

SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. Trade Name: - Indication: HIV-1 infection	Drug Substance: TMC114 Trial no.: TMC114-C213 Clinical Phase: II
Title: A Phase II randomized, controlled, partially blinded trial to investigate the efficacy, safety, and dose-response relationship of TMC114/RTV in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of TMC114/RTV. Primary efficacy analysis.	
Principal Investigator: Prof. C. Katlama, M.D.; Hopital Pitie Salpetriere; [REDACTED]; [REDACTED]	Countries: Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hungary, Italy, Portugal, Spain, Switzerland, United Kingdom
Trial Period: Start: 14-Oct-2003 End: 01-Feb-2005 (cut-off date for LPLV for primary analysis)	No. of Investigators: 57 No. of Subjects: 318
Objectives: In the original protocol, the primary objective was to evaluate the dose-response relationship of antiviral activity of the TMC114/RTV dose regimens at 24 weeks in order to determine the recommended dose. The selection of the recommended dose was based on the combined interim analyses as defined per protocol, which included 150 subjects in each of the two dose-finding trials (TMC114-C202 + TMC114-C213) who reached Weeks 16 and 24 or discontinued earlier. The amended primary objective of the dose-finding part of this trial was to compare all TMC114/RTV dose groups with control at Week 24 (the primary endpoint) by means of the confirmed virologic response (TLOVR), defined as a drop in viral load of at least 1.0 log ₁₀ versus baseline. The cut-off date for the primary efficacy analysis was set at February 1, 2005. At that time, 301 subjects reached 24 weeks of treatment or discontinued earlier in the TMC114-C213 trial. Secondary objectives were: - to evaluate safety and tolerability; - to evaluate the durability of the antiviral activity; - to investigate the dose-response by comparing the virologic response and safety parameters at different TMC114/RTV doses and exposure.	
Design: The ongoing TMC114-C213 trial consisted of 2 parts, a dose-finding and an open-label part. The dose-finding part consisted of a randomized controlled (Standard of Care), partially blinded, Phase II trial to determine the antiviral activity, safety and tolerability of 4 dose levels of TMC114, formulated as an oral tablet, and administered with a low dose of ritonavir (RTV). The pharmacokinetics of TMC114 were also assessed. After the primary efficacy analysis, subjects were instructed to switch to the recommended dose of TMC114/RTV in the open-label part of the trial. Three hundred HIV-1 infected subjects who were at least 3-class-experienced and who were on a stable PI-containing regimen at screening for at least 8 weeks and who had plasma HIV-1 RNA > 1000 copies/mL were eligible. 'Three-class-experienced' was defined as prior treatment with 2 or more NRTIs for at least 3 months in total and 1 or more NNRTI as part of a failing regimen. In addition, subjects had to have received at least one PI for at least 3 months in the past and have at least 1 primary PI mutation (according to IAS-USA definitions of March 2003) at screening. The number of subjects with 3 or more primary PI mutations was limited to 30% of the total number of subjects. Prior use of enfuvirtide (T-20) was allowed. As soon as all results to determine eligibility were available, and prior to randomization, an optimized PI-regimen and an optimized background regimen (OBR) were selected by the investigator. No later than two weeks before the baseline visit, the subjects were randomized to one of 4 TMC114/RTV treatment groups or to a control group (Standard of Care). At baseline, subjects changed their antiretroviral (ARV) therapy to an OBR consisting of NRTIs with or without T-20 plus TMC114/RTV or an investigator selected PI(s) regimen. In the original protocol, the primary objective of the trial was to evaluate the dose-response relationship in antiviral activity between the TMC114 /RTV treatment groups at 24 weeks. Two interim analyses were performed as defined by protocol. The recommended dose (TMC114/RTV 600/100 mg b.i.d.) was selected based on the first combined interim	

analysis including 150 subjects each in the TMC114-C213 trial and the similar dose-finding trial TMC114-C202 who reached Week 16 or discontinued earlier. The selection of the recommended dose was confirmed in a second combined interim analysis, performed when 150 subjects in each of the trials reached Week 24 or discontinued earlier.

