SYNOPSIS

Trial identification and protocol summary

Company: Tibotec Pharmaceuticals Ltd. **Trade name**: - **Indication**: HIV-1 infection	**Drug Substance**: TMC114 **Trial No.**: TMC114-C201 **Clinical phase**: IIa
Title: A Phase IIa, open, randomized trial to determine the antiviral activity in 60 HIV-1 positive, PI-experienced subjects, receiving either control treatment or TMC114 at various dosages for 13 days followed by a single dose on Day 14	
Investigator: A. Pozniak, St. Stephen's Centre, Chelsea & Westminster Healthcare NHS Trust, London, UK	**Country**: Austria, Germany, Great Britain, Italy, Poland, Russia, Switzerland
Reference: 0009697	
Trial period: Start: 28-Aug-2001 End: 15-Oct-2003	**No. of investigators**: 16 **No. of subjects**: 60 planned, 34 analyzed

Objectives:

The primary objective was to determine the antiviral activity of TMC114. Secondary objectives were to assess:

- the pharmacokinetics (PK) and pharmacokinetic/pharmacodynamic (PK/PD) relationships of TMC114;
- the effect of TMC114 on the degree and duration of immunologic change;
- the development of resistance to TMC114;
- the safety and tolerability of TMC114;

over the 2-week treatment period.

Trial design: A Phase IIa, open, controlled, randomized trial, in which 60 HIV-1 infected subjects, experienced to a minimum of 2 and a maximum of 4 different protease inhibitors (PIs) for a period of at least 2 months per PI, and currently on a failing PI containing regimen, were to be randomized into 5 groups. Subjects randomized to the TMC114 treatment groups received TMC114 (formulated as an oral solution, 20 mg/ml) as substitute for all PIs in the failing therapy, in 1 of the following dose regimens: 400 mg b.i.d., 800 mg b.i.d., 800 mg t.i.d, or 1200 mg t.i.d. for 13 days, followed by a single dose on Day 14. The underlying nucleoside reverse transcriptase inhibitor regimen remained unchanged until the end of the treatment period. Subjects randomized to the control group continued their current therapy. Antiretroviral activity, safety, tolerability, pharmacokinetics, immunologic change, and the development of resistance to TMC114 were assessed.

Subject selection:

Inclusion criteria:

1. male or female, aged above 18 years;
2. documented HIV-1 infection;
3. plasma viral load at screening visit above 2000 HIV-1 RNA copies/ml (assayed by RNA PCR);
4. on a currently failing antiretroviral regimen (consisting of 1 or more NRTIs combined with 1 or more PIs) for at least 8 weeks prior to screening;
5. been treated with a minimum of 2 and a maximum of 4 different PIs for a total period of at least 2 months each (a daily dose of RTV below 800 mg was not considered PI treatment; treatment with an experimental PI for a period of at least 2 months was considered PI treatment);
6. agrees not to change the current therapy until the end of the run-in period;
7. agrees not to change the NRTI(s) until the end of the treatment period;
8. no current AIDS-defining illnesses as defined in category C in the revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults (1993), with the exception of stable Kaposi's sarcoma. Subject with stable Kaposi's sarcoma were eligible for enrollment after consultation and agreement of the sponsor;
9. informed consent form signed voluntarily;
10. able to comply with the protocol requirements.

Exclusion criteria:

1. presence of an NNRTI in the current failing regimen;
2. suspicion of alcohol abuse;

