SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. (now Tibotec Pharmaceuticals)	**Drug Substance**: etravirine (ETR, TMC125)
Trade Name: INTELENCE™	**Trial no.**: TMC125-TiDP2-C197
Indication: HIV-1 infection	**Clinical Phase**: I

Title: A Phase I, open label, randomized, cross-over, 2-period, 2-way interaction trial to investigate the pharmacokinetic interaction between lopinavir/ritonavir and TMC125 both at steady-state in healthy subjects.

Investigator: D. Mazur, Institut fur Klinische Pharmakologie, Klinikum NeuKölln. Parexel International GmbH, Rudower Str. 48, 12351 Berlin, Germany	**Country**: Germany

Trial Period: Start: 16-Sep-2008 End: 19-Dec-2008	**No. of Investigators**: 1 **No. of Subjects**: 16

Objectives: The primary objectives of this trial were (a) to determine the effect of steady-state concentrations of LPV, co-administered with a low dose of ritonavir, on the steady-state pharmacokinetics of ETR, and (b) to determine the effect of steady-state concentrations of ETR on the steady-state pharmacokinetics of LPV, co-administered with a low dose of ritonavir. The secondary objective was to evaluate the short-term safety and tolerability of the concomitant use of ETR and LPV, co-administered with low-dose ritonavir in healthy subjects.

Design: This was a Phase I, open-label, randomized, 2-period, 2-way, cross-over interaction trial to investigate the pharmacokinetic interaction between lopinavir/ritonavir (LPV/rtv) and etravirine (ETR, formerly known as TMC125), both at steady-state.

The trial population consisted of 16 healthy subjects. In 2 consecutive sessions, subjects received Treatment A and Treatment B in a randomized way, 8 subjects in each sequence. In Treatment A, 200 mg ETR b.i.d. was administered for 7 days with an additional morning dose on Day 8. In Treatment B, 400/100 mg LPV/rtv b.i.d. was administered for 15 days with an additional morning dose on Day 16, while 200 mg ETR b.i.d. was co-administered from Day 9 to Day 15 with an additional morning dose on Day 16. The sessions were separated by a washout period of at least 2 weeks.

Full pharmacokinetic profiles of ETR were determined over the 12-hour dosing interval after the morning intake on Day 8 of Treatment A and on Day 16 of Treatment B. Full pharmacokinetic profiles of LPV and ritonavir were determined over the 12-hour dosing interval after the morning intake on Days 8 and 16 of Treatment B.

All treatments were administered under fed conditions and were taken within 10 minutes after a meal. Safety and tolerability evaluations were recorded continuously.

Subject Selection

Inclusion Criteria: Subjects meeting all the following criteria were eligible for the trial:
1. Male or female subjects, 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 selection;
3. Normal weight as defined by a Quetelet Index (Body Mass Index [BMI], weight in kg divided by the square of height in meters) of 18.0 to 30.0 kg/m^2, extremes included;
4. Informed Consent Form (ICF) signed voluntarily before the first trial-related activity;
5. Able to comply with protocol requirements;
6. Healthy on the basis of a medical evaluation that reveals the absence of any clinically relevant abnormality and includes a physical examination, medical history, electrocardiogram (ECG), vital signs, and the results of blood biochemistry, hematology and a urinalysis carried out at screening.

