SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals **Trade Name**: Prezista® **Indication**: HIV-1 infection	**Drug Substance**: TMC114 **Trial no**.: TMC114-TiDP29-C169 **Clinical Phase**: I
Title: A Phase I, open-label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of darunavir (DRV) to that of the commercial 300 mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low dose ritonavir.	
Investigator: D. Font Julia, MD (until 31 August 2008); F. Höppener, MD (from 1 September 2008 onwards); Kendle International B.V., Clinical Pharmacology unit, Bolognalaan 40, 3584 CJ Utrecht, the Netherlands	**Country**: the Netherlands
Trial Period: Start: 15-Apr-2008 End: 18-Aug-2008	**No. of Investigators**: 1 **No. of Subjects**: 23

Objectives:
The primary objectives of this trial were:
In Part 1:
- to compare the rate and extent of absorption of a single oral dose of 600 mg DRV administered as the suspension formulation F051 (under fed and fasted conditions) to that of the commercial tablet formulation F016 (under fed conditions), in the presence of low-dose ritonavir in healthy subjects;
- to compare the rate and extent of absorption of a single oral dose of 600 mg DRV administered as the suspension formulation F051 under fed conditions to that under fasted conditions, in the presence of low-dose ritonavir in healthy subjects.

In Part 2:
- to assess multiple dose pharmacokinetics of DRV administered as the suspension formulation F051 (under fed or fasted conditions, based on the results of Part 1), in the presence of low-dose ritonavir in healthy subjects.

The secondary objective was to evaluate short-term safety and tolerability of DRV following administration of 3 single oral doses of 600 mg (formulated as suspension and as tablet) and following administration of multiple oral doses (formulated as suspension), all in presence of low-dose ritonavir in healthy subjects.

Design: This was a Phase I, open-label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of DRV (F051) to that of the commercial tablet formulation (F016), in the presence of low-dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of DRV formulated as the suspension in the presence of low-dose ritonavir. The trial was divided into 2 parts to be conducted sequentially. Results from Part 1 were evaluated before the start of Part 2 of the trial. The trial population was planned to consist of 18 healthy adult subjects for both Part 1 and Part 2. The 18 subjects in Part 2 preferably had to be the same as those in Part 1, however, in case of dropout(s), additional subjects could be recruited for Part 2. In Part 1 of the trial, during 3 sessions each subject received in a randomized way 3 single doses of 600 mg DRV: 2 tablets of 300 mg formulated as F016 under fed conditions (Treatment A, reference), 6 mL of suspension (100 mg/mL) formulated as F051 under fasted conditions (Treatment B), and 6 mL of suspension (100 mg/mL) formulated as F051 under fed conditions (Treatment C). In Treatments A, B, and C, a single dose of 600 mg DRV was administered on Day 3, while 100 mg b.i.d. ritonavir was coadministered from Day 1 to Day 5. In each treatment session, full pharmacokinetic profiles of DRV were determined up to 72 hours after administration and full pharmacokinetic profiles of ritonavir were determined for one dosing interval (12 hours) after the morning intake on Day 3. There was a washout period of at least 7 days between subsequent DRV intakes (on Day 3 of each session) in Part 1 of the trial. In Part 2 of the trial, each subject received 6 mL of a DRV suspension (100 mg/mL, F051), twice daily from Day 1 to Day 6, with an additional morning dose on Day 7. From Day 1 to Day 9, 100 mg b.i.d. ritonavir was coadministered (Treatment D). The dose and volume of suspension of DRV and food recommendations for DRV/rtv intake for Part 2 were based on the results of Part 1 of the trial. Full pharmacokinetic profiles of DRV were determined up to 72 hours after administration on Day 7 and

full pharmacokinetic profiles of ritonavir were determined for one dosing interval (12 hours) after the morning intake on that day. Safety and tolerability were evaluated 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 selection.
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 first trial-related activity.
5. Being able to comply with protocol requirements.
6. Healthy on the basis of a medical evaluation that revealed the absence of any clinically relevant abnormality and included a physical examination, medical history, 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, barbiturates, amphetamines, 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, 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, drug allergies, food allergy, dermatitis, eczema, psoriasis, or urticaria.
8. History of allergy to drugs such as, but not limited to, sulphonamides 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 and dietary supplements. Concomitant medication had to be discontinued at least 14 days before the first dose of study 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 not be 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 allowed 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 with tubal ligation 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 study medication.
14. Donation of blood or plasma within 60 days preceding the first intake of study medication.
15. Having previously participated in a multiple-dose trial with DRV.
16. Having previously participated in more than 3 single-dose trials with DRV.
17. 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 upper limit of laboratory normal range [ULN]);
    - lipase and/or pancreatic amylase grade 1 or greater (≥ 1.1 x ULN);
    - hemoglobin grade 1 or greater (≤ 10.9 g/dL or ≤ 6.6 mmol/L);
    - platelet count grade 1 or greater (< 125 x 10^9/L);
    - white blood cell count grade 1 or greater (≤ 2500 x 10^6/L);
    - absolute neutrophil count grade 1 or greater (≤ 1.3 x 10^9/L);
    - aspartate aminotransferase or alanine aminotransferase 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 red blood cell/high power field). A urine retest for proteinuria and microscopic hematuria could be performed in women after the menstrual period.

