SYNOPSIS

Study Identification and Protocol Summary

Company: Tibotec Pharmaceuticals **Trade Name**: Intelence™ **Indication**: HIV-1 infection	**Drug Substance**: etravirine (ETR, formerly known as TMC125) **Study no**.: CR015775, TMC125-TiDP2-C188 **Clinical Phase**: I
Title: A Phase I, open-label study to investigate the pharmacokinetic effects of multiple-dose TMC125 on buprenorphine and norbuprenorphine administered in HIV-negative subjects on stable buprenorphine/naloxone maintenance therapy.	
Investigator: Professor J. White, Dept. of Clinical and Experimental Pharmacology, University of Adelaide, Adelaide, Australia. From April 1, 2010 onwards: School of Pharmacy and Medical Sciences, University of South Australia, City East Campus, North Terrace, SA 5000, Australia.	**Country**: Australia
Study Period: Start: 02-Mar-2009 End: 23-Nov-2009	**No. of Investigators**: 1 **No. of Subjects**: 22
Objectives: The primary objective of this study was to determine the effect of multiple dose etravirine (ETR) on the steady-state pharmacokinetics of buprenorphine and its metabolite norbuprenorphine in human immunodeficiency virus (HIV)-negative subjects. Secondary objectives were to determine (a) the steady-state pharmacokinetics of ETR in subjects on stable individualized buprenorphine/naloxone treatment; (b) the pharmacodynamic effects of opiate excess or withdrawal during 2 weeks of co-administration with ETR; (c) the short-term safety and tolerability of the co-administration of ETR and buprenorphine/naloxone.	
Design: This is a Phase I, open-label, add-on study in subjects who are on stable sublingual buprenorphine/naloxone maintenance therapy, to investigate the potential pharmacokinetic effect of multiple-dose etravirine (ETR, formerly known as TMC125) on buprenorphine and norbuprenorphine administered as buprenorphine/naloxone. The study population consisted of HIV-negative opioid dependent subjects on stable individualized sublingual buprenorphine/naloxone maintenance therapy; 16 subjects were to be included. Subjects first participated in a 2 week run-in period with supervised buprenorphine/naloxone intake. Subsequently, subjects received ETR 200 mg b.i.d. for 14 days added to their buprenorphine/naloxone treatment. During the treatment period from Day 1 to Day 14, the individualized buprenorphine/naloxone treatment was continued with co administration of ETR. Full pharmacokinetic profiles of buprenorphine and norbuprenorphine were determined on Days –1 and 14 up to 24 hours postdose. Full pharmacokinetic profiles of ETR were determined on Day 14 up to 12 hours postdose. Pharmacodynamic assessments of symptoms of opiate withdrawal and excess were performed. The short-term safety and tolerability were assessed throughout the study.	

Subject Selection: Inclusion criteria

1. Male or female opioid-dependent subjects, aged between 18 and 55 years, extremes included.
2. Body Mass Index (BMI) of 18.0 to 30.0 kg/m^2, extremes included.
3. Informed Consent Form (ICF) signed voluntarily before the first study-related activity.
4. Receiving once daily buprenorphine/naloxone maintenance therapy at a stable individualized dose formulated and administered as sublingual tablets with a maximum daily dose of 16/4 mg of buprenorphine/naloxone. Subjects using buprenorphine only are also eligible if they switch to buprenorphine/naloxone minimally 2 weeks before randomization.
5. The subject agreed (a) not to change the current buprenorphine/naloxone therapy from Screening until Day 14 included (switching buprenorphine to buprenorphine/naloxone between Screening and Day -14 is allowed); (b) to have a daily observed and documented buprenorphine/naloxone intake from Day –14 until Day 15.
6. Able to comply with protocol requirements.
7. The subject had obtained written approval from his/her addiction physician for participation in this study. The physician agreed to provide medical care for the subject after discharge.
8. General medical condition, in the investigator's opinion, did not interfere with the assessments and the completion of the study.