Exclusion Criteria: Subjects meeting 1 or more of the following criteria were not eligible for the trial:
1.   A positive HIV-1 or HIV-2 test at Screening;
2.   Female, except if postmenopausal since more than 2 years, or documented post-hysterectomy or post-tubal ligation (without reversal operation);
3.   History or suspicion of alcohol, barbiturate, amphetamine, recreational or narcotic drug use, which in the investigator's opinion compromised subject's safety or compliance with trial procedures;
4.   Hepatitis A infection (confirmed by hepatitis A antibody IgM), or hepatitis B infection (confirmed by hepatitis B surface antigen), or hepatitis C infection (confirmed by hepatitis C virus antibody) at Screening;
5.   A positive urine drug test at 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, nervous system, 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 allergies, dermatitis, eczema, psoriasis, or urticaria;
9.   Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication administered in this trial;
10. Use of concomitant medication, including over-the-counter products and dietary supplements.
     Over-the-counter systemic medication had to be discontinued at least 7 days prior to the first dose of trial medication; prescribed medication and all products containing *Hypericum perforatum* had to be discontinued at least 14 days before first dose of trial medication, except for paracetamol/acetaminophen and ibuprofen.
11. Participation in an investigational drug trial within 60 days prior to the first intake of trial medication;
12. Donation of blood or plasma within 60 days preceding the first intake of trial medication;
13. Subjects with the following laboratory abnormalities at Screening as defined by the enhanced toxicity grading severity list:
     - serum creatinine grade 1 or greater ($\geq$ 1.1 x ULN);
     - lipase grade 1 or greater ($\geq$ 1.1 x ULN);
     - hemoglobin decrease grade 1 or greater ($\leq$ 10.9 g/dL);
     - platelet count grade 1 or greater ($\leq$ 124.999 x 10^9/L);
     - absolute neutrophil count grade 1 or greater ($\leq$ 1.3 /mm^3);
     - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) grade 1 or greater ($\geq$ 1.25 x ULN);
     - any other toxicity grade 2 or above, including proteinuria (spot urine) > 2+, and gross hematuria (> 10 red blood cell [RBC]/high power field [HPF]). A urine retest for proteinuria and microscopic hematuria could be performed in women after the menstrual period.
14. 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 a rash, erythema, or urticaria while participating in a trial with the aforementioned compounds;
15. Inability to understand the protocol requirements, instructions and trial-related restrictions, the nature, scope, and possible consequences of the trial;
16. Unlikely to comply with the protocol requirements, instructions and trial-related restrictions; e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the trial;
17. Subject is the Investigator or any Sub-Investigator, research assistant, pharmacist, trial coordinator, other staff or relative thereof directly involved in the conduct of the trial;
18. Vulnerable subjects (e.g. persons kept in detention).

Treatment	Treatment A: ETR	Treatment B: LPV/rtv and ETR
Concentration Dosage Form (F No.) Usage	100 mg Tablets (F060) Oral	200/50 mg Kaletra® (Meltrex™ formulation) Oral
Batch Number	7ET00	62270VA
Dose Regimen	ETR: 200 mg b.i.d.	LPV/rtv: 400/100 mg b.i.d. / ETR: 200 mg b.i.d.
Duration of Treatment	Day 1-7 + morning dose on Day 8	LPV/rtv: Day 1-15 + morning dose on Day 16 ETR: Day 9-15 + morning dose on Day 16
Duration of Trial	38 days excluding screening and follow-up	
Disallowed Medication: All systemic over-the-counter medication was discontinued at least 7 days before the first administration of trial medication and all prescribed medication had to be discontinued at least 14 days before first administration of trial medication, except for paracetamol (acetaminophen) and ibuprofen. Products containing *Hypericum perforatum* (e.g., St. John's Wort) were not allowed from 14 days before the first trial medication intake up to 7 days after the last trial medication intake. Paracetamol and ibuprofen could be used up to 3 days before trial medication administration in each session. The use of paracetamol (up to 1000 mg t.i.d.) and of ibuprofen (up to 400 mg/day) was permitted from 3 days before until 96 hours after trial medication intake.		

Assessments						
Assessments at Screening (≤ 21 days)	In addition to the assessments in the flow-chart: Informed consent, subject characteristics and demographics, eligibility, medical and surgical history & concomitant diseases, family history related to skin disease, smoking habits, HIV-1 and HIV-2 & hepatitis A, B, C test, urine drug screening, physical examination, concomitant medication, serum pregnancy test for women.					