Treatment	darunavir (DRV) Treatment A	darunavir (DRV) Treatment B, C, and D	ritonavir (rtv) Treatment A, B, C, and D
Concentration Dosage Form (F No.) Usage	300 mg F016, tablet oral	100 mg/mL F051, suspension oral	100 mg capsule oral
Batch Number	7JG3081-X	08B28, 08E05, 08D14	44446VA, 6KT00
Dose Regimen	<u>Treatment A:</u> Days 1-5 ritonavir b.i.d. and a single dose of 600 mg DRV (F016) on Day 3 (fed conditions) <u>Treatment B:</u> Days 1-5 ritonavir b.i.d. and a single dose of 600 mg DRV (F051) on Day 3 (fasted conditions) <u>Treatment C:</u> Days 1-5 ritonavir b.i.d. and a single dose of 600 mg DRV (F051) on Day 3 (fed conditions) <u>Treatment D:</u> Days 1-9 ritonavir b.i.d. and 600 mg DRV (F051) b.i.d. on Days 1-6, and an additional morning dose on Day 7 (fed conditions)		
Duration of Treatment	24 days		
Duration of Trial	24 days (excluding a screening period of maximum 21 days, a washout period of at least 7 days between subsequent DRV intakes in Part 1 of the trial, 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 study medication (Day 1 of Session I), except for paracetamol (acetaminophen). Subjects were not allowed to use any medication other than the study medication up to 7 days after the last intake of study medication, except for paracetamol. Subjects were also not allowed to use any systemic herbal medications or dietary supplements including products containing *Hypericum perforatum* (St. John's wort) from 14 days before the first intake of study medication and up to 7 days after the last intake of study medication.		

Disallowed Medication, cont'd	Paracetamol could be used up to 3 days before the first intake of study medication in each session. After that, the clinical investigator could permit the use of paracetamol from 3 days before the first intake of study medication until the last day of study medication intake in each session at no more than 3 x 500 mg per day or no more than 3 grams 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 study medication. 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.
Assessments	
Pharmacokinetics	Blood samples were taken for determination of DRV and/or ritonavir concentrations for: <u>Part 1 (Treatments A, B, and C):</u> - at Day 1 (determination of ritonavir only) - at Day 3 (predose, 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 9 h, and 12 h after study medication intake) - at Days 4, 5, and 6 - at time of dropout or the following morning <u>Part 2 (Treatment D):</u> - at Day 1, 5, 6, 8, 9 and Day 10 - at Day 7 (predose, 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 9 h, and 12 h after study 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 - <u>Part 1 (Treatments A, B, and C):</u> at Days 1, 3 (predose), and 6 <u>Part 2 (Treatment D):</u> at Day 1, Day 7 (predose and 12 h after study medication intake), and Day 10 - at time of dropout or the following morning - 5-7 and 30-32 days after last intake of study medication or after dropout
Cardiovascular Safety	ECG and vital signs were taken for: - at screening - <u>Part 1 (Treatments A, B, and C):</u> at Day 1, Day 3 (predose and 3 h after intake of study medication), and Day 6 <u>Part 2 (Treatment D):</u> at Day 1, Day 7 (predose, and 3 h and 12 h after study medication intake), and at Day 10 - at time of dropout or the following morning - 5-7 and 30-32 days after last intake of study medication or after dropout

Physical Examination	Physical examination (including skin examination) was performed: - at screening - Part 1 (Treatments A, B, and C): at Day 6 Part 2 (Treatment D): at Day 10 - at time of dropout or the following morning - 5-7 and 30-32 days after last intake of study 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 = 23		
Baseline Characteristics			
Number of Male/Female Subjects Entered	18/5		
Age: median (range), yrs	30.0 (20-53)		
Subject Disposition	**Part 1**	**Part 2**	**All subjects**
Number of Subjects Entered, N	20	18[a]	23
Number of Subjects Completed, N	15	16	16
Number of Subjects Discontinued, N (total)	5	2	7
Reason:			
AE	1	1	2[b]
Consent withdrawn	1	1	2
Subject ineligible to continue the trial	1	0	1
Other	2	0	2

N = number of subjects

[a] The trial population was planned to consist of 18 subjects for both Part 1 and Part 2, who preferably had to participate in both parts. Since 15 subjects completed Part1, 3 additional subjects were recruited in order to have 18 subjects in Part 2 of the trial.

