SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: - **Indication**: Hepatitis C virus infection	**Drug Substance**: TMC435350 **Trial no**.: TMC435350-TiDP16-C104 **Clinical Phase**: I
Title: Phase I, open-label trial in healthy subjects to evaluate the drug-drug interaction between ritonavir at steady-state and TMC435350, a viral protease inhibitor against hepatitis C virus, after the first and the last dose of a multiple dosing regimen.	
Investigator: I. Demeyer, MD; Phone: +32 53 72 49 97; Fax: +32 53 72 45 05	**Country**: Belgium
Trial Period: Start: 02-Nov-2007 End: 22-Jan-2008	**No. of Investigators**: 1 **No. of Subjects**: 12
Objectives: The objectives of this trial were to investigate the effect of steady-state ritonavir on the plasma pharmacokinetics of TMC435350 after the first and last dose of a multiple dosing regimen and to explore the short-term safety and tolerability of multiple doses of TMC435350 200 mg q.d. administered alone and in combination with ritonavir 100 mg b.i.d.	
Design: This was a Phase I, open-label, single arm trial in 12 healthy subjects to investigate the effect of steady-state ritonavir, a potent CYP3A4 inhibitor, on the plasma pharmacokinetics of TMC435350 after the first and the last dose of a multiple dosing regimen. The trial consisted of 2 sequential sessions: – In Session 1, each subject received TMC435350 200 mg once daily (q.d.) (oral dosing) for 7 days under fed conditions. – In Session 2, each subject received ritonavir 100 mg twice daily (b.i.d.) from 5 days before until 3 days after dosing of TMC435350 (Day 1 to 15). TMC435350 200 mg q.d. (oral dosing) was taken for 7 days (Day 6 to 12). All intakes were under fed conditions. There was a washout period of at least 7 days between Session 1 and Session 2. Full pharmacokinetic profiles of TMC435350 were determined on Days 1 and 7 of Session 1 and on Days 6 and 12 of Session 2. These results were compared to evaluate a potential pharmacokinetic drug interaction effect by ritonavir. Safety and tolerability were recorded continuously.	
Subject Selection Inclusion Criteria: Subjects had to meet all of the following inclusion criteria: 1. Aged between 18 and 55 years, extremes included. 2. Non-smoking for at least 3 months prior to selection. 3. Normal weight as defined by a Quetelet Index (Body Mass Index: 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, prior to the first trial related activity. 5. Able to comply with protocol requirements. 6. Normal 12-lead electrocardiogram (ECG) (in triplicate) at screening including: a. Normal sinus rhythm (heart rate between 40 and 100 bpm); b. QTc interval ≤ 450 ms; c. QRS interval < 120 ms d. PR interval ≤ 220 ms. 7. Healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, vital signs, and the results of blood biochemistry, blood coagulation, and hematology tests and a urinalysis carried out at screening.	

Exclusion Criteria

Subjects could not have any of the following characteristics:

