1.0)
Day 7	98	55 (56.1)	26 (26.5)	12 (12.2)	0	5 (5.1)
Day 14	99	74 (74.7)	21 (21.2)	3 (3.0)	0	1 (1.0)
Day 28	99	91 (91.9)	5 (5.1)	2 (2.0)	1 (1.0)	0

m-ITT = modified-Intent to Treat , NA = not applicable

Pharmacokinetic results

Table 8 shows plasma concentration, weight-corrected vaginal discharge concentration, and potassium-corrected vaginal discharge concentration of fluconazole in 157 Japanese subjects with vulvovaginal candidiasis following a single oral administration of fluconazole 150 mg. Following the single oral administration of fluconazole 150 mg, fluconazole was rapidly absorbed and the mean plasma fluconazole concentration reached the maximum at 2 hours after dose administration. Thereafter, it was moderately eliminated, and plasma fluconazole concentration was detected over 168 hours after dose administration in all subjects for whom samples were collected, except for 1 subject.

Fluconazole was relatively moderately transferred from the systemic circulation to the vaginal discharge, and both the mean weight-corrected and mean potassium-corrected fluconazole concentration in vaginal discharge showed maximum values at 24 hours after dose administration. Thereafter, both concentrations moderately decreased similarly as the plasma concentration. The weight-corrected and potassium-corrected fluconazole concentration in vaginal discharge was detected at 168 hours after dose administration in all subjects for whom samples were collected, but the potassium-corrected concentration in vaginal discharge could not be calculated in 2 subjects as potassium concentration in vaginal discharge was below the quantifiable limit.

Table 8. Plasma and Vaginal Discharge Fluconazole Concentration (μg/mL) in Japanese Subjects with Vulvovaginal Candidiasis Following a Single Oral Administration of Fluconazole 150 mg

Sample	Nominal Time Post Dose (h)	2	24	48	168
Plasma	Number of subjects	157	66	154	146
	Mean±SD	3.76±1.13	2.44±0.414	1.06±0.431	0.138±0.115
Vaginal Discharge (weight-corrected)	Number of subjects	157	65	153	140
	Mean±SD	1.06±0.763	1.65±0.685	0.793±0.493	0.118±0.180
Vaginal Discharge (potassium-corrected)	Number of subjects	154	65	153	138
	Mean±SD	1.32±1.06	2.10±1.03	0.839±0.553	0.107±0.105

Table 9 summarizes the ratio of vaginal discharge fluconazole concentration (weight-corrected and potassium-corrected) to plasma fluconazole concentration in each subject. The mean ratios of vaginal discharge concentration (weight-corrected and potassium-corrected) to plasma concentration of fluconazole were 0.28 and 0.35, respectively, at 2 hours after dose administration. After 24 hours post dose, the ratios of both weight-corrected and potassium-corrected concentration to plasma concentration were 0.67 or more through 168 hours after dose administration when the last samples for pharmacokinetics analysis were collected.

Table 9. Descriptive Summary of the Ratio of Vaginal Discharge Fluconazole Concentration to Plasma Fluconazole Concentration in Japanese Subjects with Vulvovaginal Candidiasis Following a Single Oral Administration of Fluconazole 150 mg

Adjustment concentration	Nominal Time Post Dose (h)	2	24	48	168
Weight-corrected	Number of subjects	157	65	152	140
	Mean±SD	0.28±0.19	0.67±0.22	0.74±0.32	0.92±1.2
Potassium-corrected	Number of subjects	154	65	152	138
	Mean±SD	0.35±0.27	0.84±0.37	0.81±0.45	0.81±0.49