[b] In addition, 2 other subjects (CRF IDs 169-0050 and 169-0051) discontinued study medication due to rash but completed the follow-up visits as per protocol.

Pharmacokinetics for Darunavir in Part 1 of the Trial

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	**600 mg DRV F016 + 100 mg rtv b.i.d. (fed) (Trt A, reference)**	**600 mg DRV F051 + 100 mg rtv b.i.d. (fasted) (Trt B, test 1)**	**600 mg DRV F051 + 100 mg rtv b.i.d. (fed) (Trt C, test 2)**
n	17[a]	17	17
C_{max}, ng/mL	5654 ± 1478	5176 ± 1411	5885 ± 1724
t_{max}, h	3.0 (2.5-5.0)	2.0 (1.0-3.0)	4.0 (1.5-4.0)
AUC_{last}, ng.h/mL	85240 ± 38020	83510 ± 33540	88410 ± 32590
AUC_{∞}, ng.h/mL	87330 ± 40890	88520 ± 35570	92270 ± 33540
$t_{1/2term}$, h	15.04 ± 7.884	16.08 ± 7.236	15.36 ± 6.438
LSmean ratio (90% CI), %			
	-	**Test 1 vs reference**	**Test 2 vs reference**
n	-	17 vs 17[b]	17 vs 17[b]
C_{max}	-	91.34 (84.89 - 98.27)	104.4 (99.38 - 109.8)
AUC_{last}	-	99.92 (92.15 - 108.4)	107.5 (101.1 - 114.4)
AUC_{∞}	-	101.5 (92.98 - 110.8)	107.0 (100.3 - 114.1)
	-	-	**Test 2 vs Test 1**
n	-	-	17 vs 17
C_{max}	-	-	114.3 (105.9 - 123.3)
AUC_{last}	-	-	106.9 (100.1 - 114.1)
AUC_{∞}	-	-	105.7 (98.66 - 113.3)

Trt = treatment

[a] n=16 for AUC_{∞} and $t_{1/2\ term}$

[b] n=16 for AUC_{∞}

Pharmacokinetics for Ritonavir in Part 1 of the Trial

Pharmacokinetics of ritonavir (mean ± SD, t_{max}: median [range])	**600 mg DRV F016 + 100 mg rtv b.i.d. (fed) (Trt A, reference)**	**600 mg DRV F051 + 100 mg rtv b.i.d. (fasted) (Trt B, test 1)**	**600 mg DRV F051 + 100 mg rtv b.i.d. (fed) (Trt C, test 2)**
n	17[a]	17	17
Day 3			
C_{0h}, ng/mL	463.2 ± 250.1	437.6 ± 214.9	399.1 ± 169.9
C_{min}, ng/mL	292.6 ± 134.1	333.8 ± 160.1	260.3 ± 113.5
C_{max}, ng/mL	1543 ± 504.4	2066 ± 909.8	1486 ± 407.2
t_{max}, h	4.0 (3.0-5.0)	2.0 (1.0-4.0)	4.0 (2.5-5.0)
AUC_{12h}, ng.h/mL	8819 ± 2961	11260 ± 4502	8311 ± 2374
Day 4			
C_{0h}, ng/mL	331.8 ± 166.7	330.1 ± 163.0	325.5 ± 124.3
Day 5			
C_{0h}, ng/mL	375.0 ± 200.3	348.8 ± 123.7	361.1 ± 179.8
Day 6			
C_{0h}, ng/mL	357.0 ± 188.1	333.5 ± 144.7	353.0 ± 167.7

[a] n = 16 for C_{0h} on Day 5 and Day 6

Pharmacokinetics for Darunavir in Part 2 of the Trial

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	**600 mg DRV F051 b.i.d. + 100 mg rtv b.i.d. (fed) (Treatment D)**
n	17
C_{0h}, ng/mL	4029 ± 1677
C_{min}, ng/mL	3345 ± 1172
C_{max}, ng/mL	7390 ± 1540
t_{max}, h	3.0 (2.0-4.0)
AUC_{12h}, ng.h/mL	58550 ± 17570