This report describes the primary efficacy analysis. The cut-off date for this analysis was February 1, 2005. At that time, 301 subjects in the TMC114-C213 trial reached 24 weeks of treatment or discontinued earlier (318 subjects were included in the primary efficacy analysis; 17 subjects had not reached 24 weeks of treatment). Around the cut-off date of the primary efficacy analysis, the recommended dose was communicated to relevant parties and subjects were instructed to switch to the recommended dose of TMC114/RTV after this date. The primary efficacy analysis was performed on all 318 subjects enrolled in the trial. The amended primary objective of the dose-finding part of the trial was to compare all TMC114/RTV groups to the control group by means of the confirmed virologic response at Week 24, defined as a drop in viral load of at least 1.0 log₁₀ versus baseline. In addition, long term safety, tolerability and the durability of antiviral efficacy of TMC114/RTV in 3-class-experienced HIV-1 infected subjects were evaluated.

The trial includes a screening period of a maximum of 6 weeks, and a 96-week treatment period followed by a 4-week follow-up period. The current maximum duration of the trial is 106 weeks. All subjects who continue to benefit from treatment with TMC114/RTV can remain in the study until they no longer benefit from TMC114/RTV as judged by the investigator, or until they meet one of the withdrawal criteria. The protocol will be amended to allow the subjects reaching Week 96 to continue treatment within the trial.

Subject Selection

Inclusion Criteria

1. Male or female subjects, aged 18 years or older;
2. Subjects with documented HIV-1 infection;
3. Subjects receiving a PI-containing regimen at screening initiated at least 8 weeks prior to screening with plasma HIV-1 RNA > 1000 copies/mL (assayed by RNA PCR Standard specimen procedure);
4. Prior use of more than 1 NRTI for at least 3 months in total;
Note: Tenofovir counted as an NRTI;
Note: Treatment with an investigational NRTI for a period of at least 3 months counted as an NRTI treatment;
5. Prior use of one or more NNRTIs (investigational included) as part of a failing regimen;
Note: Treatment with an investigational NNRTI counted as an NNRTI treatment;
Note: A regimen could have failed virologically or due to intolerance; approved NNRTIs must not represent a worthy treatment option;
Note: Subjects with documented NNRTI resistance were allowed even when previous NNRTI use could not be documented;
6. Subjects having at least 1 primary PI mutation at screening as defined by the IAS-USA guidelines (D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V, L90M);
Note: Subjects with 3 primary PI mutations were allowed in the trial, however this subject population was limited to 30% of the total number of subjects;
7. Subjects experienced to at least one PI for a total period of at least 3 months;
8. Subjects who voluntarily signed the informed consent form;
9. Subjects who could comply with the protocol requirements (see concomitant medication [Section 3.3.3](#) and [Section 3.3.7](#));
10. Subjects had a general medical condition that, in the investigator's opinion, did not interfere with the assessments and the completion of the trial.

Exclusion Criteria

1. Presence of any currently active AIDS defining illness (Category C conditions according to the CDC Classification System for HIV Infection 1993) with the following exceptions, which had to be discussed with the sponsor prior to enrollment:
 - 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.
 - Wasting syndrome due to HIV infection if, in the investigator's opinion, it was not actively progressive and its treatment would not require hospitalization or compromise the subject's safety or compliance to adhere to the study protocol procedures. If subjects were on maintenance therapy (which could have included human Growth Hormone, appetite stimulants and anabolic steroids) for previously diagnosed wasting, they could be eligible for the trial only if such treatment was not included in the list of disallowed medications.
- Note: Primary and secondary prophylaxis for an AIDS defining illness was allowed in case the medication used was not part of the disallowed medication as specified in [Section 3.3.7](#).*