| Day | Time | Blood Sample | | Urine Sample | ECG, HR, BP | Other[a] |
		Drug	Safety[b]			
-21			X	X	X	Screening visit. Additional assessments: see list above
Treatment A						
-1				X		Admission to unit, urine drug screening, physical examination, alcohol breath test, overnight at unit
1	Predose	X[c,d]	X[c,e]	X[c]	X[c]	Standardized breakfast at the unit
	0 h					Morning intake ETR 200 mg at unit; Discharge from unit; Evening intake ETR 200 mg at home
2-6		X[d,f]	X[c,g]	X[c,g]		Breakfast at unit, Morning intake ETR 200 mg at unit; Evening intake ETR 200 mg at home
7		X[d,f]				Breakfast at unit, Morning intake ETR 200 mg at unit; Admission to unit; Physical examination, Dinner; ETR 200 mg at unit; Overnight at unit
8	-2 h					Stop water intake
	Predose	X[d,f]	X[c]	X[c]	X[c]	Standardized breakfast at unit
	0 h					Morning intake ETR 200 mg at unit
	0.5h, 1h, 2h, 3h, 4h, 6h, 9h, 12h	X[d]			X at 4 h	Resume water intake at 2 h; Resume usual diet at 4 h
9	24		X	X	X	Physical examination, discharge from unit
Treatment B						
-1				X		Admission to unit, urine drug screen, physical examination, alcohol breath test
1	Predose	X[c,d,h]	X[c,e]	X[c]	X[c]	Standardized breakfast at the unit
	0 h					LPV/rtv 400/100 mg morning intake at unit, Discharge from unit, LPV/rtv 400/100 mg evening intake at home
2-6		X[f,h]	X[c,g]	X[c,g]		Breakfast at unit, Skin examination[g], LPV/rtv 400/100 mg morning intake at unit, evening intake at home
7		X[f,h]				Breakfast at unit, LPV/rtv 400/100 mg morning intake at unit, Admission to unit, Physical exam, Dinner, LPV/rtv 400/100 mg evening intake at unit, overnight at unit
8	-2					Stop water intake
	Predose	X[f,h]	X[c]	X[c]	X[c]	Standardized breakfast at unit
	0					LPV/rtv 400/100 mg morning intake at unit
	0.5h, 1h, 2h, 3h, 4h, 6h, 9h, 12h	X[h]			X at 4 h	Resume water intake at 2h, Resume usual diet at 4h; LPV/rtv 400/100 mg evening intake at unit; Overnight in the unit
9			X[c]	X[c]	X[c]	Breakfast at unit, LPV/rtv 400/100 mg and ETR 200 mg morning intake at unit, Physical examination, Discharge from unit, LPV/rtv 400/100 mg and ETR 200 mg evening intake at home
10-14		X[d,f,h]	X[c,g]	X[c,g]		Breakfast at unit; Skin examination[g]; LPV/rtv 400/100 mg and ETR 200 mg morning intake at unit; LPV/rtv 400/100 mg and ETR 200 mg evening intake at home

[a] Adverse events and concomitant medication were monitored continuously from signing the Informed Consent Form onwards until the last trial-related activity.
[b] Fasted for at least 10 hours, before breakfast
[c] Within 2 hours before drug intake
[d] For the determination of ETR plasma concentration
[h] For the determination of lopinavir and ritonavir plasma concentrations

[e] Including pharmacogenetic assessment in Session 1
[f] Immediately before drug intake
[g] Only on Day 6 and Day 14

Assessments are continued on the next page

| | | Blood Sample | | Urine | ECG, HR, | |
Day	Time	Drug	Safety[b]	Sample	BP	Other[a]
15		X[d,f,h]				Breakfast at unit, LPV/rtv 400/100 mg and ETR 200 mg morning intake at unit, Admission to unit, Physical examination, Dinner, LPV/rtv 400/100 mg and ETR 200 mg evening intake at unit, overnight at unit
16	-2					Stop water intake
	Predose	X[d,f,h]	X[c]	X[c]	X[c]	Standardized breakfast at unit
	0					LPV/rtv 400/100 mg and ETR 200 mg morning intake at unit
	0.5h, 1h, 2h, 3h, 4h, 6h, 9h, 12h	X[d,h]			X at 4 h	Resume water intake at 2h, Resume usual diet at 4h
17			X	X	X	Physical examination; Discharge from unit
Washout between Session I and Session II: at least 2 weeks						
Day 1						Treatment A Day 8 = Washout Period Day 1 Treatment B Day 16 = Washout Period Day 1
Day 7			X	X		Skin examination
Flowchart for additional safety visits after last session						
Follow-up after 7 days			X	X	X	Physical examination
Follow-up after 30, 31 or 32 days			X	X	X	Physical examination
At time of dropout[c]		X	X	X	X	Physical examination
7 days after last intake			X[d]	X	X	Physical examination
10 days after first intake of ETR[e]						Skin examination
30, 31 or 32 days after last drug intake			X[d]	X	X	Physical examination

[a] Adverse events and concomitant medication were monitored continuously from signing the Informed Consent Form onwards until the last trial-related visit.