Exclusion Criteria

1. A positive HIV-1 or HIV-2 test at Screening.
2. Female, except if postmenopausal since more than 2 years, or posthysterectomy, or post-tubal ligation (without reversal operation).
3. Evidence of current use of barbiturate, amphetamine, recreational or narcotic drug use (cocaine, inhalants, stimulants), sedative hypnotics (benzodiazepines), excessive alcohol or opioids. The drug screening involves analysis for amphetamines, barbiturates, benzodiazepines, cocaine and opioids.
   Positive drug screening tests resulting from cannabinoids and alcohol breath test results below 0.5 (2 standard drinks per day for men and 1 for women) were not considered exclusionary.
   A positive urine drug screen for benzodiazepines at Screening were not considered exclusionary in case the repeated drug screen is negative prior to Day -14.
4. Hepatitis A infection (confirmed by hepatitis A antibody IgM), or hepatitis B infection (confirmed by hepatitis B surface antigen) at Screening.
5. Chronic hepatitis C unless aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are < 3 x ULN, subject was clinically stable, did not meet the definition of decompensated liver function, AST and ALT had been stable (no increase in DAIDS grade for these parameters) over the 3 months prior to Screening, and platelets were within laboratory normal range. Decompensated liver function was defined as clinical or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels (International Normalized Ratio [INR] > 1.5, or albumin < 30 g/L or bilirubin ≥ 2.5 x upper limit of normal [ULN]).
6. Currently active gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, renal, hepatic, respiratory, inflammatory, or infectious disease.
7. Currently significant diarrhea, gastric stasis, or constipation (other than the pharmacodynamic (PD) effects of buprenorphine/naloxone) that, in the investigator's opinion, could influence drug absorption or bioavailability.
8. Currently active significant psychiatric disease other than drug dependency.
9. Any history of significant skin disease such as, but not limited to, rash or eruptions, drug allergies, food allergy, dermatitis, eczema, psoriasis, or urticaria.
10. Previously demonstrated clinically significant allergy or hypersensitivity to ETR or any of the excipients.
11. Use of disallowed concomitant medication during the 14 days prior to the first dose of study medication. Concomitant therapy that was allowed could not be changed between Day -14 and Day 15, except for ibuprofen and paracetamol (see section 3.3.6).
12. Participation in an investigational drug study (i.e. last intake of study medication) within 60 days prior to the first intake of investigational medication (ETR).
13. Donation of blood or plasma within 60 days preceding the first intake of study medication.
14. Subjects with the following laboratory abnormalities at Screening as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS grading table") and in accordance with the normal ranges of the clinical laboratory:
    - serum creatinine grade 1 or greater (≥ 1.1 x ULN);
    - lipase grade 1 or greater (≥ 1.1 x ULN);
    - hemoglobin decrease grade 1 or greater (≤ 10.9 g/dL);
    - platelet count grade 1 or greater (≤ 124.999 x 10^9/L);
    - absolute neutrophil count grade 1 or greater (≤ 1.3 x 10^9/L);
    - AST or ALT grade 1 or greater (≥ 1.25 x ULN), with exception of subjects with chronic hepatitis C as described in exclusion criterion 5;
    - any other laboratory abnormality of grade 2 or above, including proteinuria (spot urine) > 2+, and microscopic hematuria (> 10 RBC/HPF). A urine retest for proteinuria and microscopic hematuria could be performed in women after the menstrual period.
15. Having participated in more than 1 study (single or multiple doses) with ETR (etravirine), TMC120 (dapivirine) and/or TMC278 (rilpivirine, formerly known as R278474) or having developed rash, erythema, or urticaria while participating in a study with the aforementioned compounds.
16. Lack of reasonable venous access as judged by the attending physician or study nurse.