1. Past history of heart arrhythmias (extrasystoli, tachycardia at rest) or having baseline prolongation of QTc interval > 450 ms, history of risk factors for Torsade de Pointes syndrome (hypokalemia, family history of long QT Syndrome…).
2. Female, except if postmenopausal for more than 2 years, or post-hysterectomy or post-tubal ligation (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 the trial procedures.
4. Hepatitis A infection (confirmed by hepatitis A antibody immunoglobulin M), or hepatitis B infection (confirmed by hepatitis B surface antigen), or hepatitis C infection (confirmed by hepatitis C virus antibody), or human immunodeficiency virus type 1 (HIV-1) or HIV-2 infection (confirmed by positive HIV-1/2 test) at screening.
5. A positive urine drug test at screening. Urine was tested for the presence of amphetamines, benzodiazepines, cocaine, cannabinoids and opioids.
6. Currently active or underlying gastrointestinal, cardiovascular, neurological, 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. History of drug allergy such as, but not limited to, sulfonamides and penicillins, or drug allergy witnessed in previous trials with experimental drugs.
10. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication administered in this trial.
11. Use of concomitant medication, except for paracetamol (acetaminophen) and ibuprofen in a period of 14 days before the first study medication intake.
12. Participation in an investigational drug trial within 60 days prior to the first intake of study medication.
13. Donation of blood or plasma in the 60 days preceding the first intake of study medication.
14. Subjects with 1 or more of the following laboratory abnormalities as defined by the Division of Microbiology and Infectious Diseases Adult Toxicity Table. (see addendum 2 of the clinical trial protocol)
    - Serum creatinine grade 1 or greater (> 1.0 x upper limit of laboratory normal range [ULN]);
    - Pancreatic amylase or lipase grade 2 or greater (> 1.5 x ULN);
    - Hemoglobin grade 1 or greater (≤ 10.5 g/dL);
    - Platelet count grade 1 or greater (≤ 99.999 10^9/L);
    - Absolute neutrophil count grade 1 or greater (≤ 1500/mm³);
    - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) grade 1 or greater (≤ 1.25 x ULN);
    - Any other toxicity grade 2 or above.

Treatment	**TMC435350**	**Ritonavir (Norvir®)**
Concentration Dosage Form (F No.) Usage	100 mg capsule Capsule (F007) Oral	100 mg capsule Capsule Oral
Batch Number	07J15/F007	53015VA
Dose Regimen	Session 1: TMC435350 200 mg q.d. for 7 days; Session 2: TMC435350 200 mg q.d. for 7 days (Day 6-12) + ritonavir 100 mg b.i.d. from 5 days before until 3 days after the first intake of TMC435350 in Session 2 (Days 1-15). There was a washout period of at least 7 days between both treatment sessions.	
Duration of Treatment	22 days (excluding screening, the washout period, and follow-up)	
Duration of Trial	Approximately 11 weeks (counting a screening period of 3 weeks, a 1-week washout period, and a 4-week follow-up period)	

Disallowed Medication	During the entire trial, subjects could not use any medication other than the study medication. All medication had to be discontinued at least 14 days before first drug administration, except for paracetamol (acetaminophen) or ibuprofen. Subjects could also not use any herbal medications or dietary supplements including products containing *Hypericum perforatum* (St. John's wort) from 14 days before the start of the trial and throughout the duration of the trial. Paracetamol and ibuprofen could be used up to 3 days before the first administration of study medication. After that, the investigator could permit the use of paracetamol or ibuprofen from 3 days before the first administration of study medication in each session until the last pharmacokinetic blood sample had been taken in each session at no more than 3 x 500 mg per day and no more than 3 grams per week (paracetamol) and at no more than 1 x 400 mg per day (ibuprofen). Hormone replacement therapy was allowed in postmenopausal women. Other comedication was allowed in the following cases: - 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. - In case of nausea, the use of antiemetics was permitted. - In case of diarrhea, the use of loperamide was permitted. In case any of these medications were used, the indication, the dose and dose regimen had to be recorded in the Concomitant Therapy Section of the CRF. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition had to be documented in the Adverse Event (AE) Section of the Case Report Form (CRF).
Assessments	
Pharmacokinetics	Blood samples for the determination of **TMC435350** concentration were taken: In Session 1: – predose on Days 1[a], 2[b], 6[b], and 7[b]; – 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, and 12h post dose on Days 1 and 7; – on Day 8 (24h and 36h after last dosing, respectively); – on Days 9, 10 and 11 (i.e., 48h, 72h, and 96h after last dosing, respectively); – in case of dropout or the following morning. In Session 2: – predose on Days 6[b], 7[b], 11[b] and 12[b]; – 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, and 12h post dose on Days 6 and 12; – on Day 13 (24h and 36h after last dosing, respectively); – on Days 14, 15, and 16 (i.e., 48h, 72h, and 96h after last dosing, respectively); – in case of dropout or the following morning. Blood samples for the determination of **ritonavir** concentration were taken in Session 2: – on Day 1 (predose[a]); – on Days 4, 5, 6, 7, 11, 12, 13 and 14 (predose[b]); – on Days 6 and 12 (2h and 12h post dose); – on Days 13[b] and 15[b] (i.e., 24h and 48h postdose); – in case of dropout or the following morning. [a] within 2 hours before morning study medication intake [b] immediately before study medication intake

