SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd (now Tibotec Pharmaceuticals) **Trade Name**: INTELENCE™ **Indication**: HIV-1 infection	**Drug Substance**: etravirine **Trial no.**: TMC125-TiDP2-C187 **Clinical Phase**: I
Title: A Phase I, open-label trial to investigate the pharmacokinetic interaction between TMC125 and two antifungal agents (fluconazole and voriconazole), all at steady-state in healthy volunteers.	
Investigator: P. Kaldeway M.D., Kendle Netherlands, Bolognalaan 40, 3584 CJ Utrecht, The Netherlands.	**Country**: The Netherlands
Trial Period: Start: 08-Sep-2008 End: 13-Jan-2009	**No. of Investigators**: 1 **No. of Subjects**: 18

Objectives: The objectives of this trial were to determine the effect of steady-state concentrations of voriconazole and fluconazole on the steady-state pharmacokinetics of ETR, the effect of steady state concentrations of ETR on the steady state pharmacokinetics of voriconazole and fluconazole and the short-term safety and tolerability of the co-administration of voriconazole or fluconazole and ETR.

Design: This was a Phase I, open-label, 3-period crossover trial to investigate the pharmacokinetic interaction between etravirine (ETR, formerly known as TMC125) and fluconazole, and between ETR and voriconazole, all at steady-state in 18 healthy subjects.

During the first two sessions, each subject received 2 treatments (Treatments A and B) in a randomized way. In Treatment A, 200 mg ETR b.i.d. was administered from Day 1 to Day 7 with an additional morning dose on Day 8. In Treatment B, 200 mg fluconazole q.a.m. was administered from Day 1 to Day 16, co-administered with 200 mg ETR b.i.d. from Day 9 to Day 16.

These sessions were followed by a third session, Treatment C, in which 400 mg voriconazole b.i.d. was administered on Day 1 and 200 mg voriconazole b.i.d. was administered from Day 2 to Day 15, with an additional morning dose on Day 16. From Day 9 to Day 15, 200 mg ETR b.i.d. was co-administered, with an additional morning dose on Day 16.

All ETR and fluconazole intakes were under fed conditions, within 10 minutes after a meal. Voriconazole was administered 1.5 hours before a meal. Between subsequent treatment sessions, there was a washout period of at least 2 weeks.

Full pharmacokinetic profiles were determined for one dosing interval (12 hours) for ETR on Day 8 of Treatment A and on Day 16 of Treatments B and C. For fluconazole, full pharmacokinetic profiles were determined for one dosing interval (24 hours) on Days 8 and 16 of Treatment B. For voriconazole, full pharmacokinetic profiles were determined for one dosing interval (12 hours) on Days 8 and 16 of Treatment C.

Safety and tolerability were monitored continuously throughout the trial.

Subject Selection

Inclusion Criteria

1. Aged between 18 and 55 years, extremes included.
2. Non-smoking or smoking no more than 10 cigarettes, or 2 cigars, or 2 pipes per day for at least 3 months prior to screening.
3. Body Mass Index (BMI) of 18.0 to 30.0 kg/m^2, extremes included. BMI was calculated as the weight (in kg) divided by the square of height (in m).

Inclusion Criteria (cont'd.)

4. Informed Consent Forms signed voluntarily before first trial-related activity
5. Able to comply with protocol requirements.
6. Healthy on the basis of medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination (including skin examination), medical and surgical history, electrocardiogram (ECG), vital signs and the results of blood biochemistry, hematology and a urinalysis carried out at Screening.