Treatment	Etravirine	Buprenorphine/naloxone (Suboxone®)
Concentration Dosage Form (F No.) Usage	100 mg tablet (F060) oral	2 mg/0.5 mg or 8 mg/2 mg tablet (sublingual) oral
Batch Number	8JT09, 8KT0H, 8KT0G	Separate drug accountability was not performed
Dose Regimen	1. Subjects were to receive ETR 200 mg b.i.d. for 14 days, in addition to their current buprenorphine/naloxone maintenance therapy which was taken at a maximum of 16/4 mg q.d. (individualized dose) from Day -14 until Day 14.	
Duration of Treatment	14 days	
Duration of Study	29 days (excluding screening and follow-up)	

Disallowed Medication:
All investigational drugs were disallowed from 90 days prior to the first intake of study medication and throughout the study. The following medications were not allowed from Day –14 until Day 15:

- Cytochrome P450 inducers: rifamycins: rifabutin, rifampicin/rifampin, rifapentin;
  anticonvulsants: phenobarbital, phenytoin, carbamazepine;
  systemic dexamethasone;
  all products containing *Hypericum perforatum* (St. John's Wort).
- Cytochrome P450 inhibitors and inhibitors of transporting proteins:
  - systemic azole antifungals: ketoconazole and voriconazole;
  - macrolide antibiotics: erythromycin, clarithromycin, and troleandomycin.
- The antiarrhythmics amiodarone and quinidine;
- Benzodiazepines;
- Warfarin.

Any other medication the subject was using had to be discussed with the Sponsor prior to inclusion on a case-by-case basis, except for ibuprofen and paracetamol. Concomitant therapy that was allowed could not be changed (started, stopped, or change in regimen) between Day -14 and Day 15, except for ibuprofen and paracetamol. If there was a need to change concomitant therapies during the study, dosage and regimen had to be discussed in advance with the Sponsor. Ibuprofen and paracetamol could be used up to 3 days before the first administration of study medication. After that, the clinical investigator could permit the use of ibuprofen and paracetamol from 3 days before the first study medication intake until 12 hours after the last study medication intake at no more than 400 mg and 3000 mg per day, respectively. In case ibuprofen and paracetamol were used, the dose, dosage regimen and the indication for use had to be recorded in the Concomitant Therapy section of the CRF.
Comedication was allowed in the following cases:

- In case of cutaneous event/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.
- In case of nausea, the use of antiemetics was permitted.
- In case of diarrhea, the use of loperamide was permitted.

Assessments	
Pharmacokinetics	Blood samples for measurement of ETR concentrations were taken: - on Days 3, 5, 9, and 12 (predose); - on Day 14 (predose, at 0.5h, 1h, 2h, 3h, 4h, 6h, 9h, and 12h postdose); - at time of dropout or the following morning. Blood samples for measurement of buprenorphine and norbuprenorphine concentrations were taken: - on Day -2, 3, 5, 9, and 12 (predose); - on Day -1 (predose, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 9h, 12h postdose); - on Day 14 (predose, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 9h, 12h and 24h postdose); - at time of dropout or the following morning.
Safety	
AEs	AEs were monitored continuously from signing of the ICF onwards till the last study-related visit.
Clinical Laboratory	Safety blood samples were taken at Screening and on Days -14, Day-1 (predose), Day 1, 3, 5, 9, 12, 14, 15 (predose), and twice in follow-up, i.e., 5-7 and 30-32 days after the last ETR intake. All biochemistry samples, except those taken at time of dropout, had to be taken fasted for at least 10 hours. A safety blood sample had to be taken at the time of dropout or the following morning Urine samples were taken at Screening and on Day -14, -2, 3, 5, 9, 12, 14, and twice in follow-up, i.e., 5-7 and 30-32 days after the last ETR intake. A urine sample had to be taken at the time of dropout or the following morning;
Cardiovascular safety	ECG and vital signs were recorded at Screening, on Day -14 (predose), on Day -1 (predose and 4h postdose), on Days 3, 5, 9, 12 (predose), on Day 14 (predose and 4 h postdose, on Day 15 (predose), and twice in follow-up, i.e., 5-7 and 30-32 days after the last ETR intake.
Other Safety Observations	Physical examination (including skin examination) was performed at Screening, on Day 15, and twice in follow-up, i.e., 5-7 and 30-32 days after the last ETR intake. Pupillometry was performed on Day -1 and Day 14 (predose and 1.5h postdose on both days). Short Opiate Withdrawal Scale (SOWS), and Desires for Drugs Questionnaire Scale (DDQ) were completed on Day -14 (predose), Day -1 (predose), Day 1-15 (predose). The Buprenorphine Toxicity Assessment was completed on the same days, 1.5 h postdose.
Statistical Methods	Intent-to-treat (ITT) analysis, descriptive statistics, linear mixed effects modeling, frequency tabulations

