SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals **Trade Name**: - **Indication**: HIV infection	**Drug Substance**: TMC310911 **Trial no**.: TMC310911-TiDP21-C201 **Clinical Phase**: IIa
Title: A Phase IIa, open-label, randomized trial in treatment-naïve HIV-1-infected subjects to determine the antiviral activity of 14 days of monotherapy with 4 different dose regimens of TMC310911 coadministered with ritonavir.	
Investigator: H-J. Stellbrink, M.D., ICH Study Center, [redacted], Germany	**Country**: Germany
Trial Period: Start: 27-Apr-2009 End: 21-Feb–2011	**No. of Investigators**: 4 **No. of Subjects**: 32 subjects planned and 33 subjects treated

Objectives:

The primary objective of the trial was to evaluate the antiviral activity as measured by the change in viral load from baseline in the 14 days following initiation of treatment with 4 different dose regimens of TMC310911 coadministered with ritonavir (rtv).

The secondary objectives were:

- To assess the viral characteristics during a 14-day treatment of 4 different dose regimens of TMC310911 coadministered with 100 mg ritonavir;
- To assess the pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of a 14-day treatment of 4 different dose regimens of TMC310911 coadministered with 100 mg ritonavir;
- To assess the safety and tolerability of a 14-day treatment of 4 different dose regimens of TMC310911 coadministered with 100 mg ritonavir.

Design:

This was a Phase IIa, open-label, randomized, Proof-of-Concept trial in 33 treatment-naïve Human Immunodeficiency Virus-1 (HIV-1)-infected subjects to assess the antiviral activity, plasma pharmacokinetics, safety, and tolerability of 4 different dose regimens of the HIV protease inhibitor (PI) TMC310911 coadministered with 100 mg ritonavir.

The trial population consisted of 33 HIV-1-infected adult subjects who had not been treated with a therapeutic HIV vaccine within 1 year prior to enrollment and who had never been treated with an antiretroviral (ARV) drug indicated for the treatment of HIV-infection or ARVs for treatment of hepatitis B-infection with anti-HIV activity (e.g., adefovir, lamivudine, and emtricitabine) prior to screening. In addition, subjects had to have confirmed measurable viral load (i.e., above 5,000 HIV-1 ribonucleic acid [RNA] copies/mL).

All subjects received treatment with TMC310911 coadministered with 100 mg ritonavir. Sixteen subjects were randomized in a 1:1 ratio, meaning 8 subjects in each dosing regimen, to either TMC310911 150 mg twice daily (b.i.d.) (first treatment arm) or 300 mg b.i.d. (second treatment arm), both coadministered with 100 mg ritonavir b.i.d. for 14 days. A third and fourth treatment arm were added to the trial following protocol amendments and were done sequentially. In the third treatment arm, 9 subjects received TMC310911 75 mg b.i.d. coadministered with 100 mg ritonavir b.i.d. for 14 days. In the fourth treatment arm, 8 subjects received TMC310911 300 mg once daily (q.d.) coadministered with 100 mg ritonavir q.d. for 14 days. TMC310911 was formulated as an oral solution. All intakes of TMC310911 and ritonavir were under fed conditions.

The trial consisted of a screening period of maximum 6 weeks, a treatment period with TMC310911 of 2 weeks, and a follow-up period of 4 weeks.

Highly active antiretroviral therapy (HAART) could be started from Day 15 onwards at the discretion of the investigator, in consultation with the subject, and according to local standard of care. HAART therapy was to be determined by the investigator according to the general treatment guidelines and based upon the resistance profile of the subject.

Viral load was assessed at the screening visit and the run-in visit 1 week before start of trial medication. Thereafter, viral load was determined every day during the first 4 days of treatment (i.e., on Day 1, 2, 3 and 4), every second day for the remainder of the treatment period (i.e., on Day 6, 8, 10, 12 and 14), on Day 15, and at the first (1-2 weeks after last TMC310911 intake) and second (4 weeks after last TMC310911 intake) follow-up visit

to assess the antiviral activity of TMC310911/rtv. Viral kinetics were studied throughout the trial.

Viral characteristics were evaluated by genotypic and phenotypic analysis.