Table 10 summarizes the pharmacokinetics parameters estimated from the plasma concentration, weight-corrected vaginal discharge concentration, and potassium-corrected vaginal discharge concentration of fluconazole in 157 Japanese subjects with vulvovaginal candidiasis following a single oral administration of fluconazole 150 mg. Following the single oral administration of fluconazole 150 mg, the geometric means of maximum observed concentration (C_{max}) for plasma concentration, weight-corrected vaginal discharge concentration, and potassium-corrected vaginal discharge concentration were 3.71, 1.33, and 1.53 μg/mL, respectively; the median time to reach maximum observed concentration (T_{max}) were 1.9, 20.5, and 20.5 hours, respectively; and the geometric means of area under the concentration-time curve from zero to time of last measurable concentration (AUC_{last}) were 156.1, 79.5, and 85.3 μg•h/mL, respectively. Because of the limited numbers of sample collection points, half-life ($t_{½}$) and area under the concentration-time curve from time zero to infinity (AUC_{inf}) could not be estimated in half or more of the subjects, and the summary statistics for these parameters were not calculated.

Table 10. Descriptive Summary of Pharmacokinetics Parameters for Plasma and Vaginal Discharge Fluconazole Concentration in Japanese Subjects with Vulvovaginal Candidiasis Following a Single Oral Administration of Fluconazole 150 mg

Sample		C_{max} (μg/mL)	T_{max}[a] (h)	AUC_{last} (μg•h/mL)
Plasma	Number of subjects	157	157	149
	Geometric Mean (%CV)	3.71 (24)	1.9 (1.8 – 70.3)	156.1 (22)
Vaginal Discharge (weight-corrected)	Number of subjects	157	157	144
	Geometric Mean (%CV)	1.33 (49)	20.5 (1.8 – 116.6)	79.5 (43)
Vaginal Discharge (potassium-corrected)	Number of subjects	157	157	142
	Geometric Mean (%CV)	1.53 (59)	20.5 (1.8 – 116.6)	85.3 (48)

a. Median (range)
C_{max} = maximum observed concentration, T_{max} = time to reach maximum observed concentration, AUC_{last} = area under the concentration-time curve from zero to time of last measurable concentration, CV = coefficient of variation

Table 11 shows the ratio of pharmacokinetics parameters (C_{max} and AUC_{last}) for the vaginal discharge fluconazole concentration to the corresponding parameters for the plasma

fluconazole concentration. The mean ratios of pharmacokinetics parameters for the vaginal discharge fluconazole concentration (weight-corrected and potassium-corrected) to the corresponding parameters for the plasma fluconazole concentration were 0.41 and 0.49 for $C_{max,}$ and 0.55 and 0.60 for AUC_{last}, respectively. As AUC_{inf} could not be estimated in half or more of the subjects, the summary statistics for the ratio of AUC_{inf} were not calculated.

Table 11. Descriptive Summary of the Ratio of Pharmacokinetics Parameters for Vaginal Discharge Fluconazole Concentration to the Corresponding Pharmacokinetics Parameters for Plasma Fluconazole Concentration in Japanese Subjects with Vulvovaginal Candidiasis Following a Single Oral Administration of Fluconazole 150 mg

Adjustment concentration		C_{max}	AUC_{last}
Weight-corrected	Number of subjects	157	143
	Mean±SD	0.41±0.22	0.55±0.19
Potassium-corrected	Number of subjects	157	141
	Mean±SD	0.49±0.28	0.60±0.26

C_{max} = maximum observed concentration, AUC_{last} = area under the concentration-time curve from zero to time of last measurable concentration

Safety Results: A summary of the adverse events is shown in Table 12. Among the 157 subjects who received the investigational product, 37 subjects (23.6%) reported all-causality adverse events (49 events) and 12 subjects (7.6%) reported treatment-related adverse events (14 events)

Table 12. Summary of Adverse Events

Number (%) of subjects:	N=157	
	All-causalities	Treatment-related
Number of adverse events	49	14
Subjects with adverse events	37 (23.6)	12 (7.6)
Subjects with serious adverse events	0	0
Subjects with severe adverse events	0	0
Subjects discontinued due to adverse events	1 (0.6)	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0

Common adverse events are shown in Table 13. The most common (≥2 subjects) all-causality adverse events were nasopharyngitis (8 subjects, 5.1%); cystitis, genital herpes, and eczema (4 subjects, 2.5%, each); diarrhoea, nausea, and genital haemorrhage (3 subjects, 1.9%, each); and pyrexia and bronchitis (2 subjects, 1.3%, each). The most common (≥2 subjects) treatment-related adverse events were diarrhoea and nausea (3 subjects, 1.9%, each). All adverse events were mild or moderate in severity and no severe adverse events were reported.