Exclusion Criteria

1. A positive HIV-1 or HIV-2 test at study screening
2. Female, except if postmenopausal for more than two years, or post-hysterectomy or surgically sterilized (without reversal operation).
3. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational or narcotic drug use which in the investigator's opinion would compromise subject's safety and/or compliance with study procedures.
4. Hepatitis A infection (confirmed by hepatitis A antibody IgM), hepatitis B infection (confirmed by hepatitis B surface antigen), or hepatitis C infection (confirmed by hepatitis C virus antibody) at study screening.
5. A positive urine drug test at study screening or on Day –1 of each session. Urine was tested for the presence of amphetamines, benzodiazepines, cocaine, cannabinoids and opioids.
6. Currently active or underlying gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, renal, hepatic, respiratory, inflammatory or infectious disease.
7. Currently significant diarrhea, gastric stasis or constipation that in the investigator's opinion could influence drug absorption or bioavailability.
8. Any history of significant skin disease such as but not limited to rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis or urticaria.
9. Previously demonstrated clinically significant allergy or hypersensitivity to fluconazole, voriconazole and/or any of the excipients of the investigational medication administered in this trial.
10. Clinical evidence or history of long QT syndrome and history of additional risk factors for Torsade de Pointes, such as cardiomyopathy, heart failure, hypokalemia, family history of known Long QT Syndrome, or sudden unexplained death at a young age ($\leq$ 40 years) in a first-degree relative (i.e., biological parent, sibling, or offspring).
11. Clinically relevant heart rhythm disturbances known or suggested by history, or on 12-lead ECG at screening or on Day 1 (predose) of the first treatment period.
12. Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia), grade 2 or greater, within 21 days prior to intake of the investigational medication.
13. History of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.
14. Use of concomitant medication, including over-the-counter products and dietary supplements. Systemic over-the-counter medication must have been discontinued at least 7 days prior to the first dose of study medication; prescribed medication and all products containing *Hypericum perforatum* (e.g., St John's Wort) must have been discontinued at least 14 days before the first dose of study medication, except for paracetamol
15. Participation in an investigational drug trial within 60 days prior to the first intake of trial medication.
16. Donation of blood or plasma within the 60 days preceding the first drug intake.
17. Having participated in more than 1 trial (single or multiple dose) with ETR, TMC120 (dapivirine) and/or TMC278 (rilpivirine, formerly known as R278474) or having developed rash, erythema or urticaria while participating in a trial with the aforementioned compounds.

Exclusion Criteria (cont'd.)

18. Subjects with the following laboratory abnormalities at screening as defined by the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events ("DAIDS grading table") and in accordance with the normal ranges of clinical laboratory:
    - Serum creatinine grade 1 or greater (≥ 1.1 x upper limit of laboratory normal range (ULN)),
    - Lipase grade 1 or greater (≥ 1.1 x ULN),
    - Hemoglobin decreased grade 1 or greater (≤ 10.9 g/dL),
    - Platelet count grade 1 or greater (≤ 124.999/mm^3),
    - Absolute neutrophil count grade 1 or greater (≤ 1.3/mm^3),
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) grade 1 or greater (≥ 1.25 x ULN),
    - Any other toxicity grade 2 or above, including: proteinuria (spot urine) > 2+ and gross hematuria

Treatment	**ETR**	**Fluconazole**	**Voriconazole**	
Concentration	200 mg b.i.d.	200 mg q.a.m.	200 mg b.i.d.	400 mg b.i.d.
Dosage Form (F No.)	F060	n/a	n/a	n/a
Usage	oral	oral	oral	oral
Batch Number	7EL7J02	4011	810195940 810275148	810195940 810275148
Dose Regimen	Treatment A: 200 mg ETR b.i.d. on Day 1 to Day 7 with an additional morning dose on Day 8. Treatment B: 200 mg fluconazole q.a.m. on Day 1 to Day 16 + 200 mg ETR b.i.d. on Day 9 to Day 16. Treatment C: 400 mg voriconazole b.i.d. on Day 1 and 200 mg voriconazole b.i.d. on Day 2 to Day 15, with an additional morning dose on Day 16 + 200 mg ETR b.i.d on Day 9 to Day 15, with an additional morning dose on Day 16.			
Duration of Treatment	40 days			
Duration of Trial	10 weeks (excluding Screening and Follow-up)			
Disallowed Medication	All systemic over-the-counter medication, herbal medications or dietary supplements had to be discontinued at least 7 days before the first administration of trial medication and all prescribed medication and products containing *Hypericum perforatum* had to be discontinued at least 14 days before first administration of trial medication, until 7 days after the last trial medication intake, except for paracetamol (acetaminophen), which could be used up to 3 days before drug administration in each session. After that, the clinical investigator could permit the use of paracetamol (from 3 days before until 96 hours after the drug intake in each session; at no more than 1000 mg t.i.d.). In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine (Zyrtec®), levocetirizine (Xyzal®), topical corticosteroids, or antipruritic agents in the recommended dosing scheme was permitted. The use of antiemetics in case of nausea, and the use of loperamide in case of diarrhea was also permitted.			