Full pharmacokinetic profiles of TMC310911 and ritonavir were determined on Day 1 and Day 14 (i.e., predose and 0.5, 1, 2, 3, 5, 8, and 12 hours postdose). On the other days (i.e., Days 2, 3, 4, 6, 8, 10, 12, and 15), a single predose sample was taken for pharmacokinetic analysis of TMC310911 and ritonavir.

Safety and tolerability were evaluated throughout the trial.

Subject Selection

Inclusion Criteria

1. Male or female subjects, aged between 18 and 60 years, inclusive;
2. Documented HIV-1 infection for at least 6 months prior to the screening date;
3. Subject had not been treated with a therapeutic HIV vaccine within 1 year prior to enrolment and had never been treated with an ARV drug indicated for the treatment of HIV-infection or ARVs for treatment of hepatitis B-infection with anti-HIV activity (e.g., adefovir, lamivudine, and emtricitabine);
4. Subject agreed not to start antiretroviral therapy (ART) before the baseline visit;
5. Informed Consent Form (ICF) signed voluntarily before the first trial-related activity;
6. Able to comply with the protocol requirements and having good accessible veins;
7. HIV-1 plasma viral load at screening visit above 5,000 HIV-1 RNA copies/mL;
8. CD4+ cell count above 200 cells/mm^3 at screening.

Exclusion Criteria

1. Any condition (including but not limited to alcohol and drug use), which, in the opinion of the investigator, could compromise the subject's safety and adherence to the protocol;
2. HIV-2-infected patients and/or patients with any active or chronic hepato-renal disease;
3. Life expectancy of less than 6 months;
4. Subject had a documented acute (primary) HIV-1 infection;
   Note: Primary or acute HIV infection is the first phase of HIV disease, occurring in the weeks immediately following infection by HIV and lasting for approximately 3 to 6 months. A viral load test at this stage usually shows extremely high levels of HIV in the blood - often higher than at any other stage of HIV infection, and may therefore not be reliable when evaluating the need for initiating antiretroviral therapy.
5. Subject had pre-existing PI drug resistance, based upon the presence of one or more primary PI mutations in the screening sample, using the most recent list of the International AIDS Society (IAS-USA) (2010).
6. Subject had any currently active Acquired Immunodeficiency Syndrome (AIDS)-defining illness (Category C conditions according to the Centers for Disease Control and Prevention [CDC] Classification System for HIV Infection 1993) with the following exceptions (was discussed and agreed on with the sponsor prior to enrolment):
   - Stable, cutaneous Kaposi's Sarcoma (i.e., no pulmonary or gastrointestinal involvement other than oral lesions) that was unlikely to require any form of systemic therapy during the trial period;
   - Wasting syndrome due to HIV infection if, in the investigator's opinion, it was not actively progressive and its treatment did not require hospitalization or compromised the subject's safety or compliance with the trial protocol procedures. If the subject was on maintenance therapy (which could include human Growth Hormone, appetite stimulants, and anabolic steroids) for previously diagnosed wasting, he/she could be eligible for the trial only if such treatment was not included in the list of disallowed medications;

   Note: Primary or secondary prophylaxis for an AIDS-defining illness was allowed in case the medication used was not part of the disallowed medication.
7. Any active clinically significant disease (e.g., pancreatitis, cardiac dysfunction) or findings during screening, medical history, or physical examination that, in the investigator's opinion, would have compromised the outcome of the trial;
8. Receipt of any investigational drug or vaccine within 90 days prior to the first trial drug administration;
9. Previously demonstrated clinically significant allergy or hypersensitivity;

Exclusion Criteria (Continued)

10. Nonvasectomized heterosexually active males who had a female partner of childbearing potential without the use of effective birth control methods or not willing to continue practicing these birth control methods from screening onwards until 30 days after the end of the trial.
    Note: All HIV-1-infected male subjects were advised to use a condom to reduce the risk of transmitting HIV-1. Since the effects of TMC310911 on conception are unknown, nonvasectomized heterosexual male subjects and their female partners had to agree to use one of the following birth control methods:
    - a double barrier method (at least 2 barrier methods) to prevent pregnancy. Barrier contraceptives included the following methods: a male condom, diaphragm, cervical cap, vaginal sponge, or female condom; or **Note**: Spermicides were not to be used as this can potentially increase the rate of HIV-1 transmission. A female condom and a male condom were not to be used together as friction between the two can result in failing of either product.
    - a barrier method combined with either hormonal contraceptives or intrauterine device (IUD) for the female partner; or
    - refrain from heterosexual intercourse.

