SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd (now Tibotec Pharmaceuticals) **Trade Name**: Prezista **Indication**: HIV-1 infection	**Drug Substance**: TMC114 **Trial no**.: TMC114-TiDP3-C181 **Clinical Phase**: I
Title: Phase I, open-label, randomized, 3-way crossover trial to assess the pharmacokinetics of darunavir (DRV) given once-daily with different doses of ritonavir in healthy subjects.	
Investigator: P. Chandler, M.D., Charles River Clinical Services Northwest, Inc., 3615 Pacific Avenue, Tacoma WA 98418, USA	**Country**: USA
Trial Period: Start: 02-Sep-2008 End: 21-Dec-2008	**No. of Investigators**: 1 **No. of Subjects**: 21

Objectives: The primary objective of this study was to determine the effect of different ritonavir doses (20, 50, 100 mg ritonavir) on DRV exposure following once daily (q.d.) oral dosing of DRV/rtv for 7 days, in order to establish an optimal ritonavir boosting dose for DRV.
The secondary objective was to evaluate short-term safety and tolerability of DRV following administration of DRV 800 mg q.d. in the presence of different doses (20, 50 and 100 mg, respectively) of ritonavir for 7 days in healthy subjects.

Design: This was a Phase I, open-label, randomized, 3-way crossover trial in healthy subjects to assess the pharmacokinetics of darunavir (DRV) coadministered with different doses of ritonavir.

The trial population was planned to include 18 healthy adult subjects. During 3 subsequent sessions, each subject received Treatments A, B and C in a randomized way. In Treatment A, 800 mg DRV q.d. and 100 mg ritonavir q.d. were administered. In Treatment B, 800 mg DRV q.d. and 50 mg ritonavir q.d. were administered. In Treatment C, 800 mg DRV q.d. and 20 mg ritonavir q.d. were administered. All treatments were administered for 7 days and intake of DRV and ritonavir was under fed conditions.

DRV was formulated as a 400-mg tablet; ritonavir was formulated as an oral solution containing 80 mg/mL ritonavir.

In each treatment session, full pharmacokinetic profiles of DRV and ritonavir were determined up to 24 hours after administration on Day 1 and up to 72 hours after administration on Day 7.

There was a washout period of at least 7 days between subsequent treatments.

Safety and tolerability were evaluated continuously throughout the trial.

Subject Selection
Inclusion Criteria
1. Healthy volunteers, aged between 18 and 55 years, extremes included.
2. Nonsmokers, or subjects not having smoked cigarettes, pipes or cigars, or subjects not having chewed tobacco within the past 6 months.
3. Normal weight as defined by a 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, at the investigators discretion, and includes a physical examination, medical history, electrocardiogram (ECG), vital signs, and the results of blood biochemistry, blood coagulation and hematology tests and a urinalysis carried out at screening.

Exclusion Criteria
1. A positive HIV-1 or HIV-2 test at screening.
2. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational or narcotic drug use, which in the investigator's opinion would have compromised the subject's safety and/or compliance with the trial procedures.

3. Hepatitis A, B, or C infection (confirmed by hepatitis A antibody IgM, hepatitis B surface antigen [with a positive hep B PCR], or hepatitis C virus antibody, respectively) at screening.
4. A positive urine drug test at screening. Urine was tested to check the current use of amphetamines, benzodiazepines, cocaine, cannabinoids, and opioids.
5. Currently active or underlying gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, endocrinologic, genitourinary, renal, hepatic, respiratory, inflammatory, or infectious disease.
6. Currently significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could have influenced drug absorption or bioavailability.
7. Any history of significant skin disease such as, but not limited to, rash or eruptions, food or drug allergy, dermatitis, eczema, psoriasis, folliculitis, or urticaria.
8. History of significant allergy to drugs such as, but not limited to, sulfonamides and penicillines.
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, herbal preparations and dietary supplements. Concomitant medication had to be discontinued at least 14 days before the first dose of trial medication except for paracetamol (acetaminophen), hormone replacement therapy and hormonal contraceptives.
11. Female subject of childbearing potential without use of effective nonhormonal birth control methods, or not willing to continue practicing these birth control methods for at least 30 days after the end of the treatment period;

    Note: Estrogen hormonal based contraception could be not reliable when taking DRV/rtv, therefore to be eligible for this trial, women of childbearing potential had to either:
    - use a double barrier method to prevent pregnancy (i.e., using a condom with either diaphragm or cervical cap)* or;
    - use non-estrogen hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap, or female condom) or;
    - use a intrauterine device in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap, or female condom) or;
    - be only non-heterosexually active, practice heterosexual abstinence, or have a vasectomized partner (confirmed sterile).