Assessments

Screening

Day	Time	Blood Sample		Urine Sample	ECG, PR, BP	Other [a]
		Drug	Safety[b]			
Screening (≤ 21 days before Day 1 of Session I)			X	X	X	Informed consent, subject characteristics, demographics, inclusion/exclusion criteria, medical and surgical history, concomitant diseases, family history related to skin disease, smoking habits, physical examination (including skin examination), HIV-1 and HIV-2, hepatitis A, B, and C test, urine drug screening, serum pregnancy test (if applicable)

[a] Adverse events (AEs) and concomitant medication were monitored continuously from the signing the ICF onwards until the last trial-related activity.
[b] All biochemistry samples had to be taken fasted for at least 10 hours.

Treatment A

Day	Time	Blood Sample		Urine Sample	ECG, PR, BP	Other[a]
		Drug	Safety[b]			
-1						Admission to the unit in the evening Urine drug screen; physical examination; alcohol breath test.
1	Morning predose	X[c,d,g]	X[d,e]	X[d]	X[d]	Standardized breakfast in unit **ETR 200 mg** morning intake in unit Discharge from unit **ETR 200 mg** evening intake at home [h]
2-5						**ETR 200 mg b.i.d.** intake at home [h]
6		X[c,f]	X[d]	X[d]		Breakfast in unit **ETR 200 mg** morning intake in unit Dinner in unit **ETR 200 mg** evening intake in unit Overnight stay in the unit optional
7		X[c,f]				Breakfast in unit **ETR 200 mg** morning intake in unit Admission to the unit in the evening Physical examination Dinner in unit **ETR 200 mg** evening intake in unit
8	-2 h					Stop water intake
	Morning predose	X[c,f]	X[d]	X[d]	X[d]	Standardized breakfast in unit
	0 h					**ETR 200 mg** morning intake in unit Treatment A Day 8 = Washout Period Day 1
	0.5 h	X[c]				
	1 h	X[c]				
	2 h	X[c]				Resume water intake
	3 h	X[c]				
	4 h	X[c]			X	Resume usual diet
	6 h	X[c]				
	9 h	X[c]				
	12 h	X[c]				
9	24 h		X		X	Physical examination; discharge from the unit

[a] AEs and concomitant medication were monitored continuously from the signing of the ICF onwards until the last trial-related activity.
[b] All biochemistry samples had to be taken fasted for at least 10 hours.
[c] For determination of ETR plasma concentrations.
[d] Within 2 hours before the intake of ETR.
[e] Included pharmacogenetic assessment (first session only)
[f] Immediately before the intake of ETR.
[g] For determination of fluconazole plasma concentrations.
[h] Time of medication intake and stop time of the accompanied meals at home were recorded in diary cards.

Treatment B

Day	Time	Blood Sample		Urine Sample	ECG, PR, BP	Other[a]
		Drug	Safety[b]			
-1						Admission to the unit in the evening Urine drug screen; physical examination; alcohol breath test
1	Predose	X[,e,d]	X[d,h]	X[d]	X[d]	Standardized breakfast in unit **Fluconazole 200 mg** morning intake in unit Discharge from unit
2-5						**Fluconazole 200 mg** q.a.m. intake at home[g]
6		X[c,f]	X[d]	X[d]		Breakfast in unit **Fluconazole 200 mg** morning intake in unit Overnight stay in the unit optional
7		X[c,f]				Breakfast in unit **Fluconazole 200 mg** morning intake in unit Admission to the unit in the evening Physical examination
8	-2 h					Stop water intake
	Predose	X[c,f]	X[d]	X[d]	X[d]	Standardized breakfast in unit
	0 h					**Fluconazole 200 mg** morning intake in unit
	0.5 h	X[c]				
	1 h	X[c]				
	2 h	X[c]				Resume water intake
	3 h	X[c]				
	4 h	X[c]			X	Resume usual diet
	6 h	X[c]				
	9 h	X[c]				
	12 h	X[c]				
9	24 h	X[c,f]	X[d]	X[d]	X[d]	Breakfast in unit **Fluconazole 200 mg** morning intake in unit **ETR 200 mg** morning intake in unit Physical examination Discharge from unit **ETR 200 mg** evening intake at home [g]
10-13						**Fluconazole 200 mg q.a.m.** intake at home [g] **ETR 200 mg b.i.d.** intake at home [g]