Exclusion Criteria, cont'd

2. Current or past history of alcohol and/or drug use which, in the investigator's opinion, would compromise the subject's safety or compliance to the study protocol procedures;
3. Subjects on a treatment interruption at screening;
4. Subjects for whom an investigational ARV was part of the regimen at screening, (with the following exceptions: T-20, FTC, atazanavir and fosamprenavir) or use of any other non-ARV investigational agents at least 90 days prior to screening;
5. Use of disallowed concomitant therapy (as specified in [Section 3.3.7](#));
6. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication (TMC114/RTV/placebo) (for subjects with a sulfonamide allergy see [Section 3.4.7.5.1](#));
Note: TMC114 is a sulfonamide. Subjects who previously experienced a sulfonamide allergy were allowed to enter the trial, however the potential for cross sensitivity between drugs in the sulfonamide class and TMC114 was unknown.
7. Life expectancy of less than 6 months;
8. Pregnant or breast feeding;
9. Female subject of childbearing potential without use of effective non-hormonal birth control methods or not willing to continue practicing these birth control methods from screening until at least 14 days after the end of the treatment period;
Note: Hormonal based contraception may not be reliable when taking TMC114, therefore to be eligible for this study women of childbearing potential had to either:
 - (1) use a double barrier method to prevent pregnancy (i.e. using a condom with either diaphragm or cervical cap), or,
 - (2) use hormonal based contraceptives in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap or female condom), or,
 - (3) use IUD in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap or female condom), or,
 - (4) be non-heterosexually active, practice sexual abstinence or have a vasectomized partner (confirmed sterile).*Note: Women who were postmenopausal for at least 2 years, women with total hysterectomy and women with tubal ligation were considered of non-childbearing potential.*
10. Subjects with clinical or laboratory evidence of active liver disease, liver impairment/dysfunction or cirrhosis irrespective of liver enzyme levels;
Note: Subjects co-infected with hepatitis B or C were allowed to enter the trial if their condition was clinically stable and would not require treatment during the study period. Subjects diagnosed with hepatitis A at screening were not allowed in the trial.
11. Any active or unstable medical condition (e.g. tuberculosis; cardiac dysfunction; acute viral infections) or findings during screening of medical history or physical examination that, in the investigator's opinion, would compromise the subjects safety or outcome of the study;

Exclusion Criteria, cont'd

12. Subjects with the following laboratory abnormalities as defined by ACTG grading scheme (see [Protocol, Addendum 4 in Appendix 7.1.1](#): ACTG grading severity list):

- Renal impairment: serum creatinine grade 2 or greater ($> 1.5 \times \text{ULN}$)
- Lipase grade 2 or greater ($> 1.5 \times \text{ULN}$)
- Hemoglobin toxicity grade 2 or greater ($\leq 7.9 \text{ g/dL}$)
- Platelet count grade 2 or greater ($< 75000/\text{mm}^3$)
- Absolute neutrophil count grade 2 or greater ($\leq 999/\text{mm}^3$)
- ALT, AST grade 2 or greater ($> 2.5 \times \text{ULN}$)
- Total bilirubin grade 2 or greater ($> 1.5 \times \text{ULN}$) unless clinical assessment foresaw an immediate health risk to the subject. For subjects receiving indinavir or atazanavir at screening the total bilirubin could not exceed $3 \times \text{ULN}$.
- Any grade 3 or 4 toxicity with the following exceptions unless clinical assessment foresaw an immediate health risk to the subject:
 - o Subjects with pre-existing diabetes or assessments under non-fasted conditions who experienced a glucose grade 3 or 4;
 - o Subjects with triglyceride or cholesterol elevation of grade 3 or 4 under non-fasted conditions;
 - o Subjects who experienced asymptomatic triglyceride or cholesterol elevations of grade 3 or 4;
 - o Subjects who experienced an asymptomatic and isolated GGT grade 3 or 4 elevation with all other LFTs and bilirubin within normal ranges.

13. Subjects who had been randomized to a TMC114 treatment arm in a previous TMC114 trial.

Retesting of abnormal screening values that led to exclusion or full rescreening of subjects having completed the Trial Termination Form needed to be discussed with the sponsor and was only approved (after discussion, review and approval in writing from the sponsor) on an exceptional basis.