Safety	
Adverse Events	Adverse events were monitored continuously from signing of the ICF until the last trial-related activity.
Clinical Laboratory	Urine samples and blood samples for hematology, general biochemistry[a], coagulation, and additional testing were taken: – At screening; – predose[b] of Days 1 and 7 in Session 1 and Days 1, 6, and 12 in Session 2; – 4h (blood and urine samples) and 8h (urine samples only) post dosing on Days 1 and 7 in Session 1 and Days 6 and 12 in Session 2; – on Day 11 in Session 1; – on Days 15 and 16 in Session 2; – in case of dropout or the following morning, and at 10-14 days and 30-35 days after dropout; – at the first (10-14 days after last drug intake) and second (30-35 days after last drug intake) follow-up visit. [a] All biochemistry samples had to be taken fasted for at least 10 hours, except for the samples taken 4h post dose. [b] within 2 hours before morning study medication intake
Cardiovascular safety	ECG and vital signs were measured: – At screening; – predose[a] on Days 1 and 7 in Session 1 and Days 1, 6, and 12 in Session 2; – 4h, 6h[b], 8h, and 12h postdose on Days 1 and 7 in Session 1 and Days 6 and 12 in Session 2; – on Day 11 in Session 1; – on Days 15 and 16 in Session 2; – in case of dropout or the following morning, and at 10-14 days and 30-35 days after dropout; – at the first and second follow-up visit. [a] within 2 hours before morning study medication intake [b] only ECG
Statistical Methods	Intent-to-Treat analysis, descriptive statistics, frequency tabulations, Wilcoxon matched-pairs signed-ranks test, linear mixed effects modeling, nonparametric test (t_{max})

Main Features of the Subject Sample and Summary of the Results

Parameter	All Subjects N = 12
Number of subjects entered Male/ Female	12 12/0
Age, years Median (range)	 35.5 (18-54)
Height, cm Median (range)	 181.0 (164-189)
Weight, kg Median (range)	 80.0 (60-100)
BMI, kg/m^2 Median (range)	 24.8 (20-28)
Number of discontinuations, n (%)	0

Pharmacokinetics of TMC435350 (mean ± SD, t_{max}: median [range])	**TMC435350 alone, Day 1 (Session 1) (reference 1)**	**TMC435350 alone, Day 7 (Session 1) (reference 2)**	**TMC435350 + ritonavir, Day 6 (Session 2) (test 1)**	**TMC435350 + ritonavir, Day 12 (Session 2) (test 2)**
n	12	12	12	12[b]
C_{0h}, ng/mL	-	1140 ± 970.4	-	14050 ± 6987
C_{24h}, ng/mL	-	1304 ± 1197	-	15680 ± 6964
C_{min}, ng/mL	-	1030 ± 971.6	-	11730 ± 5651
C_{max}, ng/mL	2194 ± 801.5	4617 ± 2788	2978 ± 1393	20150 ± 7861
t_{max}, h	6.0 (4.0 – 8.0)	6.0 (4.0 – 12.0)	6.0 (6.0 – 12.0)	6.0 (0.0 – 12.0)
$C_{ss,av}$, ng/mL	-	2514 ± 1724	-	16290 ± 6320
FI, %	-	155.5 ± 42.55	-	54.97 ± 19.81
AUC_{24h}, ng.h/mL	22510 ± 8236	60340 ± 1370	42180 ± 17670	391000 ± 151700
λ_z, 1/h	-	0.06262 ± 0.01065	-	0.008831[c] ± 0.004067[c]
$t_{1/2term}$, h	-	11.39 ± 2.095	-	121.1[c] ± 119.7[c]
Acc. Ratio, y/x, %[a]	-	250.2 ± 74.09	-	1005 ± 353.7
LS mean ratio (90% CI), %				
			Test 1 versus Reference 1	**Test 2 versus Reference 2**
n	-	-	12 versus 12	12 versus 12
C_{0h}, ng/mL	-	-	-	1478 (1086-2011)
C_{min}, ng/mL	-	-	-	1435 (1029-2001)
C_{max}, ng/mL	-	-	129.6 (107.6 – 156.1)	470.2 (383.7 – 576.2)
AUC_{24h}, ng.h/mL	-	-	183.3 (164.1 – 204.6)	717.6 (563.1 – 914.5)