[b] If consent not withdrawn

[c] At the time of discontinuation or the following morning

[d] Fasted for at least 10 hours, before breakfast

[e] Only applicable in case of dropout for a cutaneous event/rash, if ETR was administered and if this time point was been reached yet at time of dropout. In case of a cutaneous event/rash, the "visit schedule for cutaneous events/rash follow-up" had to be followed.

Statistical Methods: Descriptive statistics, linear mixed effects modeling, nonparametric test (Koch for t_{max} of ETR and Wilcoxon signed rank test for t_{max} of LPV and ritonavir)

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	Treatment sequence A/B N = 8	Treatment sequence B/A N = 8	All Subjects N = 16
Number of Subjects Entered (M/F)	6 / 2	5 / 3	11 / 5
Age at screening: median (range), yrs	45.5 (38-53)	41.0 (20-52)	44.5 (20-53)

Pharmacokinetics of etravirine mean ± SD, t_{max}: median (range)	ETR (reference) N = 16		LPV/rtv + ETR (test) N = 16[a]		
Day 8 / Day 16 C_{0h}, ng/mL	493.6	± 148.1	273.4	±	90.50
C_{min}, ng/mL	451.4	± 120.9	252.7	±	84.22
C_{max}, ng/mL	904.8	± 186.5	642.6	±	163.0
t_{max}, h	4.0 (2.0-9.0)		4.0 (3.0-6.0)		
AUC_{12h}, ng.h/mL	8036	± 1779	5250	±	1416
$C_{ss,av}$, ng/mL	669.6	± 148.2	437.5	±	118.0
FI, %	70.26	± 24.83	89.93	±	13.97
LSmean ratio (90% CI), %			**test vs reference (16 vs 16[a])**		
C_{min}			54.74 (48.51 - 61.78)		
C_{max}			70.20 (63.54 - 77.56)		
AUC_{12h}			64.66 (58.85 - 71.04)		

[a] n = 15 for C_{0h} on Day 1 and C_{min} and FI on Day 16

Pharmacokinetics of lopinavir mean ± SD, t_{max}: median (range)	LPV/rtv (reference) N = 16[a]		LPV/rtv + ETR (test) N = 16		
Day 8 / Day 16 C_{0h}, ng/mL	6746	± 2217	5523	±	2010
C_{min}, ng/mL	5333	± 1850	4322	±	1527
Cmax, ng/mL	11170	± 2909	9792	±	1906
t_{max}, h	4.0 (2.0-6.0)		4.0 (2.0-4.0)		
AUC_{12h}, ng.h/mL	96790	± 21790	84520	±	17710
$C_{ss,av}$, ng/mL	8065	± 1816	7043	±	1476
FI, %	73.28	± 24.53	80.55	±	26.75
LSmean ratio (90% CI), %			**test vs reference (16 vs 16)**		
C_{min}			80.05 (73.16 - 87.60)		
C_{max}			88.72 (81.80 - 96.22)		
AUC_{12h}			87.31 (82.52 - 92.39)		

Pharmacokinetics of ritonavir mean ± SD, t_{max}: median (range)	LPV/rtv (reference) N = 16[a]	LPV/rtv + ETR (test) N = 16
Day 8 / Day 16　C_{0h}, ng/mL	197.4　±　135.5	162.1　±　84.03
C_{min}, ng/mL	125.0　±　71.82	106.9　±　52.57
C_{max}, ng/mL	844.9　±　451.7	668.4　±　341.2
t_{max}, h	4.0 (2.0-6.0)	4.0 (3.0-6.0)
AUC_{12h}, ng.h/mL	4415　±　1792	3925　±　1472
$C_{ss,av}$, ng/mL	367.9　±　149.3	327.1　±　122.6
FI, %	191.4　±　69.69	169.4　±　38.19
LSmean ratio (90% CI), %		**test vs reference (16 vs 16)**
C_{min}		86.23 (76.47 - 97.23)
C_{max}		81.31 (69.39 - 95.27)
AUC_{12h}		89.13 (80.83 - 98.29)