    * A male and female condom was not to be used together due to risk of breakage or damage caused by latex friction.

    Women who were postmenopausal for at least 2 years, women with total hysterectomy and women who had been surgically sterilized, were considered of non-childbearing potential.
12. A positive pregnancy test or breast feeding at screening.
13. Participation in an investigational drug trial within 60 days prior to the first intake of trial medication.
14. Donation of blood or plasma within 60 days preceding the first intake of trial medication.
15. 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 and/or pancreatic amylase grade 1 or greater (≥ 1.1 x ULN);
    - hemoglobin grade 1 or greater (≤ 10.9 g/dL);
    - white blood cell (WBC) count grade 1 or greater (≤ 2.500 x 10^9/L);
    - absolute neutrophil count grade 1 or greater (≤ 1.3 x 10^9/L);
    - platelet count grade 1 or greater (≤ 124.999 x 10^9/L);
    - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) grade 1 or greater (≥ 1.25 x ULN);
    - total bilirubin grade 1 or greater (≥ 1.1 x ULN);
    - 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.
16. Having previously participated in a multiple-dose trial with DRV.
17. Having previously participated in more than 3 single-dose trials with DRV.
18. Subjects with the following ECG findings: abnormal PR, QRS, and QTc intervals; rhythm abnormalities; evidence of acute ischemic changes.

Treatment	DRV	Ritonavir (Norvir®)
Concentration Dosage Form (F No.) Usage	400 mg tablet (F030) oral	80 mg/mL solution oral
Batch Number	8BG5094-X	66020AF22
Dose Regimen	Treatment A: DRV/rtv 800/100 mg q.d. for 7 days Treatment B: DRV/rtv 800/50 mg q.d. for 7 days Treatment C: DRV/rtv 800/20 mg q.d. for 7 days	
Duration of Treatment	21 days	
Duration of Trial	21 days (excluding a screening period of maximum 21 days, a washout period of at least 7 days between subsequent DRV intakes, and a follow-up period of 30 to 32 days)	
Disallowed Medication	All medication had to be discontinued at least 14 days before the first intake of trial medication (Day 1 of Session I), except for paracetamol (acetaminophen). Subjects were not allowed to use any medication other than the trial medication up to 7 days after the last intake of trial medication, except for paracetamol. Subjects were also not allowed to use any systemic herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's wort) from 14 days before the first intake of trial medication and up to 7 days after the last intake of trial medication. Paracetamol could be used up to 3 days before the first intake of trial medication in each session. After that, the clinical investigator could permit the use of paracetamol from 3 days before the first intake of trial medication until the last day of trial medication intake in each session at no more than 3 x 500 mg per day or no more than 3 g per week. Female subjects of childbearing potential had to use birth-control methods and had to be willing to continue practicing these birth-control methods throughout the trial and for at least 30 days after the last intake of trial medication. Hormonal 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.	

Assessments	
Pharmacokinetics	Blood samples for measurement of DRV and ritonavir concentrations were taken: - at Day 1 (predose, 1, 2, 3, 4, 6, 8 and 12 h after trial medication intake); - at Day 2 (24 h after trial medication intake); - at Day 5 and 6 (before trial medication intake); - at Day 7 (predose, 1, 2, 3, 4, 6, 8 and 12 h after trial medication intake); - at Day 8 (24 h after trial medication intake); - at Day 9 (48 h after trial medication intake); - at Day 10 (72 h after trial medication intake); - at time of dropout or the following morning.
Safety	
Adverse Events	Adverse events (AEs) were checked at every visit and reported from signing the ICF onwards until the last trial-related visit. Severity and drug relationship of AEs towards DRV and ritonavir were recorded.
Clinical Laboratory	Samples for hematology/biochemistry measurements (taken fasted for at least 10 h before breakfast) and urine were taken: - at screening; - at Days 1 (predose), 7 (predose), and 8; - at time of dropout or the following morning; - 5 - 7 and 30 - 32 days after last intake of trial medication or after dropout A urine drug screen was performed: - at screening; - at Day -1 A urine pregnancy test was performed: - at Day -1; - at Day 8 A serum pregnancy test was performed: - at screening; - 30 - 32 days after last intake of trial medication or after dropout HIV-1 and -2, hepatitis A, B and C, and coagulation were tested at screening.
Cardiovascular Safety	ECG was measured: - at screening; - at Day 8 (24 h after trial medication intake); - at time of dropout or the following morning (only in last treatment session). Vital signs were measured: - at screening; - at Days 1 (predose), 7 (predose), and 8 (24 h after trial medication intake); - at time of dropout or the following morning; - 5 - 7 and 30 - 32 days after last intake of trial medication or after dropout.
Physical Examination	Physical examination (including skin examination) was performed: - at screening; - at Day 8 (24 h after trial medication intake); - at time of dropout or the following morning - 5 - 7 and 30 - 32 days after last intake of trial medication or after dropout
Statistical Methods	Descriptive statistics, frequency tabulations, intent-to-treat analysis, linear mixed effects modeling, nonparametric test (Koch) (for t_{max})