Treatment	TMC114		TMC114 placebo		RTV (Norvir®)
	200 mg tablets	400 mg tablets	200 mg tablets matching TMC114	400 mg tablets matching TMC114	
Concentration	200 mg tablets	400 mg tablets	200 mg tablets matching TMC114	400 mg tablets matching TMC114	100 mg capsules
Dosage Form (F No.)	F002	F001	TMC114	TMC114	
Usage	Oral	Oral	Oral	Oral	Oral
Dose Regimen	400/100 mg TMC114/RTV q.d. 800/100 mg TMC114/RTV q.d. 400/100 mg TMC114/RTV b.i.d. 600/100 mg TMC114/RTV b.i.d.				
Duration of Treatment	96 weeks				
Duration of Trial	106 weeks (screening: max 6 weeks, treatment period: 96 weeks, follow-up: 4 weeks)				
Disallowed Medication	<p>Control and TMC114/RTV treatment groups</p> <p>ARVs:</p> <ul style="list-style-type: none"> - from screening until baseline: investigational ARVs (except FTC, T-20, atazanavir and fosamprenavir) - from baseline until the end of the treatment period: tipranavir, all investigational PIs with exception of fosamprenavir, abacavir, investigational NRTIs, all approved and investigational NNRTIs <p>Non-ARVs:</p> <ul style="list-style-type: none"> - from screening until baseline: amphetamines and amphetamine derivatives, all products containing <i>Hypericum perforatum</i> (St John's Wort) or <i>Echinacea</i>, rifampin, rifapentine, phenobarbital, phenytoin, carbamazepine - from screening until the end of the treatment period: experimental vaccines (approved vaccines were allowed as long as these were given outside the 4-week time frame preceding a plasma viral load measurement), dexamethasone 				

Disallowed Medication, cont'd	<p>TMC114/RTV treatment groups: from baseline until the end of the treatment period: amphetamines and amphetamine derivatives, all products containing <i>Hypericum perforatum</i> (St John's Wort) or <i>Echinacea</i>, rifampin, rifapentine, phenobarbital, phenytoin, carbamazepine, systemic use of ketoconazole and itraconazole at > 200 mg/day, amiodarone, bepridil, flecainide, propafenone, quinidine, systemic lidocaine, mexiletine, disopyramide, astemizole, terfenadine, ergot derivatives: dihydroergotamine, ergonovine (ergometrine), ergotamine, methylergonovine, cisapride, pimozide, midazolam, triazolam, lovastatin, simvastatin, cerivastatin, pravastatin, rosuvastatin, cholestyramine and colestipol, telithromycin, cyclosporine, tacrolimus, rapamycin, serolimus, warfarin, calcium channel blockers (e.g. felodipine, nifedipine, nicardipine, verapamil etc.), meperidine (pethidine)</p>
Assessments	
Pharmacokinetics	<p>In the pharmacokinetic substudy, subjects underwent a 12-hour (b.i.d. dosing regimens) or 24-hour (q.d. dosing regimens) pharmacokinetic sampling period at Week 4, Week 24 and optionally Week 40.</p> <p>In the pharmacokinetic main study in all subjects; the time points of sample collection were at baseline and, at Weeks 2, 4, 8, 12, 24, 48, 72, and 96 (or early withdrawal).</p> <p>One sample was collected (except Week 4) and there were no requirements for the time after intake of study medication. At Week 4, 2 samples were drawn: just before intake of TMC114/RTV (trough concentration) and at least 1 hour after drawing of the first sample.</p>
Resistance Determinations	<p>Samples for phenotype and genotype determinations were taken at screening, Day -14, and baseline, at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal), at both follow-up visits.</p> <p>Analysis of samples taken at Weeks 1, 4, 8, 12, 16, 20, 32, 40, 60, 72, 84 and at follow-up (1 and 4 weeks after withdrawal) depended on the judgement of the Protocol Virologist.</p>
Efficacy	
Plasma viral load	<p>Samples for plasma viral load determinations were taken at screening, Day -14, and baseline, at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal), at both follow-up visits (1 and 4 weeks after withdrawal).</p>
Immunology	<p>Samples for immunology assessment were taken at screening, Day -14, and baseline, at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal).</p>
Safety	
<p>Adverse Events</p> <p>Clinical Laboratory</p>	<p>Adverse events were checked at every visit and reported from screening onwards until the last study-related activity.</p> <p>Samples for hematology, biochemistry (fasted) and coagulation testing were taken at every visit, i.e., at screening, Day -14, and baseline, at Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal), at both follow-up visits (1 and 4 weeks after withdrawal).</p> <p>At Weeks 3, 6 and 10, only LFTs and bilirubin (total, indirect, and direct) were assessed. Urinalysis was performed at screening, Day -14, and baseline, at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal).</p>