[a] n = 15 for C_{0h} on Day 6 and Day 7

Safety (N = number of subjects with data)	ETR N = 16	LPV/rtv N = 16	LPV/rtv + ETR N = 16	Whole trial N = 16
At least 1 AE	**11 (68.8)**	**8 (50.0)**	**6 (37.5)**	**14 (87.5)**
AEs reported in > 1 subject, n (%)				
Headache	4 (25.0)	1 (6.3)	1 (6.3)	6 (37.5)
Dizziness	2 (12.5)	2 (12.5)	0	3 (18.8)
Diarrhea	0	2 (12.5)	1 (6.3)	3 (18.8)
Flatulence	1 (6.3)	1 (6.3)	2 (12.5)	3 (18.8)
Hot flush	2 (12.5)	1 (6.3)	0	3 (18.8)
Any fatal SAE	0	0	0	0
Any other SAE	0	0	0	0
Any AE leading to permanent stop	0	0	0	0
Any grade 3 or 4 AE	0	0	1 (6.3)	1 (6.3)
One subject experienced rash on Day 5 of the co-administration phase (grade 1, possibly related to ETR and LPV/rtv). The AE lasted 9 days and resolved without sequelae before the end of the treatment phase. There was 1 grade 3 AE, blood triglycerides increased, reported in 1 subject (6.3%) in the co-administration phase of the trial.				
Clinical Laboratory Tests				
Any grade 1 laboratory abnormality	9 (56.3)	11 (68.8)	10 (62.5)	13 (81.3)
Any grade 2 laboratory abnormality	5 (31.3)	6 (37.5)	10 (62.5)	12 (75.0)
Any grade 3 laboratory abnormality	0	0	2 (12.5)	2 (12.5)
There were no treatment-emergent grade 4 laboratory abnormalities in this trial. A grade 3 elevation of triglycerides was observed in the co-administration phase in 1 subject, and was reported as an AE by the investigator. Another subject developed grade 3 LDL and total cholesterol levels in the co-administration phase; in the subsequent ETR treatment phase and during follow-up the values returned to the level recorded at Baseline. No urinalysis abnormalities were reported throughout the trial.				
Cardiovascular Safety There were no consistent or clinically relevant median changes in vital signs or ECG parameters, and no clinically relevant individual abnormalities.				
Physical and skin examination The physical and skin examination did not reveal any new clinical findings in the course of the trial.				

Conclusions

The results of this trial demonstrate that etravirine C_{min}, C_{max} and AUC_{12h} were decreased by 45%, 30%, and 35%, respectively, when co-administered with LPV/rtv 400/100 mg b.i.d. compared to treatment with etravirine alone. The effect of etravirine 200 mg b.i.d. on the pharmacokinetics of lopinavir and ritonavir was limited. In the presence of etravirine, lopinavir C_{min} was decreased by 20% compared to treatment with LPV/rtv alone. The 90% CIs of the LSmean ratios for C_{max} and AUC_{12h} were within the limits for bioequivalence (80% to 125%). Ritonavir C_{min} and C_{max} were decreased by 14% and 19%, respectively, in the presence of etravirine compared to LPV/rtv alone; no effect on AUC_{12h} was observed. The decreases in ETR, LPV and ritonavir plasma concentrations are not considered clinically relevant. ETR and LPV/rtv can be coadministered without dose adjustments.

Short-term co-administration of ETR with LPV/rtv in 16 healthy subjects was generally safe and well tolerated. No new or clinically significant safety issues were identified for ETR with respect to the parameters studied, including AEs, laboratory and cardiovascular safety, and physical and skin examination.

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