Main Features of the Subject Sample and Summary of the Results

	All Subjects N = 21
Baseline Characteristics	
Number of Male/Female Subjects Entered	13/8
Age: median (range), yrs	28.0 (18 - 54)
Subject Disposition	
Dropouts	4
Reason	
AE	2
Consent withdrawn	1
Lost to follow-up	1

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	**DRV/rtv 800/100 mg q.d. (reference)**	**DRV/rtv 800/50 mg q.d. (test 1)**	**DRV/rtv 800/20 mg q.d. (test 2)**
Day 1			
n	18	16	17
C_{max}, ng/mL	5612 ± 1533	5017 ± 1176	3621 ± 1213
t_{max}, h	4.0 (2.0 - 4.0)	3.5 (2.0 - 4.0)	3.0 (2.0 - 6.0)
AUC_{24h}, ng.h/mL	64600 ± 21940	49140 ± 14510	23650 ± 13000
Day 7			
n	15[b]	16[c]	17[d]
C_{0h}, ng/mL	2124 ± 802.6	1666 ± 639.4	497.5 ± 269.0
C_{min}, ng/mL	1988 ± 700.8	1452 ± 663.7	430.8 ± 282.2
C_{max}, ng/mL	6166 ± 1265	6144 ± 1325	5745 ± 1352
t_{max}, h	3.0 (1.0 - 4.0)	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)
AUC_{24h}, ng.h/mL[a]	77200 ± 23520	68510 ± 20560	46530 ± 13140
$t_{1/2term}$, h	8.563 ± 3.806	7.512 ± 3.050	6.432 ± 2.286
LS mean ratio (90% CI), % (Day 7 PK parameters)			
	-	**test 1 vs reference**	**test 2 vs reference**
n	-	16[c] vs 15[b]	17 vs 15[b]
C_{0h}	-	75.28 (65.93 - 85.95)	21.66 (16.03 - 29.26)
C_{min}	-	68.31 (58.40 - 79.90)	19.23 (13.93 - 26.56)
C_{max}	-	97.25 (90.02 - 105.1)	91.86 (83.67 - 100.9)
AUC_{24h}	-	87.16 (80.98 - 93.81)	59.97 (55.18 - 65.17)

[a] $AUC_{24h} = AUC_{tcom}$
[b] n = 17 for C_{0h}, C_{min}, C_{max}, $t_{max}$and Ratio $C_{max,\ Day7/Day\ 1}$
[c] n = 17 for C_{0h}, C_{min}, λ_z and $t_{1/2term}$
[d] n = 16 for Ratio $C_{max,\ Day\ 7/Day\ 1}$ and Ratio $AUC_{24h,\ Day\ 7/Day\ 1}$

Pharmacokinetics of ritonavir (mean ± SD, t_{max}: median [range])	DRV/rtv 800/100 mg q.d.	DRV/rtv 800/50 mg q.d.	DRV/rtv 800/20 mg q.d.
Day 1			
n	18	16	13
C_{max}, ng/mL	332.9 ± 158.5	86.31 ± 36.00	12.56 ± 6.017
t_{max}, h	6.0 (3.0 - 8.0)	6.0 (4.0 - 8.0)	6.0 (3.0 - 6.0)
AUC_{24h}, ng.h/mL	3230 ± 1222	880.8 ± 324.9	104.6 ± 87.27
Day 7			
n	15[a]	16[b]	17
C_{0h}, ng/mL	60.92 ± 39.03	18.75 ± 9.341	0 ± -
C_{min}, ng/mL	56.13 ± 39.06	15.45 ± 7.948	0 ± -
C_{max}, ng/mL	548.6 ± 416.6	122.4 ± 40.10	22.84 ± 8.130
t_{max}, h	4.025 (3.0 - 8.0)	5.025 (3.0 - 8.0)	6.0 (4.0 - 8.0)
AUC_{24h}, ng.h/mL	4851 ± 2156	1342 ± 393.6	193.5 ± 71.29