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition		**All subjects N = 22**
Number of Subjects Entered (male/female)		22 / 0
Age (years), median (range)		45.0 (28-53)
Race: Caucasian, n (%)		22 (100)
Height (cm), median (range)		180.5 (167-194)
Body Mass Index (kg/m^2), median (range)		26.0 (19-34)
Number of subjects with buprenorphine/naloxone dose:	16/4 mg	5 (22.7)
	14/3.5 mg	7 (31.8)
	12/3 mg	2 (9.1)
	10/2.5 mg	1 (4.5)
	8/2 mg	3 (13.6)
	6/1.5 mg	2 (9.1)
	5/1.25 mg	1 (4.5)[a]
	4/1 mg	1 (4.5)

[a] Subject used half of a 2 / 0.5 mg tablet.

Pharmacokinetics of Buprenorphine (mean ± SD, t_{max}: median [range])	**Individualized buprenorphine/naloxone therapy Day -1 - Reference**	**Individualized buprenorphine/naloxone therapy + ETR 200 mg b.i.d. Day 14 - Test**
Six subjects who received ETR 100 mg b.i.d. throughout the co-administration phase were excluded from the PK analysis.		
n	16	16[a]
C_{0h}, pg/mL	847.0 ± 435.1	523.4 ± 307.5
C_{min}, pg/mL	847.0 ± 435.1	503.8 ± 281.0
C_{max}, pg/mL	5259 ± 2439	4473 ± 2021
t_{max}, h	1.5 (1.0-2.0)	1.5 (0.5-2.0)
AUC_{24h}, pg.h/mL	40910 ± 16460	28860 ± 9950
$C_{ss,av}$, pg/mL	1705 ± 686.0	1202 ± 416.5
Fluctuation index (FI), %	255.7 ± 61.76	330.4 ± 69.54
LSmean ratio (90% CI)		
		Test vs. reference
n		16[a] vs 16
C_{min}	-	0.595 (0.523-0.678)
C_{max}	-	0.894 (0.760-1.052)
AUC_{24h}	-	0.746 (0.659-0.844)

[a] n = 15 for AUC_{24h}, $C_{ss,av}$ and FI

Pharmacokinetics of Norbuprenorphine (mean ± SD, t_{max}: median [range])	**Individualized buprenorphine/naloxone therapy Day -1 - Reference**	**Individualized buprenorphine/naloxone therapy + ETR 200 mg b.i.d. Day 14 - Test**
Six subjects who received ETR 100 mg b.i.d. throughout the co-administration phase were excluded from the PK analysis.		
n	16	16[a]
C_{0h}, pg/mL	2079 ± 1313	1564 ± 905.3
C_{min}, pg/mL	2034 ± 1235	1461 ± 755.8
C_{max}, pg/mL	3846 ± 2416	3981 ± 2328
t_{max}, h	1.5 (1.5-12.0)	1.5 (1.0-24.0)
AUC_{24h}, pg.h/mL	62180 ± 39720	52460 ± 29050
$C_{ss,av}$, pg/mL	2591 ± 1655	2184 ± 1212
FI, %	68.94 ± 17.49	118.8 ± 33.59
LSmean ratio (90% CI)		
		Test vs. reference
n		16[a] vs 16
C_{min}	-	0.764 (0.671-0.869)
C_{max}	-	1.079 (0.947-1.229)
AUC_{24h}	-	0.879 (0.806-0.959)

[a] n = 15 for AUC_{24h}, $C_{ss,av}$ and FI

Parent/metabolite ratios of C_{min}, C_{max} and AUC_{24h} were decreased by 22%, 17% and 15%, respectively, after the combined intake of buprenorphine/naloxone and ETR.