    The use of the above-mentioned birth control methods did not apply if the male HIV-1-infected subject had been vasectomized minimally one month prior to screening or if the female sexual partner had had a double tubal ligation (or another surgery with the same goal and efficiency) or surgical sterilization or a hysterectomy or if she was post-menopausal for at least 2 years.
11. Women of childbearing potential;
12. Any confirmed grade 3 or 4 toxicity according to the Division of AIDS (DAIDS) grading scale at screening, except for:
    - Asymptomatic grade 3 pancreatic amylase elevation;
    - Asymptomatic grade 3 triglyceride/cholesterol/hyperglycemia;
    - Asymptomatic grade 4 triglyceride elevation.
13. Subject had any kind of clinically significant cardiac disease including:
    - Heart block, arrhythmias, congestive heart, and others;
    - A confirmed prolongation of QT/QTc interval, e.g., repeated demonstration of QTcF interval > 480 ms in the screening electrocardiogram (ECG) (i.e., retesting to reassess eligibility was allowed once using an unscheduled visit during the screening period);
    - Risk factors for Torsade de Pointes (e.g., heart failure, hypokalemia);
    - Intraventricular conduction delay with QRS duration > 120 ms;
    - Bradycardia as defined by sinus rate < 40 bpm;
    - Syncopal episodes.

Treatment	**TMC310911**	**ritonavir (Norvir®)**	
Concentration Dosage Form (F No.) Usage	25 mg/mL solution (F003) oral	100 mg capsule[a] oral	100 mg tablet[b] oral
Batch Numbers	08L11/F003, 09A19/F003, 09A26/F003, 10A07/F003, 10G08/F003	70042VA, 68696VA	861778D
Dose Regimen	TMC310911 at 75 mg b.i.d. (N = 9), 150 mg b.i.d. (N = 8), 300 mg b.i.d. (N = 8), or 300 mg q.d. (N = 8) on Days 1 to 14 + ritonavir 100 mg b.i.d. or q.d. on Days 1 to 14 [a] In the b.i.d. treatment arms (treatment arms 1-3), ritonavir was formulated as an oral capsule containing ritonavir eq. 100 mg. [b] In the q.d. treatment arm (treatment arm 4), ritonavir was formulated as a film-coated tablet containing ritonavir eq. 100 mg.		
Duration of Treatment	14 days		
Duration of Trial	Screening: maximum 6 weeks (including 1-week run-in) Treatment: 2 weeks Follow-up: 4 weeks		

Disallowed Medication	The following medications were not allowed: ***Prior to treatment:*** - Any ARV therapy indicated for the treatment of HIV-infection; - ARVs for treatment of hepatitis B-infection with anti-HIV activity (e.g., adefovir, lamivudine, and emtricitabine); - Any therapeutic HIV vaccine (within 1 year prior to enrollment); - Cytochrome P450 enzyme 3A (CYP3A) inducers: rifabutin, rifampin, carbamazepine, phenytoin, phenobarbital, products containing *Hypericum perforatum* (St. John's wort), systemic dexamethasone, modafinil. ***During 14 days treatment with TMC310911/rtv:*** - Any ARV therapy indicated for the treatment of HIV-infection; - ARVs for treatment of hepatitis B-infection with anti-HIV activity (e.g., adefovir, lamivudine, and emtricitabine); - Any vaccine; Because of the interaction potential of TMC310911 with medications that are substrates, inhibitors, or inducers of CYP 3A or 2D6, a list of currently marketed medications that could interact via these enzymes was presented in the protocol. These drugs were not to be used during the treatment period. ***During follow-up:*** - Any ARV therapy, other than those ARVs used in the selected HAART; Note: From Day 15 onwards, HAART could be started at the investigators discretion, in consultation with the subject, and according to local standard of care. - Any vaccine.
Assessments	
Antiviral Activity	Plasma samples for viral load (VL) determinations were obtained at each visit for testing by using the Roche Amplicor HIV-1 monitor® test (version 1.5). Samples for immunology assessments were taken at screening, Days 1 and 8, at end of treatment (Day 15) or withdrawal, and follow-up (1-2 weeks and 4 weeks after last study medication intake).
Resistance Determinations	Samples for genotypic and phenotypic resistance testing (using virco®TYPE HIV-1 and Antivirogram®, respectively) were taken at screening, baseline (Day 1), and at end of treatment (Day 15) or withdrawal. At screening and baseline only genotyping was performed. If a sufficient volume of blood was left over from the VL determinations, the samples could be used for resistance testing at additional time points if deemed necessary by the trial virologist.
Pharmacokinetics	Samples to determine TMC310911 and ritonavir plasma concentrations were taken on Days 1 and 14 (predose and 0.5, 1, 2, 3, 5, 8, and 12 h postdose), Days 2, 3, 4, 6, 8, 10, and 12 (all predose), Day 15 (12 h [b.i.d. regimen] or 24 h [q.d. regimen] after last study medication intake), and at time of withdrawal.