[a] AEs and concomitant medication were monitored continuously from the signing of the ICF onwards until the last trial-related activity.
[b] All biochemistry samples had to be taken fasted for at least 10 hours.
[c] For determination of fluconazole plasma concentrations.
[d] Within 2 hours before drug intake.
[e] For determination of ETR plasma concentrations.
[f] Immediately before drug intake.
[g] Time of medication intake and stop time of the accompanied meals at home were recorded in diary cards.
[h] Included pharmacogenetic assessment (first session only).

Treatment B, Cont'd

Day	Time	Blood Sample		Urine sample	ECG, PR, BP	Other[a]
		Drug	Safety[b]			
14		X[c,e,f]	X[d]	X[d]		Skin examination Breakfast in unit **Fluconazole 200 mg** morning intake in unit **ETR 200 mg** morning intake in unit Dinner in unit **ETR 200 mg** evening intake in unit Overnight stay in the unit was optional
15		X[c,e,f]				Breakfast in unit **Fluconazole 200 mg** morning intake in unit **ETR 200 mg** morning intake in unit Admission to the unit in the evening Physical examination Dinner in unit **ETR 200 mg** evening intake in unit
16	-2 h					Stop water intake
	Morning predose	X[c,e,f]	X[d]	X[d]	X[d]	Standardized breakfast in unit
	0 h					**Fluconazole 200 mg** morning intake in unit **ETR 200 mg** morning intake in unit Treatment C Day 16 = Washout Period Day 1
	0.5 h	X[c,e]				
	1 h	X[c,e]				
	2 h	X[c,e]				Resume water intake
	3 h	X[c,e]				
	4 h	X[c,e]			X	Resume usual diet
	6 h	X[c,e]				
	9 h	X[c,e]				
	12 h	X[c,e,f]				Dinner in unit **ETR 200 mg** evening intake in unit
17	24 h	X[c]	X		X	Physical examination; discharge from the unit

[a] AEs and concomitant medication were monitored continuously from the signing of the ICF onwards until the last trial-related activity.
[b] All biochemistry samples had to be taken fasted for at least 10 hours.
[c] For determination of fluconazole plasma concentrations.
[d] Within 2 hours before drug intake.
[e] For determination of ETR plasma concentrations.
[f] Immediately before drug intake.
[g] Time of medication intake and stop time of the accompanied meals at home were recorded in diary cards.
[h] For determination of voriconazole plasma concentrations.

Treatment C

Day	Time	Blood Sample		Urine Sample	ECG, PR, BP	Other[a]
		Drug	Safety[b]			
-1						Admission to the unit in the evening Urine drug screen; physical examination; alcohol breath test
1	Predose	X[e,d,h]	X[c,d]	X[d]	X[d]	**Voriconazole 400 mg** morning intake in unit Breakfast in unit (1.5 hours after drug intake) Discharge from unit **Voriconazole 400 mg** evening intake at home[g]
2-5						**Voriconazole 200 mg b.i.d.** intake at home [g]
6		X[c,f]	X[d]	X[d]		**Voriconazole 200 mg** morning intake in unit **Voriconazole 200 mg** evening intake at home[g] Overnight stay in the unit optional
7		X[c,f]				**Voriconazole 200 mg** morning intake in unit **Voriconazole 200 mg** evening intake in unit Admission to the unit in the evening Physical examination
8	-2 h					Stop water intake
	Predose	X[c,f]	X[d]	X[d]	X[d]	
	0 h					**Voriconazole 200 mg** morning intake in unit
	0.5 h	X[c]				
	1 h	X[c]				
	1.5 h	X[c]				Standardized breakfast in unit
	2 h	X[c]				
	3 h	X[c]				
	4 h	X[c]				Resume water intake
	6 h	X[c]			X	Resume usual diet
	9 h	X[c]				
	12 h	X[c,f]				**Voriconazole 200 mg** evening intake in unit
	13.5 h					Dinner in unit
9	24 h		X[d]	X[d]	X[d]	**Voriconazole 200 mg** morning intake in unit Breakfast in unit **ETR 200 mg** morning intake in unit Physical examination Discharge from unit **Voriconazole 200 mg** evening intake at home[g] **ETR 200 mg** evening intake at home [g]
10-13						**Voriconazole 200mg b.i.d.** intake at home [g] **ETR 200 mg b.i.d.** intake at home [g]