Cardiovascular safety	Vital signs (pulse, BP) were assessed at screening, Day -14, and baseline, at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal). Central ECG readings were performed at screening, Day -14, and baseline, at Weeks 4, 12, 24, 48, 72, and 96 (or early withdrawal).
Physical examination	Physical examination was performed at screening and baseline, at Weeks 12, 24, 48, 72, and 96 (or early withdrawal).
Anthropometric measurements	Height was measured at screening. Weight and waist and hip circumference were determined at screening and baseline, at Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96 (or early withdrawal).
Questionnaires	The subjects completed a quality of life questionnaire at baseline at Weeks 4, 12, 24, 48, 72, and 96 (or early withdrawal).
Statistical Methods	Descriptive statistics, frequency tabulations, intent-to-treat analysis, Wilcoxon (matched-pairs) signed-ranks test; Kruskal-Wallis test, logistic regression model, Cox proportional hazards model, general linear mixed model, method of Jacqmin-Gadda, linear regression, ANOVA, ANCOVA

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	TMC114/RTV (mg)				Control	All subjects
	400/100 q.d.	800/100 q.d.	400/100 b.i.d.	600/100 b.i.d.		
Number of subjects (M/F)	64 (58/6)	63 (55/8)	63 (50/13)	65 (55/10)	63 (55/8)	318 (273/45)
Age: median (range), yrs	44.0 (28; 68)	40.0 (29; 65)	42.0 (20; 71)	41.0 (28; 65)	42.0 (25; 65)	42.0 (20; 71)
Plasma viral load: mean (SD), log ₁₀ copies/mL	4.48 (0.87)	4.58 (0.75)	4.33 (0.80)	4.59 (0.69)	4.40 (0.78)	4.48 (0.78)
CD4+ count: median (range), 10 ⁶ cells/L	176 (6; 606)	164 (3; 783)	171 (9; 816)	176 (6; 708)	197 (6; 736)	179 (3; 816)
Duration of HIV infection: median (range), years	11.5 (4.0; 19.1)	11.3 (4.1; 20.9)	11.0 (3.2; 21.0)	11.1 (1.9; 21.2)	11.4 (2.9; 21.1)	11.3 (1.9; 21.2)
Time since first ART initiation: median (range), months	108.7 (33; 196)	102.3 (47; 179)	107.1 (25; 179)	112.3 (23; 193)	111.5 (16; 217)	108.0 (16; 217)
Previous PI treatment duration: median (range), months	74.7 (16.2; 103.8)	71.9 (12.9; 112.0)	73.0 (8.1; 106.5)	71.4 (4.7; 111.1)	76.2 (10.3; 103.6)	73.5 (4.7; 112.0)
Number of PI resistance-associated mutations, median (range)	8 (3;11)	8 (2;11)	8 (1;13)	8 (0;12)	8 (3;13)	8 (0;13)
Previous ARV experience, n (%)						
PI: ≥ 2	62 (96.9)	59 (93.7)	62 (98.4)	61 (93.8)	63 (100.0)	307 (96.5)
NNRTI: ≥ 1	60 (93.8)	57 (90.5)	62 (98.4)	61 (93.8)	62 (98.4)	302 (95.0)
NRTI: ≥ 4	61 (95.3)	61 (96.8)	59 (93.7)	61 (93.8)	62 (98.4)	304 (95.6)
FI: 1	8 (12.5)	5 (7.9)	8 (12.7)	7 (10.8)	6 (9.5)	34 (10.7)
Discontinuations – Reason n (%)	7 (10.9)	3 (4.8)	12 (19.0)	3 (4.6)	39 (61.9)	64 (20.1)
Adverse event/HIV related event	2 (3.1)	1 (1.6)	8 (12.7)	1 (1.5)	4 (6.3)	16 (5.0)
Lost to follow-up	0	0	0	0	1 (1.6)	1 (0.3)
Withdrew consent	1 (1.6)	0	0	0	0	1 (0.3)
Reached virologic endpoint	3 (4.7)	2 (3.2)	4 (6.3)	2 (3.1)	34 (54.0)	45 (14.2)
Other	1 (1.6)	0	0	0	0	1 (0.3)