Pharmacokinetics for Ritonavir in Part 2 of the Trial

Pharmacokinetics of ritonavir (mean ± SD, t_{max}: median [range])	**600 mg DRV F051 b.i.d. + 100 mg rtv b.i.d. (fed) (Treatment D)**
n	17
C_{0h}, ng/mL	316.5 ± 139.6
C_{min}, ng/mL	210.0 ± 82.46
C_{max}, ng/mL	1189 ± 553.3
t_{max}, h	4.0 (2.5-5.0)
AUC_{12h}, ng.h/mL	6436 ± 2145

Safety

Safety	Single DRV Dose						Multiple DRV Dose
	Trt A (DRV tablet, fed)		Trt B (DRV suspension, fasted)		Trt C (DRV suspension, fed)		Trt D (DRV suspension, fed)
	rtv N = 17	DRV/rtv N = 17	rtv N = 19	DRV/rtv N = 17	rtv N = 18	DRV/rtv N = 17	DRV/rtv N = 18
Adverse Events							
Most frequently reported AEs (reported in > 4 subjects during the whole trial), n (%)							
Headache	3 (17.6)	2 (11.8)	2 (10.5)	2 (11.8)	2 (11.1)	3 (17.6)	4 (22.2)
Diarrhea	1 (5.9)	1 (5.9)	2 (10.5)	0	1 (5.6)	1 (5.9)	3 (16.7)
Nausea	0	1 (5.9)	0	1 (5.9)	1 (5.6)	0	2 (11.1)
n (%) with 1 or more AEs	7 (41.2)	8 (47.1)	8 (42.1)	9 (52.9)	7 (38.9)	7 (41.2)	13 (72.2)
n (%) of deaths	0	0	0	0	0	0	0
n (%) with 1 or more other serious AEs	0	0	0	0	0	0	0
n (%) of discontinuations due to an AE	0	0	0	0	1 (5.6)	0	3 (16.7)
n (%) with 1 or more grade 3 or 4 AEs	0	0	0	0	0	0	0

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

Clinical Laboratory Tests	All laboratory abnormalities were grade 1 or 2 in severity following administration with ritonavir alone and DRV/rtv; no treatment-emergent grade 3 or 4 abnormalities were observed. The most frequent abnormalities following DRV/rtv administration were increased low-density lipoprotein, increased total cholesterol, and high-density lipoprotein below normal. Other laboratory abnormalities were observed in at most 2 subjects following DRV/rtv administration, except for hematocrit below normal observed in 4 (23.5%) subjects in Treatment B (DRV suspension, fasted). No laboratory abnormalities or abnormalities related to urinalysis were reported as AE during this trial.
Cardiovascular Safety	No clinically relevant changes in vital signs or ECG parameters were observed. Vital signs-related abnormalities were at most grade 1 in severity, except for treatment-emergent grade 2 standing DBP, observed in 1 subject each following a single dose of DRV in Treatment B (suspension, fasted) and multiple doses of DRV in Treatment D (suspension, fed). No treatment-emergent abnormal QTc values of > 480 ms or increases in QTc of > 60 ms were observed during the trial. One subject had a QTcB value > 450 ms to ≤ 480 ms following a single dose of DRV in Treatment A (DRV tablet, fed, i.e., reference). Following ritonavir administration, 1 subject had a QTcB value > 450 ms to ≤ 480 ms with a change from reference between 30 and 60 ms during Treatment A and 1 subject had a QTcF value > 450 ms to ≤ 480 ms during Treatment B (suspension, fasted). No AEs related to ECG or vital signs were reported.

Physical Examination	Five (21.7%) subjects were reported with one or more new abnormal findings (i.e., not present at screening) during the trial. Rash was reported as AE for 3 subjects and aphthous stomatitis for 1 subject..

Conclusions

Coadministration of a single 600 mg dose of DRV with low-dose ritonavir resulted in comparable C_{max}, AUC_{last}, and AUC_{∞} values of DRV under both fed and fasted conditions following administration of an oral suspension (F051) and commercial tablet (F016) with 90% confidence intervals within the limits of bioequivalence for all comparisons. In addition, following multiple dose of 600/100 mg b.i.d. of the oral suspension (F051) under fed conditions, DRV pharmacokinetics were comparable to those observed in previous trials with the commercial tablet formulation (F016) administered at the same dose.

Administration of the DRV suspension formulation (F051) was generally safe and well tolerated.

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