3. suspicion of recreational drug abuse leading to non-compliance with trial procedures and/or medication intake;
4. use of disallowed concomitant therapy;
5. history of significant drug allergy induced by PIs (e.g., Stevens-Johnson syndrome, grade 3 or 4 drug rash);
6. history of allergy to any of the constituents of the oral solution and more specific to PEG400;
7. CD4 count < 50 x 10^6/l;
8. life expectancy of less than 6 months;
9. pregnant or breast-feeding females;
10. female of childbearing potential without use of an effective non-hormonal birth control method, or not willing to continue practicing this birth control method for at least 14 days after the end of the treatment period;
    As hormonal based contraception may not be reliable when combined with TMC114, women of childbearing potential eligible for this study had to use either:
    - a double barrier method to prevent pregnancy (i.e., a condom with either spermicidal creme/foam/gel, or diaphragm, or cervical cap); or
    - hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm, or cervical cap with spermicide, or female condom with spermicide); or
    - an intra-uterine device in combination with a barrier contraceptive (i.e., male condom, diaphragm, or cervical cap with spermicide, or female condom with spermicide); or
    - be non-heterosexually active, practice heterosexual abstinence or have a vasectomized partner;
11. receipt of an investigational drug within 30 days prior to the trial drug administration (tenofovir [Viread®] was not considered an experimental drug for this trial);
12. acute hepatitis A infection (confirmed by hepatitis A antibody IgM), or acute or chronic hepatitis B infection (confirmed by hepatitis B surface antigen, and/or hepatitis B core antibody IgM), or acute or chronic hepatitis C infection (confirmed by hepatitis C virus antibody and HCV RNA; the latter was performed only if the test for HCV antibodies was positive);
13. renal impairment: serum creatinine > 2 x upper limit of normal (ULN);
14. pancreatic amylase or lipase > 1.5 x ULN;
15. hemoglobin < 5.7 mmol/l (9.1 g/dl) for men; < 5.6 mmol/l (8.9 g/dl) for women;
16. platelet count < 75 x 10^9/l (75000/µl);
17. absolute neutrophil count < 1.0 x 10^9 cells/l (1000 cells/µl);
18. alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), or total bilirubin of ACTG toxicity grade 2 or more;
19. previously having been randomized in a trial with TMC114 (including subjects in control groups);
20. any grade 4 toxicity according to the ACTG grading severity list, except for non-drug-related glucose elevations, and asymptomatic triglyceride/cholesterol grade 4 elevations.

Treatment	TMC114			
Concentration Dosage form (TF No.) Usage	20-mg/ml solution TF019 oral			
Medication	Treatment A 400 mg b.i.d.	Treatment B 800 mg b.i.d.	Treatment C 800 mg t.i.d.	Treatment D 1200 mg t.i.d.
Batch number (expiry date)	First supply (25 Nov 2001): 20 ml, 88509; 30 ml, 88704. Second supply (13 May 2003): 20 ml, 119458; 30 ml, 119475. Third supply (9 Sep 2003): 20 ml, 127675; 30 ml, 127733.			
Dose regimen	TMC114 administered under fasted condition for 13 days (b.i.d. or t.i.d.), followed by a single morning intake on Day 14; NRTIs administered at the same time as TMC114			
Duration of treatment	14-days			
Duration of trial	Screening (maximum 3 weeks), run-in (7 days), treatment period (14 days), and follow-up (6 weeks)			
Disallowed medication	• Not allowed from 2 days before the start of treatment until the end of treatment: - any anti-HIV therapy (including hydroxy-urea) not in agreement with the inclusion criteria or prohibited based on the exclusion criteria; - HIV vaccines;			

	- CYP3A4 inhibitors: azole antifungals ketoconazole, itraconazole and fluconazole (except local application), macrolide antibiotics (erythromycin, clarithromycin, troleandomycin); SSRIs (nefazodone, fluvoxamine), H2-antagonist (cimetidine); - CYP3A4 substrates with a small therapeutic index: terfenadine, astemizole, cisapride, amiodarone, quinidine, triazolam, midazolam, ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine, ergotamintartate), simvastatin, sildenafil, cyclosporin, tacrolimus; - cholestyramine, colestipol, lovastatin and atorvastatin. • Not allowed from 14 days before the start of treatment until the end of treatment: rifamycins (rifabutin, rifampicin); anticonvulsants (phenobarbital, phenytoin, carbamazepine); all products containing hypericum perforatum (St John's Wort). • Administration of immediate release (buffered) didanosine formulations and TMC114 had to be separated by at least 2 hours. • The use of methadone during the trial was allowed. As methadone levels may be altered by treatment with TMC114, the methadone dose could be adjusted pending clinical symptoms. • For women of childbearing potential, see exclusion criterion 10. • In case of rash, treatment with antihistaminics, topical corticosteroids, or antipruritic agents, could be prescribed as medically indicated and taking into account the above mentioned disallowed medication. • Amphetamines and amphetamine derivatives could not be used for the duration of the whole trial period.

Assessments	Screening[a]	Run-in		Treatment											Follow-up			
		Day		Day											[b]	Week		
		-7	-3	1	2	3	4	5	6	7	8	10	12	14	1	1	3	6
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Informed consent	x																	
Demographics	x																	
Pregnancy test[c]	x			x											x		x	
In-/exclusion crit.	x			x														
Hepatitis A, B, C[d]	x			x							x				x			
Med. & surg. history/ Conc. Diseases				x														
Phys. exam.	x			x											x			
Witnessed TMC114 admin.				x	x	x	x	x	x	x	x	x	x	x				
Urinalysis	x			x		x					x			x	x			
Hematology	x			x		x					x		x	x	x	x	x	x
Biochemistry	x			x		x		x			x	x	x	x	x	x	x	x
ECG	x			x		x					x			x	x			
Vital signs	x	x	x	x		x					x			x	x			
TDM[e]		x	x	x							x			x				
PK[f]				x	x	x	x	x	x	x	x	x	x	x	x			
Protein binding														x				
Pheno-/genotyping	x			x											x		x	
Viral load	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Immunologic ass.	x			x							x				x	x	x	x