Safety	
Adverse Events	Adverse events were checked at every visit and reported from screening onwards until the last study-related activity.
Clinical Laboratory	- Blood samples for biochemistry[a], hematology[b], and coagulation measurements were taken at screening, on Days 1, 3, and 8, Day 14 (only for biochemistry in the 75 mg b.i.d. and 300 mg q.d. arm), at end of treatment (Day 15) or withdrawal, and at follow-up (1-2 weeks and 4 weeks after last study medication intake; blood coagulation assessments only if abnormalities were seen during treatment). - Urine samples for urinalysis were taken at screening, on Days 1, 3, and 8, at end of treatment (Day 15) or withdrawal, and at follow-up (1-2 weeks and 4 weeks after last study medication intake). In the 75 mg b.i.d. and 300 mg q.d. treatment arms, subjects had to collect their urine for 24 h on Day 14. - At screening, samples were taken for hepatitis A, B, C tests (hepatitis A antibody IgM, HBsAg, and HCV antibody, respectively). For females only, a serum pregnancy test was performed at screening and a urine pregnancy test was performed at baseline, at end of treatment (Day 15) or withdrawal, and at 4 Weeks follow-up. [a] All biochemistry samples had to be taken fasted for at least 10 hours, except at the time of dropout. [b] In the 75 mg b.i.d. and 300 mg q.d. treatment arm: 10 blood smears were taken per subject to evaluate the presence of vacuoles in peripheral white blood cells (WBCs) in addition to routine hematology on Days 1 and 15.
Cardiovascular Safety	Vital signs and 12-lead electrocardiograms (ECGs) were recorded at screening, on Days 1, 3, and 8, at end of treatment (Day 15) or withdrawal, and at 4 Weeks follow-up (vital signs only).
Physical Examination	Physical examinations were performed at screening, Day 1, at end of treatment (Day 15) or withdrawal, and at follow-up (1-2 weeks and 4 weeks after last study medication intake).
Statistical Methods Performed	Intent-to-Treat analysis, descriptive statistics, and frequency tabulations, graphical presentation