[a] AEs and concomitant medication were monitored continuously from the signing of the ICF onwards until the last trial-related activity.
[b] All biochemistry samples had to be taken fasted for at least 10 hours.
[c] For determination of voriconazole plasma concentrations.
[d] Within 2 hours before drug intake.
[e] For determination of ETR plasma concentrations.
[f] Immediately before drug intake.
[g] Time of medication intake and stop time (ETR) or start time (voriconazole) of the accompanied meals at home were recorded in diary cards.
[h] For determination of fluconazole plasma concentrations.

Treatment C, cont'd

Day	Time	Blood Sample		Urine sample	ECG, PR, BP	Other[a]
		Drug	Safety[b]			
14		X[c,e,f]	X[d]	X[d]		Skin examination **Voriconazole 200 mg** morning intake in unit Breakfast in unit **ETR 200 mg** morning intake in unit **Voriconazole 200 mg** evening intake in unit Dinner in unit **ETR 200 mg** evening intake in unit Overnight stay in the unit was optional
15		X[c,e,f]				**Voriconazole 200 mg** morning intake in unit Breakfast in unit **ETR 200 mg** morning intake in unit **Voriconazole 200 mg** evening intake in unit Dinner in unit **ETR 200 mg** evening intake in unit Admission to the unit in the evening Physical examination
16	-2 h					Stop water intake
	Morning predose	X[c,e,f]	X[d]	X[d]	X[d]	
	0 h					**Voriconazole 200 mg** morning intake in unit Treatment B Day 16 = Washout Period Day 1
	0.5 h	X[c]				
	1 h	X[c]				
	1.5 h	X[c]				Standardized breakfast in unit
	2 h	X[c,e,f]				**ETR 200 mg** morning intake in unit
	2.5 h	X[e]				
	3 h	X[c, e]				
	4 h	X[c, e]				Resume water intake
	5 h	X[e]				
	6 h	X[c, e]			X	Resume usual diet
	8 h	X[e]				
	9 h	X[c]				
	11 h	X[e]				
	12 h	X[c]				
	14 h	X[e]				Dinner in unit
17	24 h		X		X	Physical examination; discharge from the unit

[a] AEs and concomitant medication were monitored continuously from the signing of the ICF onwards until the last trial-related activity.
[b] All biochemistry samples had to be taken fasted for at least 10 hours.
[c] For determination of voriconazole plasma concentrations.
[d] Within 2 hours before drug intake.
[e] For determination of ETR plasma concentrations.
[f] Immediately before drug intake.
[g] Time of medication intake and stop time (ETR) or start time (voriconazole) of the accompanied meals at home were recorded in diary cards.

Flowchart for washout period and follow-up after last session:

Day	Blood sample		Urine sample	ECG, PR, BP	Other[a]
	Drug	Safety[b]			
Additional safety visits after Sessions I and II (during washout period of at least 14 days between subsequent sessions)					
7 days after last drug intake		X	X	X	Skin examination
Additional safety visits after last session (during follow-up period)					
7 days after last drug intake		X	X	X	Physical examination
30, 31 or 32 days after last drug intake		X	X	X	Physical examination

[a] AEs and concomitant medication were monitored continuously from the signing of the ICF onwards until the last trial-related activity.
[b] All biochemistry samples had to be taken fasted for at least 10 hours.