0 = NQ = Not Quantifiable (< 5.00 ng/mL)
[a] n = 17 for C_{0h}, n = 16 for C_{min}, C_{max} and t_{max}
[b] n = 17 for C_{0h} and C_{min}

Safety	Treatment A DRV/rtv 800/100 mg q.d. N = 20	Treatment B DRV/rtv 800/50 mg q.d. N = 18	Treatment C DRV/rtv 800/20 mg q.d. N = 19
Adverse Events (AEs)			
Most frequently reported AEs (> 2 subjects), n (%)			
Headache	8 (40.0)	7 (38.9)	7 (36.8)
Somnolence	3 (15.0)	1 (5.6)	0
Nausea	1 (5.0)	3 (16.7)	2 (10.5)
Pharyngitis	2 (10.0)	2 (11.1)	3 (15.8)
Pruritus	3 (15.0)	0	1 (5.3)
n (%) with at least 1 AE	13 (65.0)	14 (77.8)	11 (57.9)
n (%) of deaths	0	0	0
n (%) with at least 1 SAE	0	0	0
n (%) of treatment stopped due to AEs	0	0	2 (10.5)
n (%) with at least 1 grade 3 or 4 AE	0	0	0
n (%) with at least 1 AE considered at least possibly related to DRV	11 (55.0)	12 (66.7)	9 (47.4)

N = total number of subjects, n = number of subjects with data

Clinical Laboratory Tests	All laboratory abnormalities were grade 1 or 2 in severity. The most frequent graded abnormalities were increased LDL_{cal}, and increased total cholesterol. Hematocrit, neutrophil percentage, and insulin (all below normal), were the most frequent non-graded abnormalities. Two subjects had laboratory abnormalities that were reported as an AE. One subject (treatment sequence BAC) had grade 2 increased ALT and increased AST (this subject discontinued due to these AEs in combination with the AE pyelonephritis on Day 2 of Session III), and 1 subject (BCA) had grade 3 increased LDL_{cal} (at the Week-1 follow-up visit).
Cardiovascular Safety	There were no clinically relevant vital sign abnormalities, and no treatment-emergent abnormal QTc values of > 500 ms, or increases in QTc of > 60 ms were observed during the trial. No AEs related to vital signs or ECG abnormalities were reported.
Physical Examination	Two subjects had a treatment-emergent physical examination finding that was reported as an AE. Subject 181-0008 had a grade 2 rash, and discontinued due to this AE on the third day of the washout period after having completed Treatment C in Session I. Subject 181-0011 had grade 1 abdominal pain on Day 20 since the first medication intake. No other findings were considered clinically relevant.

Conclusions

Comparison of the effectiveness of 20, 50 and 100 mg q.d. doses of ritonavir to increase DRV exposure when combined with 800 mg q.d. DRV demonstrated that the 50 and 100 mg q.d. doses of ritonavir resulted in comparable steady-state DRV AUC_{24h} and C_{max}. The 90% confidence intervals of the LS means ratios for C_{max} and AUC_{24h} fell within the [80%, 125%] interval. C_{0h} and C_{min} of DRV at steady-state were decreased by 25% and 32%, respectively, after coadministration with 50 mg ritonavir q.d. compared to 100 mg ritonavir q.d., based on the ratios of the LS means.

In the presence of 20 mg ritonavir q.d., C_{0h}, C_{min} and AUC_{24h} of DRV at steady-state were decreased by 78%, 81% and 40%, respectively, compared to coadministration with ritonavir at 100 mg q.d., and by 73%, 75% and 35%, respectively, compared to coadministration with ritonavir at 50 mg q.d., based on the ratios of the LS means. C_{max} of DRV at steady-state was comparable following 20, 50 and 100 mg ritonavir q.d.

Mean exposure to ritonavir (AUC_{24h}) after intake at 20, 50 and 100 mg q.d. increased in a more than dose proportional manner.

The coadministration of DRV 800 mg q.d. with the three different doses of ritonavir was generally safe and well tolerated.

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