Main Features of the Subject Sample and Summary of the Results

ITT Population	TMC310911/rtv 75/100 mg b.i.d.	TMC310911/rtv 150/100 mg b.i.d.	TMC310911/rtv 300/100 mg b.i.d.	TMC310911/rtv 300/100 mg q.d.	Total
Subject Disposition					
Number of Subjects Entered	***9***	***8***	***8***	***8***	***33***
Discontinuations - reason, n (%)	***0***	***0***	***0***	***0***	***0***
Demographic and Baseline Characteristics					
Demographics					
Gender, n (%)					
Female	1 (11.1)	0	0	0	1 (3.0)
Male	8 (88.9)	8 (100.0)	8 (100.0)	8 (100.0)	32 (97.0)
Age: median (range), years	29.0 (23-47)	42.0 (22-45)	34.0 (28-48)	40.5 (22-49)	32.0 (22-49)
Race, n (%)					
Black or African American	1 (11.1)	0	0	0	1 (3.0)
Caucasian/White	8 (88.9)	8 (100.0)	8 (100.0)	8 (100.0)	32 (97.0)
Baseline Characteristics					
Plasma $\log_{10}$ VL, mean (SE), HIV-1 RNA copies/mL	4.72 (0.245)	4.36 (0.259)	4.78 (0.161)	4.71 (0.116)	4.65 (0.103)
Baseline VL (HIV-1 RNA copies/mL), n (%)					
< 5,000	0	1 (12.5)	0	0	1 (3.0)
5,000; < 10,000	1 (11.1)	1 (12.5)	1 (12.5)	0	3 (9.1)
10,000; < 100,000	6 (66.7)	4 (50.0)	4 (50.0)	7 (87.5)	21 (63.6)
≥ 100,000	2 (22.2)	2 (25.0)	3 (37.5)	1 (12.5)	8 (24.2)
CD4+ cell count, median (range), 10^6 cells/L	586 (309-876)	415 (243-813)	422 (306-887)	479 (315-670)	457 (243-887)
Baseline CD4+ cell count, 10^6 cells/L, n (%)					
200; < 500 cells/mm^3	2 (22.2)	6 (75.0)	5 (62.5)	4 (50.0)	17 (51.5)
≥ 500 cells/mm^3	7 (77.8)	2 (25.0)	3 (37.5)	4 (50.0)	16 (48.5)
Known duration of HIV-infection, median (range), years	1.7 (0.9-8.5)	4.5 (0.4-8.1)	3.4 (0.9-11.4)	2.2 (0.7-8.0)	2.7 (0.4-11.4)
Clinical stage of HIV-infection					
Category A	7 (77.8)	6 (75.0)	5 (62.5)	7 (87.5)	25 (75.8)
Category B	2 (22.2)	2 (25.0)	3 (37.5)	1 (12.5)	8 (24.2)
Number of subjects with[a]					
0 PI RAMs	0	0	0	0	0
1 PI RAMs	2 (22.2)	0	2 (25.0)	0	4 (12.1)
2 PI RAMs	1 (11.1)	4 (50.0)	2 (25.0)	2 (25.0)	9 (27.3)
≥ 3 PI RAMs	6 (66.7)	4 (50.0)	4 (50.0)	6 (75.0)	20 (60.6)

Footnotes for this table are presented on the next page.

RAM = resistance associated mutation

[a] Based on the IAS-USA list of drug resistance mutations 2010;
PI RAMs: L10C/F/I/R/V, V11I, G16E, K20I/M/R/T/V, L24I, D30N, V32I, L33I/F/V, E34Q, M36I/L/V, K43T, M46I/L, I47A/V, G48V, I50L/V, F53L/Y, I54A/L/M/S/T/V, Q58E, D60E, I62V, L63P, I64L/M/V, H69K/R, A71I/L/T/V, G73A/C/S/T, T74P, L76V, V77I, V82A/F/I/L/S/T, N83D, I84V, I85V, N88D/S, L89I/M/V, L90M, I93L/M.

Antiviral Activity

	TMC310911/rtv 75/100 mg b.i.d. N = 9	**TMC310911/rtv 150/100 mg b.i.d. N = 8**	**TMC310911/rtv 300/100 mg b.i.d. N = 8**	**TMC310911/rtv 300/100 mg q.d. N = 8**
HIV-1 RNA (log_{10} copies/mL), mean (SE)				
Baseline value	4.72 (0.245)	4.36 (0.259)	4.78 (0.161)	4.71 (0.116)
Change from baseline on Day 8	-1.30 (0.126)	-1.14 (0.147)	-1.07 (0.104)	-1.06 (0.144)
Change from baseline on Day 15	-1.53 (0.117)	-1.79 (0.192)	-1.69 (0.103)	-1.55 (0.160)
Virologic Response at any Time Point, n (%)				
Viral load < 50 copies/mL	0	1 (12.5)	0	0
Viral load < 400 copies/mL	3 (33.3)	4 (50.0)	1 (12.5)	0
At least 1 log_{10} viral load drop	9 (100.0)	8 (100.0)	8 (100.0)	7 (87.5)

N = total number of subjects with data; n = number of observations; SE = standard error of the mean

Immunology

Mean (SE) changes from baseline in CD4+ cell count on Day 15 were generally small: -33.7 (27.04), -2.8 (31.44), and -2.0 (41.23) x 10^6 cells/L in the 75 mg b.i.d., 150 mg b.i.d., and 300 mg b.i.d. group, respectively, and +92.5 (58.70) x 10^6 cells/L in the 300 mg q.d. group.