Pharmacokinetics of ETR (mean ± SD, t_{max}: median [range])	**ETR 200 mg b.i.d. + individualized buprenorphine/naloxone therapy**	**ETR 200 mg b.i.d. alone (pooled historical controls: TMC125-C171, TMC125-C177, TMC125-C178)**
Six subjects who received ETR 100 mg b.i.d. throughout the co-administration phase were excluded from the PK analysis.		
n	16	77
C_{0h}, ng/mL	643.6 ± 319.8	509.0 ± 170.6
C_{min}, ng/mL	581.2 ± 227.4	461.7 ± 151.8
C_{max}, ng/mL	1144 ± 341.9	944.9 ± 260.5
t_{max}, h	3.0 (2.0-4.0)	4.0 (2.0-6.1)
AUC_{12h}, ng.h/mL	10070 ± 3549	8187 ± 2387
$C_{ss,av}$, ng/mL	839.1 ± 295.9	684.6 ± 199.7
FI, %	71.71 ± 31.75	71.88 ± 16.86

GCP Compliance

The study was designed and set up in line with GCP guidance by the Sponsor. However, despite increased Sponsor monitoring efforts, a substantial number of GCP-deviations occurred at the site level during the conduct of the study:

- not all protocol-specified laboratory tests were performed;
- not all screening test results were available before randomization;
- not all ECG source data could be made available by the site and part of the ECG source data did not match the info entered in the CRF.
- pupillometry measurement was not performed according to protocol;
- not all protocol-specified pupillometry tests were performed;
- protocol-specified ETR dosing was not adhered to;
- protocol-specified dosing times were not adhered to;
- inappropriate task delegation at the study site;
- protocol-specified maximum duration of screening period was not adhered to.

Safety results

Because the trial was, despite increased Sponsor monitoring efforts, not conducted in compliance with all GCP guidelines, no definite conclusions can be drawn from the safety data summarized below.

Adverse Events (AEs)	**BUP/NAL Screening + Run-in[a] N = 22**	**BUP/NAL + ETR Co-administration N = 22**	**BUP/NAL Follow-up N = 22**	**Whole Study N = 22**
Most frequently reported AEs (reported in > 1 subject during the whole study), n (%)				
Headache	0	5 (22.7)	0	5 (22.7)
Abdominal pain	1 (4.5)	3 (13.6)	0	3 (13.6)
Insomnia	3 (13.6)	1 (4.5)	0	3 (13.6)
Pruritus	0	2 (9.1)	0	2 (9.1)
Myalgia	2 (9.1)	2 (9.1)	0	2 (9.1)
n (%) with 1 or more AEs	4 (18.2)	11 (50.0)	0	12 (54.5)
n (%) of deaths	0	0	0	0
n (%) with 1 or more other serious AEs	0	0	0	0
n (%) of treatment stopped due to AEs	0	0	0	0
n (%) with 1 or more grade 2 to 4 AEs	0	0	0	0
n (%) with at least 1 AE considered at least possibly related to ETR	0	0	0	0
n (%) with at least 1 AE considered at least possibly related to buprenorphine/naloxone	1 (4.5)	0	0	1 (4.5)

All AEs were grade 1 in severity and none were considered by the investigator as possibly, probably or very likely related to ETR; one AE (lacrimation increased) was assessed as very likely related to buprenorphine/naloxone. The following treatment-emergent AEs that could possibly be due to opiate withdrawal or excess were reported in the co-administration phase (all grade 1): upper abdominal pain (2 subjects, 9.1%), muscle spasms, malaise, hypoventilation, dyspnea (1 subject each, 4.5%).