[a] for TMC435350 alone; x = Day 1 and y = Day 7; for TMC435350 + ritonavir: x = Day 6 and y = Day 12
[b] n = 10 for λ_z and $t_{1/2term}$
[c] accurate determination not possible

Pharmacokinetics of ritonavir (mean ± SD)	**TMC435350 + ritonavir Day 6[a]**	**TMC435350 + ritonavir Day 12[a]**
n	12	12
C_{min}, ng/mL	325.0 ± 278.1	582.3 ± 327.7
C_{max}, ng/mL	705.3 ± 580.5	1169 ± 589.6
AUC_{12h}, ng.h/mL	6318 ± 4581	10510 ± 5062

[a] Only 3 plasma samples were taken on Day 6 and Day 12. Therefore, mean and SD values are only indicative.

Safety (n = number of subjects with data)	**Session 1**	**Session 2**		**Whole Trial[a]**
	Phase 1 TMC435350 alone N = 12	**Phase 2 Ritonavir alone N = 12**	**Phase 3 TMC435350 + ritonavir N = 12**	**N = 12**
Most frequently reported AEs (reported in > 1 subject), n (%)				
Headache	4 (33.3)	3 (25.0)	4 (33.3)	7 (58.3)
Nasopharyngitis	3 (25.0)	0	2 (16.7)	5 (41.7)
n (%) with 1 or more AEs	7 (58.3)	5 (41.7)	7 (58.3)	12 (100.0)
n (%) of deaths	0	0	0	0
n (%) with 1 or more other SAEs	0	0	0	0
n (%) of treatment stopped due to AEs	0	0	0	0
n (%) with 1 or more grade 3 or 4 AEs	0	0	0	0
[a] *including screening and follow-up*				
No deaths or other SAEs were reported. No subjects prematurely discontinued the trial due to an AE. Overall, no relevant differences were observed in the incidence of AEs between the different treatment phases and in particular between the treatment phases when TMC435350 was given alone compared to when TMC435350 was given in combination with ritonavir.				
Clinical Laboratory Tests	No clinically relevant changes in laboratory parameters were observed over time. No grade 3 or 4 treatment-emergent graded laboratory abnormalities were observed. Overall, no difference in the incidence of abnormalities was observed between the treatment phases when TMC435350 was given alone compared to when TMC435350 was given in combination with ritonavir, apart from increases in lipid- and bilirubin levels, which were generally more frequent when TMC435350 and ritonavir were combined, compared to when both products were given alone. No laboratory-related abnormalities were reported as AEs. No abnormalities in urinalysis were observed.			
Cardiovascular Safety	No clinically relevant changes over time were seen in vital signs or ECG parameters. Overall, the incidence of treatment-emergent ECG abnormalities was low in all different treatment phases. No treatment-emergent QTc values of > 500 ms were observed during this trial. During the trial, 1 subject (8.3%) had an increase in QTc by > 60 ms (during administration of TMC435350 alone). No grade 3 abnormalities in vital signs were observed. No abnormalities in cardiovascular parameters were considered clinically relevant, and none were reported as AEs.			
Physical Examination	Three subjects (25.0%) were observed with new physical examination findings (i.e., not present at screening) (paresthesia, small nodes in the neck related to nasopharyngitis, and eczema).			

Conclusions - Removed from document.

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