Resistance Determinations

Paired baseline/Day 15 genotypes were available for 18 subjects. In 1 subject in the 75 mg b.i.d. group, a developing PI RAM (A71I/T compared to A71T at baseline) was detected on Day 15. All 18 subjects with phenotype data available on Day 15 were susceptible to all 8 currently approved PIs and TMC310911 at the end of treatment. There were no differences observed in VL changes from baseline between subjects with < 3 or ≥ 3 PI RAMs at baseline.

Pharmacokinetics of TMC310911 (mean ± SD, t_{max}: median [range])	**TMC310911/rtv 75/100 mg b.i.d.**		**TMC310911/rtv 150/100 mg b.i.d.**		**TMC310911/rtv 300/100 mg b.i.d.**		**TMC310911/rtv 300/100 mg q.d.**	
Day 1	**N**		**N**		**N**		**N**	
C_{max}, ng/mL	9	487.9 ± 450.3	8	623.0 ± 358.1	8	706.3 ± 553.2	8	1924 ± 1048
t_{max}, h	9	2.00 (0.50-5.05)	8	2.50 (1.00-5.17)	8	4.00 (2.00-5.00)	8	2.01 (1.00-3.00)
AUC_{12h}, ng.h/mL	8	2519 ± 2123	8	2735 ± 1572	7	2990 ± 2245	7	10040 ± 6122
AUC_{24h}, ng.h/mL		-		-		-	8	11580 ± 6596
Day 14								
C_{0h}, ng/mL	9	152.5 ± 248.2	8	420.9 ± 244.6	8	924.8 ± 527.9	8	209.9 ± 187.2
C_{min}, ng/mL	8	130.2 ± 205.6	7	291.4 ± 105.6	7	635.7 ± 437.7	8	144.2 ± 107.6
C_{max}, ng/mL	9	589.7 ± 554.1	8	1674 ± 652.3	8	2256 ± 961.9	8	2963 ± 1920
t_{max}, h	9	2.00 (1.00-4.98)	8	2.33 (2.00-5.02)	8	2.36 (2.00-3.00)	8	2.00 (2.00-3.00)
AUC_{12h}, ng.h/mL	8	4031 ± 3845	7	10680 ± 3147	7	16010 ± 8229	8	17520 ± 11610
AUC_{24h}, ng.h/mL		-		-		-	8	22110 ± 14870
$C_{ss,av}$, ng/mL	8	336.2 ± 321.3	7	889.6 ± 262.6	7	1340 ± 689.6	8	887.3 ± 567.5
Fluctuation index, %	8	181.0 ± 80.00	7	161.3 ± 29.22	7	129.2 ± 52.89	8	331.8 ± 55.47
Ratio $C_{max,\ Day\ 14/Day\ 1}$, %	9	210.8 ± 143.9	8	308.4 ± 147.7	8	474.1 ± 392.8	8	155.8 ± 47.20
Ratio $AUC_{t,\ Day\ 14/Day\ 1}$, %[a]	8	231.7 ± 184.2	7	446.6 ± 243.6	6	894.4 ± 1074	8	197.0 ± 74.37