Flowchart in Case of Dropout (other than withdrawal of consent):

Day	Blood sample		Urine sample	ECG, PR, BP	Other [a]
	Drug	Safety [b]			
At time of dropout or the following morning	X[d]	X	X	X	Physical examination
7 days after dropout		X	X	X	Physical examination
10 days after first intake of ETR[c]					Skin examination
30, 31 or 32 days after dropout		X	X	X	Physical examination

[a] AEs and concomitant medication were monitored continuously from the signing of the ICF onwards until the last trial-related activity.
[b] All biochemistry samples had to be taken fasted for at least 10 hours. The biochemistry sample taken at the time of discontinuation, in case of dropout, was to preferably be taken fasted for at least 10 hours.
[c] Only applicable in case of dropout for a non-cutaneous event/rash, if ETR had been administered and if this time point had not been reached at time of dropout. In case of a cutaneous event/rash, the "visit schedule for cutaneous events/rash follow-up" was to be followed.
[d] For determination of voriconazole, fluconazole and ETR plasma concentrations as appropriate.

Statistical Methods: Descriptive statistics, frequency tabulations, and linear mixed effects modeling were used to evaluate the results.

Main Features of the Subject Sample and Summary of the Results

Parameter	All Subjects N=18
Age, Years, Median (range)	28.5 (18-45)
Height, cm, Median (range)	178.0 (157-198)
Weight, kg, Median (range)	80.0 (56-101)
Body Mass Index (BMI), kg/m², Median (range)	23.5 (21-29)
Sex, n (%)	18 (100)
Female	3 (16.7)
Male	15 (83.3)
Ethnic Origin, n (%)	18 (100)
Black	2 (11.1)
Caucasian	16 (88.9)
Number of Drop-Outs – Reason, n (%)	4 (22.2)
AE	1 (5.6)
Withdrew Consent	3 (16.7)

Pharmacokinetics of ETR (mean ± SD, t_{max}: median [range])	**200 mg ETR b.i.d. (reference)**	**200 mg fluconazole q.a.m. + 200 mg ETR b.i.d. (test 1)**	**200 mg voriconazole b.i.d. + 200 mg ETR b.i.d. (test 2)**
n	16	15	14
Day 8/ Day 16			
C_{0h}, ng/mL	468.8 ± 180.4	925.1 ± 255.4	682.3 ± 267.6
C_{min}, ng/mL	426.4 ± 154.1	889.0 ± 242.0	648.2 ± 237.1
C_{max}, ng/mL	984.1 ± 250.1	1723 ± 395.4	1251 ± 365.9
t_{max}, h	3.0 (2.0-4.0)	3.0 (2.0-4.0)	4.0 (2.0-6.0)
AUC_{12h}, ng.h/mL	8105 ± 2173	15160 ± 3204	11230 ± 3794
$C_{ss,av}$, ng/mL	675.4 ± 181.1	1264 ± 267.0	935.5 ± 316.2
FI, %	84.62 ± 19.33	66.08 ± 13.82	66.51 ± 16.35
	LSmean ratio (90% CI), %		
	test 1 vs reference	**test 2 vs reference**	
n	15 vs 16	14 vs 16	
C_{min}	209.4 (190.0 - 230.7)	151.8 (140.6 - 163.9)	
C_{max}	174.7 (159.6 - 191.2)	126.3 (115.9 - 137.7)	
AUC_{12h}	185.6 (172.6 - 199.7)	135.6 (125.0 - 147.0)	