Conc. therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AE/HIV related events				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

a Within 4 weeks before baseline.
b Day 1 of follow-up, or early withdrawal.
c Females only: serum test at screening, urine test at baseline Visit (Day 1), Visit 15, and Visit 17.
d Storage of sample for hepatitis A, B & C test taken at baseline Visit (Day 1), Visit 11 (Day 8), and Visit 15.
e For all subjects before the baseline visit, and only for subjects receiving TMC114 from baseline onwards.
f Only for subjects receiving TMC114; a full pharmacokinetic profile (400-800 mg b.i.d.: pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose, and 800-1200 mg t.i.d.: pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose) was obtained on Days 1 and 14; on the other days a single pre-dose sample was taken.

Statistical methods	Intent-to-treat analysis; descriptive statistics, frequency tabulations, graphical analysis, non-linear mixed-effect modeling, ANCOVA, Fisher exact test, Kruskal-Wallis test, Wilcoxon matched-pairs signed-ranks test.

Main features of the subject sample and summary of the results

Baseline characteristics						
	TMC114 400 mg b.i.d.	TMC114 800 mg b.i.d.	TMC114 800 mg t.i.d.	TMC114 1200 mg t.i.d.	Control	All subjects
Subject disposition						
Number of subjects entered	8	8	7	6	5	34
M/F	7/1	6/2	6/1	6/0	5/0	30/4
Age (yrs): median (range)	46.0 (35 – 62)	37.5 (27 – 49)	40.0 (33 – 52)	38.5 (24 – 60)	39.0 (39 – 55)	39.5 (24 – 62)
Drop-outs - Reason						
Adverse event	1	0	1	1	0	3
Lost to follow-up	1	0	0	0	0	1
Other	1	0	0	0	0	1
PI treatment at screening						
Single PI	1 (12.5)	2 (25.0)	3 (42.9)	2 (33.3)	2 (40.0)	10 (29.4)
Single PI boosted	6 (75.0)	5 (62.5)	3 (42.9)	3 (50.0)	1 (20.0)	18 (52.9)
Double PI	0	0	0	1 (16.7)	0	1 (2.9)
Double PI boosted	1 (12.5)	1 (12.5)	1 (14.3)	0	2 (40.0)	5 (14.7)
Baseline resistance characteristics						
No. of sensitive PIs (phenotype based on Antivirogram®)[a], n (%)						
0	5 (62.5)	3 (37.5)	3 (42.9)	1 (16.7)	4 (80.0)	16 (47.1)
1	1 (12.5)	2 (25.0)	0	2 (33.3)	1 (20.0)	6 (17.6)
≥2	2 (25.0)	3 (37.5)	4 (57.1)	3 (50.0)	0	12 (35.3)
Fold change in EC_{50} values[a], median (range)						
TMC114	2.56 (0.1 – 33.8)	1.20 (0.0 – 6.7)	1.20 (0.1 – 17.2)	1.79 (0.5 – 22.6)	9.80 (1.1 – 56.6)	1.60 (0.0 – 56.6)
Baseline protease mutations (according to IAS list of mutations of March 2003[16]), median (range)						
Primary PI mutations	2.0 (0 – 3)	2.0 (0 – 3)	3.0 (1 – 3)	2.5 (0 – 4)	3.0 (2 – 4)	2.0 (0 – 4)
PI resistance associated mutations	6.0 (1 – 8)	5.0 (1 – 9)	8.0 (3 – 9)	5.5 (2 – 10)	5.0 (4 – 10)	5.5 (1 – 10)

a Baseline imputed values were used with screening data if no data at baseline were available.
Note: Cut-offs as defined by Antivirogram® (with clinical cut-off of 10 for lopinavir, and 4 for tenofovir)