[a] For b.i.d. doses t = 12 h, for q.d. dose t = 24 h

Pharmacokinetics of ritonavir (mean ± SD, t_{max}: median [range])	**TMC310911/rtv 75/100 mg b.i.d.**		**TMC310911/rtv 150/100 mg b.i.d.**		**TMC310911/rtv 300/100 mg b.i.d.**		**TMC310911/rtv 300/100 mg q.d.**	
Day 1	**N**		**N**		**N**		**N**	
C_{max}, ng/mL	9	707.8 ± 643.4	8	354.1 ± 358.0	8	304.2 ± 167.8	8	519.3 ± 340.6
t_{max}, h	9	5.02 (2.00-12.00)	8	5.00 (3.00-8.12)	8	5.06 (5.00-12.17)	8	5.00 (2.00-5.02)
AUC_{12h}, ng.h/mL	9	4558 ± 3858	8	2467 ± 2421	8	2042 ± 1021	7	3235 ± 1318
AUC_{24h}, ng.h/mL		-		-		-	8	5356 ± 2246
Day 14								
C_{0h}, ng/mL	9	700.8 ± 531.6	8	475.1 ± 193.3	8	514.6 ± 179.7	8	132.2 ± 87.32
C_{min}, ng/mL	8	373.3 ± 196.4	8	314.6 ± 106.5	8	301.3 ± 87.13	8	77.70 ± 42.65
C_{max}, ng/mL	9	2085 ± 1245	8	1297 ± 422.1	8	1079 ± 338.9	8	856.0 ± 367.7
t_{max}, h	9	4.98 (1.00-8.00)	8	3.00 (1.00-5.03)	8	3.87 (0.00-5.02)	8	3.02 (1.02-5.03)
AUC_{12h}, ng.h/mL	8	12260 ± 5524	8	8441 ± 1811	8	7741 ± 1758	8	6176 ± 2644
AUC_{24h}, ng.h/mL		-		-		-	8	8587 ± 3956
$C_{ss,av}$, ng/mL	8	1022 ± 461.2	8	704.9 ± 149.0	8	647.0 ± 147.4	8	346.6 ± 147.9
Fluctuation index, %	8	171.3 ± 50.56	8	139.4 ± 51.85	8	118.2 ± 32.93	8	225.9 ± 31.29

N = total number of subjects with data; SD = standard deviation

In conclusion, after administration of TMC310911/rtv at 75/100 mg, 150/100 mg, or 300/100 mg b.i.d., the exposure to TMC310911 expressed as mean C_{max} and AUC_{12h} increased in a less than dose proportional fashion between the dose groups after the first intake of TMC310911/rtv. For the 300/100 mg q.d. dose regimen, TMC310911 exposure was considerably higher compared to the b.i.d. dose regimens.

At steady-state, taking into account the high variability, mean C_{max} and AUC_{12h} for TMC310911 tended to increase in a dose proportional fashion within the 75 to 300 mg b.i.d. dose range. For the 300/100 mg TMC310911/rtv q.d. dose regimen, mean C_{min} at steady-state was lower compared to the 150/100 and 300/100 mg b.i.d. dose groups. Mean C_{max} was higher compared to all b.i.d. dose groups. Comparing daily exposure at steady-state (AUC_{24h}) for the 300/100 mg TMC310911/rtv q.d. dose regimen with daily exposure of the other dose regimens ($2*AUC_{12h}$) indicated that total daily TMC310911 exposure was comparable to a TMC310911/rtv dose regimen of 150/100 mg b.i.d.

Ritonavir exposure at steady-state was higher for the 75/100 mg TMC310911/rtv b.i.d. regimen, compared to the other b.i.d. regimens, while ritonavir exposure for the 300/100 mg TMC310911/rtv q.d. regimen was lower compared to all b.i.d. regimens.

The small sample size and different populations for the four panels may have played a role in the observed differences between TMC310911 and ritonavir exposure in the treatment groups, specifically after administration of the first dose of TMC310911/rtv.

Safety
Adverse Events

Treatment phase (from first TMC310911 intake to 1 day after last TMC310911 intake.)	**TMC310911/rtv 75/100 mg b.i.d. N = 9**	**TMC310911/rtv 150/100 mg b.i.d. N = 8**	**TMC310911/rtv 300/100 mg b.i.d. N = 8**	**TMC310911/rtv 300/100 mg q.d. N = 8**	**Total N = 33**
Adverse Events					
Most frequently reported AEs by preferred term (i.e., in > 2 subjects in any treatment group), n (%)					
Fatigue	3 (33.3)	2 (25.0)	4 (50.0)	0	9 (27.3)
Nausea	1 (11.1)	3 (37.5)	0	0	4 (12.1)
n (%) with 1 or more AEs	5 (55.6)	5 (62.5)	6 (75.0)	3 (37.5)	19 (57.6)
n (%) of deaths	0	0	0	0	0
n (%) with 1 or more other SAEs	0	0	0	0	0
n (%) leading to permanent discontinuation of study medication	0	0	0	0	0
n (%) with 1 or more grade 3 or 4 AE	0	1 (12.5)	0	0	1 (3.0)

N = total number of subjects with data; n = number of observations.