Pharmacokinetics of fluconazole (mean ± SD, t_{max}: median [range])	**200 mg fluconazole q.a.m. (reference)**	**200 mg fluconazole q.a.m. + 200 mg ETR b.i.d. (test)**
n	15[a]	15
Day 6/ Day 14		
C_{0h}, ng/mL	6193 ± 2390	5951 ± 1233
Day 7/ Day 15		
C_{0h}, ng/mL	6226 ± 1991	5491 ± 957.1
Day 8/ Day 16		
C_{0h}, ng/mL	6191 ± 1316	5323 ± 780.1
C_{min}, ng/mL	5786 ± 1089	5240 ± 765.2
C_{max}, ng/mL	9834 ± 2115	9209 ± 1819
t_{max}, h	3.0 (2.0-6.0)	3.0 (0.5-12.0)
AUC_{24h}, ng.h/mL	176000 ± 29290	165900 ± 23780
$C_{ss,av}$, ng/mL	7332 ± 1220	6911 ± 990.9
FI, %	56.30 ± 9.398	57.09 ± 13.38
LSmean ratio (90% CI), %		
	test vs reference	
n	15 vs 15[b]	
C_{min}	91.03 (84.48 - 98.08)	
C_{max}	92.12 (85.08 - 99.74)	
AUC_{24h}	94.08 (87.88 - 100.7)	

[a] n=17 for Day 6, n=16 for Day 7, Day 8 C_{0h} and C_{min}
[b] n=16 for C_{min}

Pharmacokinetics of voriconazole (mean ± SD, t_{max}: median [range])	**200 mg voriconazole b.i.d. (reference)**	**200 mg voriconazole b.i.d. + 200 mg ETR b.i.d. (test)**
n	14[a]	14
Day 6/ Day 14		
C_{0h}, ng/mL	837.0 ± 1312	776.4 ± 769.7
Day 7/ Day 15		
C_{0h}, ng/mL	810.5 ± 1217	599.9 ± 574.9
Day 8/ Day 16		
C_{0h}, ng/mL	746.5 ± 1247	580.9 ± 507.5
C_{min}, ng/mL	691.5 ± 1161	493.8 ± 455.1
C_{max}, ng/mL	2871 ± 1952	2455 ± 799.0
t_{max}, h	1.0 (0.5-2.0)	1.0 (0.5-2.0)
AUC_{12h}, ng.h/mL	14740 ± 17390	12660 ± 6767
$C_{ss,av}$, ng/mL	1231 ± 1457	1055 ± 563.9
FI, %	266.4 ± 119.4	208.7 ± 66.78
LSmean ratio (90% CI), %		
	test vs reference	
n	14 vs 14	
C_{min}	123.3 (86.93 - 175.0)	
C_{max}	95.33 (75.01 - 121.2)	
AUC_{12h}	113.6 (87.92 - 146.9)	

[a] n=15 for Day 6

Safety Adverse Events	None (Screening) N=18	ETR N=16	Fluconazole N=17	Fluconazole + ETR N=16	Voriconazole N=15	Voriconazole + ETR N=14	None (follow-up) N=17	Whole trial N=18
Most frequently reported AEs (>20% of subjects), n (%)								
Headache	1 (5.6)	3 (18.8)	2 (11.8)	5 (31.3)	7 (46.7)	0	1 (5.9)	11 (61.1)
Vision blurred	0	0	0	0	8 (53.3)	1 (7.1)	0	8 (44.4)
Lip dry	0	2 (12.5)	0	4 (25.0)	1 (6.7)	4 (28.6)	0	6 (33.3)
Nasopharyngitis	0	1 (6.3)	1 (5.9)	2 (12.5)	0	0	2 (11.8)	6 (33.3)
Dizziness	0	0	0	1 (6.3)	6 (40.0)	0	0	6 (33.3)
Visual impairment	0	0	0	0	5 (33.3)	0	0	5 (27.8)
Nausea	0	1 (6.3)	0	1 (6.3)	0	3 (21.4)	0	4 (22.2)
Catheter site related reaction	0	1 (6.3)	1 (5.9)	2 (12.5)	0	1 (7.1)	0	4 (22.2)
Oropharyngeal pain	0	1 (6.3)	2 (11.8)	1 (6.3)	0	0	0	4 (22.2)
Dry skin	0	1 (6.3)	0	0	0	3 (21.4)	0	4 (22.2)
n (%) with 1 or more AEs	1 (5.6)	11 (68.8)	7 (41.2)	11 (68.8)	14 (93.3)	11 (78.6)	7 (41.2)	18 (100)
n (%) of deaths	0	0	0	0	0	0	0	0
n (%) with 1 or more other SAEs	0	0	0	0	0	0	0	0
n (%) of treatment stopped due to AEs	0	0	1 (5.9)	0	0	0	0	1 (5.6)
n (%) with 1 or more grade 3 or 4 AEs	0	0	0	0	0	0	1 (5.9)	1 (5.6)