Efficacy	TMC114/RTV (mg)				Control
	400/100 q.d.	800/100 q.d.	400/100 b.i.d.	600/100 b.i.d.	
ITT	N = 60	N = 60	N = 61	N = 60	N = 60
Primary Variable Virologic response ^a : decrease of at least 1.0 log ₁₀ in VL vs. baseline at Week 24; n (%)	42 (70.0)*	43 (71.7)*	42 (68.9)*	46 (76.7)*	15 (25.0)
Secondary Variables Virologic response ^a : VL below 50 copies/mL at Week 24, n (%)	26 (43.3)*	29 (48.3)*	30 (49.2)*	32 (53.3)*	11 (18.3)
Virologic response ^a : VL below 400 copies/mL at Week 24, n (%)	38 (63.3)*	37 (61.7)*	42 (68.9)*	40 (66.7)*	15 (25.0)
Virologic response ^a : decrease of at least 0.5 log ₁₀ in VL vs. baseline at Week 24, n (%)	46 (76.7)*	49 (81.7)*	43 (70.5)*	52 (86.7)*	18 (30.0)
Change vs. baseline in log ₁₀ VL (copies/mL) at Week 24 ^b , mean (SD)	-1.78 (1.28)*	-1.83 (1.31)*	-1.69 (1.24)*	-2.03 (1.12)*	-0.63 (0.96)
Change vs. baseline in CD4+ cell count (x 10 ⁶ /L) at Week 24 ^c , mean (SD)	67.8 (94.99)*	75.0 (108.37)*	71.3 (87.60)*	124.1 (139.51)*	20.4 (107.12)
N: total number of subjects with data at Week 24 or discontinued earlier; VL: viral load; *: statistically significant in pairwise comparison with control					
^a ITT-TLOVR					
^b NC=F					
^c LOCF					
<p>The efficacy results of this trial show that all selected dosages of TMC114 co-administered with 100 mg RTV exhibited a superior antiretroviral efficacy when compared with individually optimized ARV regimens used in the control group (OBR + selected PIs). All TMC114/RTV dose regimens were associated with a significantly higher proportion of subjects achieving at least 1.0 log₁₀ reduction in viral load relative to baseline. In addition, greater reductions in log₁₀ viral load, a substantially higher proportion of subjects in the other categories of virologic response, and a larger increase in CD4+ cell count were observed in all TMC114/RTV groups as compared with the control group.</p> <p>Subgroup analysis by use of T-20 in OBR showed that the virologic response rate (at least 1.0 log₁₀ decrease in viral load relative to baseline at Week 24) was similar in T-20 naïve subjects using T-20 in their OBR and in subjects not using T-20 in their OBR (84% versus 77% in the 600/100 mg b.i.d. group). The virologic response rate for subjects in the TMC114/RTV groups not using T-20 (ranging from 69% to 77%) was higher than in control subjects, regardless of T-20 use (without T-20: 22%, T-20 naïve: 39%).</p>					

Resistance Determinations

Analysis of resistance data showed that the baseline TMC114 FC was predictive of virologic outcome at all TMC114 doses at Week 2, Week 24, and Week 32.

Moreover, the number of PI resistance-associated mutations at baseline was significantly predictive of virologic outcome at Week 24. Although a partial reduction of response to TMC114/RTV was seen with some baseline mutations (I47V and I54M), TMC114/RTV still showed a higher response than the control across a wide range of genetic backgrounds.

In more than 5 % of the TMC114 subjects, the V32I and I54L mutations were observed during treatment with TMC114/RTV. These mutations were detected during treatment, while they were not detected at baseline using population sequencing. For the groups of subjects with these emerging mutations, a TMC114 FC increase versus baseline and a less pronounced viral load change versus baseline at Week 24 as compared to the entire population of all TMC114 subjects were observed.

Further research is ongoing to determine the role of these mutations in resistance to TMC114.