The results of the trial indicated that short-term treatment with TMC310911/rtv at doses of 75/100 mg, 150/100 mg, and 300/100 mg b.i.d. and 300/100 mg q.d. was generally safe and well tolerated in the studied population. No deaths, SAEs, or AEs leading to discontinuation were reported in this trial.

Apart from 1 subject in the 150 mg b.i.d. group with grade 4 AEs during treatment (ALT and AST increased) and 1 subject in the 150 mg b.i.d. group with grade 3 paronychia during follow-up, all AEs reported in this trial were grade 1 or 2 in severity. Overall, 4 (44.4%), 5 (62.5%), 4 (50.0%), and 1 (12.5%) subjects in the 75 mg b.i.d., 150 mg b.i.d., 300 mg b.i.d., and 300 mg q.d. group, respectively, experienced at least 1 AE that was considered at least possibly related to TMC310911 and ritonavir by the investigator. By preferred term, the most frequently reported AEs during treatment (i.e., in > 2 subjects in any treatment group) were fatigue and nausea. None of the AEs during treatment or follow-up were considered related to HIV-1. No relevant differences were observed in the incidence of AEs between the different TMC310911 dose groups during the treatment phase or follow-up phase.

Clinical Laboratory Tests

There were no clinically relevant findings on laboratory parameters. Creatinine, potassium, and lipid parameters (triglycerides and total cholesterol) slightly increased during the treatment phase but these changes were not associated with increases in incidence of graded laboratory abnormalities. The small change from baseline in mean creatinine levels during 14-day treatment was not associated with mean changes from baseline in serum cystatin C (for 75 mg b.i.d. and 300 mg q.d. dosing). The absence of mean changes from baseline in serum cystatin C indicates the absence of a direct effect of TMC310911 on functional glomerular filtration rate. Mean creatinine, potassium, and lipid parameter levels returned to baseline values after TMC310911 and ritonavir dosing.

Two subjects (one in the 150 mg b.i.d. group and one in the 300 mg q.d. group) were observed with grade 4 transiently increased ALT and AST. Other treatment-emergent laboratory abnormalities were at most grade 2.

Both subjects with grade 4 transient increases in ALT and AST were reported with a laboratory-related AE: one subject (150 mg b.i.d. group) with grade 4 increased ALT and AST considered probably related to TMC310911 and ritonavir by the investigator and one subject (300 mg q.d. group) with grade 2 acute and transient cytomegalovirus hepatitis considered not related to TMC310911 and ritonavir by the investigator. No other subjects were observed with AEs during treatment related to any laboratory abnormality.

The most frequently observed treatment-emergent graded laboratory abnormalities during treatment (≥ 5 subjects across all treatment groups) were hyperglycemia (any grade; 7/33 [21.2%] subjects) and increase in total cholesterol (any grade; 7/33 [21.2%] subjects).

No relevant differences in incidences of graded or nongraded laboratory abnormalities between the treatment groups were observed.

Cardiovascular Safety

Median changes from baseline in vital signs parameters (pulse, blood pressure) and ECG parameters were generally small and not considered clinically relevant.

No AEs related to vital signs or ECG were reported during the trial.

Conclusions

In treatment-naïve HIV-1 infected subjects, combined treatment with oral TMC310911 and ritonavir for 14 days showed potent antiviral activity. No relevant difference in antiviral activity was observed between the studied TMC310911/rtv doses of 75/100 mg, 150/100 mg, 300/100 mg b.i.d., and 300/100 mg q.d.

Mean changes from baseline in CD4+ cell count on Day 15 were generally small with decreases from baseline for the b.i.d. regimens and an increase for the 300/100 mg q.d. regimen.

At steady-state, mean TMC310911 C_{max} and AUC_{12h} tended to increase in a dose proportional way. Overall, daily TMC310911 exposure at steady-state was comparable for the 300/100 mg q.d. and 150/100 mg b.i.d. regimens.

Short-term treatment with TMC310911 and ritonavir at doses of 75/100 mg, 150/100 mg, 300/100 mg b.i.d., and 300/100 mg q.d. was generally safe and well tolerated in this treatment-naïve patient population. There were no SAEs and no treatment-related discontinuations. Most AEs were grade 1 or 2 in severity. The most common AEs during treatment were nausea and fatigue. No relevant differences were observed in the incidence of AEs between the different dose groups.

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