All eighteen subjects (100.0%) experienced at least 1 AE during the trial. All AEs during the treatment period were grade 1 or 2. One subject experienced two grade 3 events (lipase increased, blood amylase increased) during the off-treatment follow up period. Fourteen subjects (77.8%) experienced an AE during treatment that was considered possibly related to ETR, the most common of which was lip dry (33.3%). None of the subjects died during the trial. The most commonly reported AEs of interest during the trial were neuropsychiatric events (14 subjects; 77.8%) of which the most frequent were headache (61.1%) and vision blurred (44.4%). There were no skin, hepatobiliary, pancreatic, or cardiac AEs of interest reported during any ETR treatment period (either alone or in combination with fluconazole or voriconazole).
One subject prematurely discontinued the trial due to an AE (grade 2 AE of leukocyturia) on Day 6 of the fluconazole treatment period. The AE was not considered related to any component of trial treatment.

Clinical Laboratory Tests	None (Screening) N=18	ETR N=16	Fluconazole N=17	Fluconazole + ETR N=16	Voriconazole N=15	Voriconazole + ETR N=14	None (follow-up) N=17	Whole trial N=18
n (%) with any treatment-emergent grade 1 laboratory abnormality	0	9 (56.3)	7 (41.2)	8 (50.0)	3 (20.0)	7 (50.0)	10 (58.8)	15 (83.3)
n (%) with any treatment-emergent grade 2 laboratory abnormality	0	3 (18.8)	1 (5.9)	1 (6.3)	0	1 (7.1)	2 (11.8)	3 (16.7)
n (%) with any treatment-emergent grade 3 laboratory abnormality	0	1 (6.3)	0	0	0	0	1 (5.9)	2 (11.1)

N = total number of subjects; n = number of subjects with observation

No consistent or clinically relevant changes over time in laboratory parameters were observed. Most laboratory abnormalities were grade 1 or 2. One subject had a grade 3 increased lipase and grade 3 increased pancreatic amylase during the off-treatment follow-up period. One subject had a grade 3 increase in PTT at the pre-dose visit on Day 8 of treatment with ETR. There were no grade 4 abnormalities reported during the trial. In one subject (5.6%) an AE related to the urinary system (leukocyturia) was reported. This AE which occurred on Day 6 of fluconazole treatment was grade 2 in severity and assessed as not related to any component of trial treatment. The event led to permanent withdrawal of treatment. None of the other laboratory abnormalities were considered clinically relevant and so none were reported as an AE.

Cardiovascular Safety	There were no consistent or clinically relevant median changes in vital signs or ECG parameters or clinically relevant individual abnormalities.
Physical examination	There were no clinically relevant changes over time in physical or skin examination findings.

Conclusions

After co-administration with fluconazole or voriconazole, C_{min}, C_{max} and AUC_{12h} for ETR were increased by 2.09-fold, 1.75-fold and 1.86-fold, respectively, and by 1.52-fold, 1.26-fold and 1.36-fold, respectively, compared to treatment with ETR alone, based on the ratios of the LSmeans. The safety analysis of this trial showed that 200 mg of ETR administered alone or in combination with fluconazole or voriconazole was generally safe and well tolerated.

ETR had no effect on the pharmacokinetics of fluconazole. Based on the LSmeans ratios, C_{min}, C_{max} and AUC_{24h} of fluconazole were comparable after treatment with fluconazole alone or in the presence of ETR. The 90% CIs of the LSmeans ratios for these parameters fell within the [80%, 125%] interval. The effect of ETR on the pharmacokinetics of voriconazole was limited. In the presence of ETR, C_{min} and AUC_{12h} of voriconazole were increased by 23% and 14%, respectively, compared to treatment with voriconazole alone, based on the ratios of the LSmeans, while C_{max} of voriconazole was decreased by 5% when combined with ETR.

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