[a] All AEs observed from the signing of the informed consent form until the start of the co-administration phase
BUP/NAL = buprenorphine/naloxone
N = total number of subjects per treatment phase, n = number of subjects with 1 or more events

Clinical Laboratory Tests: There were no consistent or clinically relevant changes over time in median and mean laboratory values for blood chemistry or hematology. There were no treatment-emergent grade 4 laboratory abnormalities in this study. One subject developed a grade 3 laboratory abnormality (hypophosphatemia) at one time point in the co-administration phase, the phosphorus level was within the normal range at all other time points of the study. Three other subjects developed a treatment-emergent grade 3 abnormality in the follow-up phase of the study (hypophosphatemia, LDL increased and AST increased). The most common treatment-emergent grade 1 or 2 laboratory abnormalities were hypoglycemia (12 subjects or 54.6%) and total cholesterol increased (10 subjects or 45.5%).
Non-graded abnormalities were reported in at most 4 subjects (18.2%) per laboratory parameter during co-administration of buprenorphine/naloxone and ETR.
None of the laboratory abnormalities were reported as an AE.
No abnormal urinalysis results were found throughout the study. The urine drug screen tests were negative throughout the study for all subjects for the substances methadone, cocaine, and barbiturates. There were positive test results for benzodiazepines, amphetamines, and opioids. The incidence of positive drug urine test was highest in the follow-up phase (15 subjects or 68.2%), and lowest in the co-administration phase (5 subjects or 22.7%).

Cardiovascular Safety: Median changes in vital signs were generally minor and none of the observed changes were considered clinically significant.
Six subjects (27.3%) had at least 1 abnormal QTcF interval prior to the first administration of ETR. Five subjects (22.7%) had a treatment-emergent abnormal QTcF interval during the co-administration phase, in 3 of them an abnormal QTcF was also recorded on the follow-up phase. One of these 5 subjects had a QTcF inteval above 500 ms in the co-administration phase and in the follow-up phase. One additional subject had an abnormal QTcF interval (>500 ms) in the follow-up phase only. Increases between 30 and 60 ms or >60 ms which did not lead to abnormal QTcF values, were observed in 10 additional subjects.
No AEs related to vital signs or ECG were reported.

Other Safety Observations:
No abnormal findings in physical examination were reported.
The SOWS indicated that subjects experienced no or mild opiate withdrawal symptoms when ETR was co-administered with buprenorphine/naloxone.
The Buprenorphine Toxicity Assessment generated one grade 1 opiate excess symptom, i.e., hypoventilation.
The DDQ showed no indication in the co-administration phase for an increased desire to use drugs.
No relevant differences in mean pupil diameter were observed between Day -1 (BUP/NAL maintenance treatment) and Day 14 (co-administration ETR and buprenorphine/naloxone).

Conclusions

Pharmacokinetic data were derived from 16 subjects eligible for the pharmacokinetic analysis. When ETR 200 mg b.i.d. was added to a stable individualized buprenorphine/naloxone maintenance therapy in the 16 subjects with evaluable pharmacokinetic data, C_{min}, C_{max} and AUC_{24h} of buprenorphine were decreased by 40%, 11% and 25%, respectively, compared to treatment with buprenorphine/naloxone alone. For norbuprenorphine, C_{min} was decreased by 24% after co-administration with ETR, while C_{max} and AUC_{24h} were comparable between both treatments. Parent/metabolite ratios of C_{min}, C_{max} and AUC_{24h} were decreased by 22%, 17% and 15%, respectively, after the combined intake of buprenorphine/naloxone and ETR. No relevant difference was observed in the pharmacokinetics of ETR when given as 200 mg b.i.d. in the presence of buprenorphine/naloxone as compared to intake of ETR alone in historical control subjects.

The study was designed and set up in line with GCP guidance by the Sponsor. However, despite increased Sponsor monitoring efforts, a substantial number of GCP-deviations occurred at the site level during the conduct of the study. Therefore, no definite conclusions can be drawn from the safety data.

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