Safety	TMC114/RTV (mg)					Control
	400/100 q.d.	800/100 q.d.	400/100 b.i.d.	600/100 b.i.d.	All TMC114	
(N = number of subjects with data)	N = 64	N = 63	N = 63	N = 65	N = 255	N = 63
<i>Mean exposure (weeks)</i>	<i>39.9</i>	<i>40.5</i>	<i>38.3</i>	<i>40.6</i>	<i>39.8</i>	<i>26.3</i>
Adverse Events (AEs) (Treatment Period)						
Most frequently reported AEs (≥ 10% of TMC114 subjects), n (%)						
Injection site reaction	19 (29.7)	18 (28.6)	18 (28.6)	15 (23.1)	70 (27.5)	13 (20.6)
Headache	8 (12.5)	16 (25.4)	11 (17.5)	9 (13.8)	44 (17.3)	15 (23.8)
Diarrhea	12 (18.8)	7 (11.1)	13 (20.6)	9 (13.8)	41 (16.1)	18 (28.6)
Nasopharyngitis	5 (7.8)	9 (14.3)	9 (14.3)	12 (18.5)	35 (13.7)	7 (11.1)
Nausea	10 (15.6)	4 (6.3)	8 (12.7)	7 (10.8)	29 (11.4)	8 (12.7)
Herpes simplex	4 (6.3)	7 (11.1)	8 (12.7)	10 (15.4)	29 (11.4)	1 (1.6)
Insomnia	10 (15.6)	12 (19.0)	3 (4.8)	3 (4.6)	28 (11.0)	6 (9.5)
n (%) with 1 or more AEs	59 (92.2)	58 (92.1)	58 (92.1)	61 (93.8)	236 (92.5)	59 (93.7)
n (%) of deaths	1 (1.6)	0	2 (3.2)	0	3 (1.2)	1 (1.6) ^a
n (%) with 1 or more other SAEs	7 (10.9)	8 (12.7)	12 (19.0)	9 (13.8)	36 (14.1)	9 (14.3)
n (%) of treatment discontinued due to AEs	2 (3.1)	1 (1.6)	8 (12.7)	1 (1.5)	12 (4.7)	4 (6.3)
n (%) with 1 or more grade 3 or 4 AEs	16 (25.0)	15 (23.8)	14 (22.2)	15 (23.1)	60 (23.5)	18 (28.6)
^a Reported two weeks after last follow-up visit						

Clinical Laboratory Tests	Mean triglyceride, VLDL cholesterol and AAG levels tended to decrease over time in all treatment groups, including the control group. Additionally, the increases in hematocrit, hemoglobin, platelets, lymphocytes, neutrophils, RBC and WBC were more pronounced in the TMC114/RTV groups than in the control group. Decreases in bilirubin levels were observed in all TMC114/RTV groups, whereas in the control group bilirubin levels increased over time. Other changes versus baseline for laboratory parameters were generally small and comparable between all treatment groups and were not found to be clinically relevant. Incidence of grade 3 or 4 laboratory abnormalities was similar in the all TMC114/RTV group and the control group. No apparent relationship between TMC114/RTV dose and incidence of observed laboratory abnormalities was noted, except for increases in VLDL (23% in the lowest dose group and 40% in the highest dose group).
Cardiovascular Safety	Minor median changes were reported for vital signs and ECG parameters. Some statistically significant changes were observed for certain parameters but no trends or relationship to dose were apparent. Individual treatment-emergent abnormalities in vital signs were reported with a similar incidence in the TMC114/RTV groups and in the control group. Overall, QTc abnormalities were more commonly reported in the control group than in the TMC114/RTV groups. No clear dose relationship was observed in the TMC114/RTV groups.

Pharmacokinetic Parameters for TMC114 Obtained From the Pharmacokinetic Substudy and Population Pharmacokinetic Assessments

PK Parameter ^a	400/100 mg q.d.		800/100 mg q.d.		400/100 mg b.i.d.		600/100 mg b.i.d.	
	Pop PK (n=62)	Wk 4 PK subst (n=7)	PopPK (n=62)	Wk 4 PK subst (n=7)	Pop PK (n=61)	Wk 4 PK subst (n=9)	Pop PK (n=64)	Wk 4 PK subst (n=6)
C _{0h} (ng/ml)	1156	874	1765	2670	3052	3235	3203	3515
AUC _{12h} (ng.h/mL)	-	-	-	-	49465	46777	55952	42604
AUC _{24h} (ng.h/mL)	51781	51958	84280	92413	-	-	-	-

^a Pharmacokinetic parameters are presented as geometric means
Pop PK: Population pharmacokinetics; Wk: Week; subst: substudy

Pharmacokinetics

Exposure to TMC114 increased with increasing dose of TMC114, however the increase appeared to be less than dose proportional for the q.d. and b.i.d. regimens. The highest daily exposure to TMC114 was observed after 600/100 mg b.i.d. Due to the low number of subjects with complete pharmacokinetic profiles that reached Week 24 and 40 (n = 20 for all dose groups), an analysis of exposure to TMC114 over time could not be reliably made at the time of analysis.