Table 13. Adverse Events (Reported for ≥2 Subjects)

System organ class preferred term MedDRA/ version 16.1	N=157 All-causalities	 Treatment-related
Gastrointestinal disorders		
diarrhoea	3 (1.9)	3 (1.9)
nausea	3 (1.9)	3 (1.9)
General disorders and administration site conditions		
pyrexia	2 (1.3)	1 (0.6)
Infections and infestations		
bronchitis	2 (1.3)	0
cystitis	4 (2.5)	1 (0.6)
genital herpes	4 (2.5)	1 (0.6)
nasopharyngitis	8 (5.1)	0
Reproductive system and breast disorders		
genital haemorrhage	3 (1.9)	1 (0.6)
Skin and subcutaneous tissue disorders		
eczema	4 (2.5)	0

MedDRA = Medical Dictionary for Regulatory Activities

No subject died or experienced serious adverse events. One subject discontinued the study due to vulvovaginitis trichomonal, which was considered unrelated to the investigational drug and was confirmed to have resolved.

Table 14. Discontinuations Due to Adverse Events

MedDRA version 16.1 Preferred term	Severity	Outcome	Causality
Vulvovaginitis trichomonal	Moderate	Resolved	Other-due to trichomonas infection

MedDRA = Medical Dictionary for Regulatory Activities

Throughout the study period, there were no apparent changes from baseline in laboratory parameters. Abnormal laboratory values reported as adverse events were blood creatine phosphokinase increased (1 subject, 0.6%) and hepatic enzyme increased (1 subject, 0.6%). Both of them were mild in severity. There were no vital sign abnormalities reported as adverse events.

CONCLUSION(S): From this multicenter, open-label, non-comparative study conducted in Japanese patients with clinical symptoms and signs of vulvovaginal candidiasis, in which a single oral dose of fluconazole 150 mg was administered, the following conclusions were obtained:

- The efficacy rate for the therapeutic outcome (primary endpoint) (considered as effective when the clinical efficacy was cure and the mycological efficacy was eradication) on Day 28 in the m-ITT population was 74.7% (95% CI: 65.0% to 82.9%), and efficacy was confirmed since the lower bound of the 95% CI was greater than 38%

of pre-specified threshold value. Regarding the secondary endpoint results on Day 28 in the m-ITT: for the clinical efficacy, the cure rate was 81.6%, and the cure or improvement rate was 95.9%. For the mycological efficacy, the eradication rate was 85.9%. For the clinical symptoms, the overall clinical symptoms improved from Day 3.

- Through 2 to 168 hours post dose, fluconazole was detected in the plasma and vaginal discharge in most of the subjects. Also, the mean ratios of vaginal discharge fluconazole concentration versus plasma fluconazole concentration were 0.67 to 0.92 for 24 to 168 hours post dose.

- The mean ratios of pharmacokinetics parameters for the vaginal discharge fluconazole concentration (weight-corrected and potassium-corrected) versus the corresponding pharmacokinetics parameters for plasma fluconazole concentration were 0.41 and 0.49 for C_{max}, and 0.55 and 0.60 for AUC_{last}, respectively.

- All adverse events were mild or moderate in severity. No death or serious adverse event was reported in the study. Adverse event resulting in study discontinuation was reported in 1 subject, but it was considered as unrelated to the investigational drug and was confirmed to have resolved.

From these findings, a single oral administration of fluconazole 150 mg is confirmed to be effective for the treatment of Japanese patients with vulvovaginal candidiasis, and no significant safety issue was reported.