The estimated pharmacokinetic parameters for TMC114 from the population pharmacokinetic analysis for the different dose regimens were in the same range as those observed in the pharmacokinetic substudy.

For each dose group, the mean trough concentration of TMC114 in plasma exceeded the predefined target trough concentration of 550 ng/mL. All subjects in the b.i.d. dosing regimens of TMC114/RTV had a plasma trough concentration of TMC114 exceeding 550 ng/mL.

A trend of higher TMC114 exposure was observed for subjects with higher concentrations of AAG in plasma at baseline for all dose regimens.

Pharmacokinetics/Pharmacodynamics

The IQ, reflecting the ratio between the concentration of TMC114 achieved in plasma and the TMC114 FC at baseline, was the strongest predictor of response. The relationship between IQ and response was primarily driven by the TMC114 FC at baseline, and to a lesser extent by the exposure to TMC114. IQs of TMC114 were generally high (mean values generally > 200) and increased with increasing daily doses of TMC114. The highest IQ was observed in the TMC114/RTV 600/100 mg b.i.d. group.

There was no apparent relationship between the pharmacokinetics of TMC114 and safety/tolerability and laboratory parameters.

Therefore, significant antiviral activity would be expected for all dose regimens, with more pronounced effects for the higher doses studied, which is in line with the efficacy results.

Conclusions

The results of this primary analysis demonstrate that TMC114/RTV co-administered with an individually optimized OBR was highly effective in this advanced population with limited to no treatment options, as compared with individually optimized ARV regimens used in the control group (OBR + selected PIs). All TMC114/RTV dose regimens were associated with a significantly higher proportion of subjects achieving at least a 1.0 log₁₀ reduction in viral load relative to baseline. In addition, greater reductions in log₁₀ viral load, a substantially higher proportion of subjects in the other categories of virologic response, and a larger increase in CD4+ cell count were observed in all TMC114/RTV groups as compared with the control group. Overall, the highest dose (TMC114/RTV 600/100 mg b.i.d.) provided the greatest efficacy. In this population, it appears that the additional effect of T-20 was limited in subjects who received TMC114/RTV 600/100 mg b.i.d.

All doses of TMC114/RTV were generally safe and well tolerated and showed an adverse event profile comparable to the control group. Exposure to study medication was approximately 50% higher in the TMC114/RTV groups. No trends related to dose and incidence of AEs, laboratory abnormalities and/or abnormal investigations were apparent. These data suggest that with administration of TMC114/RTV, routine follow-up for HIV-infected subjects receiving antiretroviral therapy is adequate. In addition, the TMC114/RTV 600/100 mg b.i.d. dose was shown to have a similar safety profile as the other TMC114/RTV doses evaluated in this trial.

All data of the primary analysis confirm the selection of TMC114/RTV 600/100 mg b.i.d. as the recommended dose, which was based on the data of the combined interim analyses.

At Week 24, TMC114/RTV treatment (600/100 mg b.i.d.) resulted in the following benefits:

- 77% responders with a decrease of at least 1.0 log₁₀ in viral load, compared to 25% in the control group (individually optimized ARV regimen: OBR + selected PIs),
- 53% responders with a viral load below 50 copies/mL, compared to 18% in the control group,
- a decrease in viral load of 2.03 log₁₀ copies/mL, compared to a decrease of 0.63 in the control group,
- an increase in absolute CD4+ cell count of 124 x 10⁶ cells/L, compared to 20 in the control group.

Based on the results of the Week 24 primary analysis of this trial, it is expected that TMC114 will fulfil an unmet medical need for treatment-experienced HIV-infected subjects.