Pharmacokinetics of TMC114				
Mean ± SD, t_{max}, free TMC114, calculated protein binding: median (range)	TMC114 400 mg b.i.d.	TMC114 800 mg b.i.d.	TMC114 800 mg t.i.d.	TMC114 1200 mg t.i.d.
Day 1				
n	6	8	7	6
t_{max}, h	0.78 (0.50 – 1.00)	1.00 (0.50 – 1.00)	0.52 (0.50 – 2.00)	1.00 (0.50 – 2.00)
C_{max}, ng/ml	4493 ± 2064	5945 ± 2722	6856 ± 1948	9973 ± 4600
AUC_{8h}, ng.h/ml	-	-	19135 ± 8890	31893 ± 12601
AUC_{12h}, ng.h/ml	13618[a] ± 6450	17714 ± 8403	-	-
Day 14				
n	6	8	6	5
C_{0h}, ng/ml	89.3 ± 38.4	179 ± 159	285 ± 245	349 ± 363
C_{min}, ng/ml	89.3 ± 38.4	160 ± 158	231 ± 197	349 ± 363
t_{max}, h	0.99 (0.50 – 2.00)	1.00 (0.50 – 1.08)	1.00 (0.50 – 1.02)	0.52 (0.50 – 1.00)
C_{max}, ng/ml	3182 ± 1382	6161 ± 3229	6650 ± 2770	7312 ± 2625
AUC_{8h}, ng.h/ml	-	-	14355 ± 5917	18845 ± 8070
AUC_{12h}, ng.h/ml	8010[a] ± 1890	15359 ± 7678	-	-
AUC_{24h}, ng.h/ml	16021[a] ± 3780	30718 ± 15356	43064 ± 17752	56535 ± 24209
$C_{ss, av}$, ng/ml	669[a] ± 159	1281 ± 642	1795 ± 741	2355 ± 1008
FI, %	395[a] ± 111	488 ± 102	370 ± 91.7	313 ± 98.6
Concentration free TMC114, ng/ml	3.2 (2 – 3)	5.1 (4 – 17)	14.9 (3 – 47)	37.1 (8 – 117)
Calculated protein binding, %	96.8 (94 – 98)	96.0 (94 – 98)	94.4 (86 – 96)	91.6 (87 – 94)

a n = 5

Efficacy					
	TMC114 400 mg b.i.d. N = 8[a]	TMC114 800 mg b.i.d. N = 8	TMC114 800 mg t.i.d. N = 7[a]	TMC114 1200 mg t.i.d. N = 6[b]	Control N = 5[c]
Primary efficacy parameter					
Change in viral load (log_{10} copies/ml) at treatment endpoint					
Median[d] (range)	-0.313 (-1.25 – +0.51)	**-0.818**** (-0.93 – -0.04)	**-1.124*** (-1.56 – +0.36)	**-0.691*** (-1.59 – -0.09)	+0.210 (-0.09 – +0.40)
LS Mean[e] (SE)	**-0.444**** (0.1334)	**-0.714**** (0.1310)	**-0.856**** (0.1447)	**-0.714**** (0.1483)	+0.269 (0.1663)
Secundary efficacy parameters					
The findings for **viral load decay rate**, **viral load DAVG**, and **nadir of the change in log_{10} viral load** generally confirmed the findings for change in log_{10} viral load.					
Decrease of at least 0.5 log_{10} in viral load at treatment endpoint					
n (%)	1 (12.5)	5 (62.5)	5 (71.4)	4 (66.7)	0
Decrease of at least 1.0 log_{10} in viral load at treatment endpoint					
n (%)	1 (12.5)	0	4 (57.1)	2 (33.3)	0
Viral load below 400 copies/ml at treatment endpoint[f]					
n (%)	1 (12.5)	0	2 (28.6)	1 (16.7)	0
CD4+ cell count (x 10^6/l) on FU Day 1 (i.e., Day 15)					
Median (range)	-69.50 (-246.0 – +67.0)	+53.00 (-49.0 – +258.0)	+19.00 (-132.0 – +177.0)	+99.00 (-295.0 – +152.0)	-3.50 (-85.0 – +242.0)
CD4+ cell count (%) on FU Day 1					

Median (range)	-0.40 (-4.5 – +2.6)	-0.55 (-5.2 – +9.6)	+0.60 (-2.6 – +7.7)	+2.15 (0.0 – + 10.8)	-0.50 (-1.9 – +1.5)
There were no statistically significant between-group differences for CD4+ cell count.					

a N = 6 on Days 7, 8, and 14
b N = 5 on Days 7, 8, and 14
c N = 4 for CD4+ cell count (x 10^6/l)
d **Bold**: statistically significant within-group changes (2-sided Wilcoxon signed rank test): * $p < 0.05$, ** $p < 0.01$
e **Bold**: statistically significant compared to control group (ANCOVA): * $p < 0.05$, ** $p < 0.01$.
f No subjects had a viral load below 50 copies/ml at treatment endpoint.
Treatment endpoint: last value after baseline, up to and including Day 14 (but excluding baseline)

Resistance determination
The baseline TMC114 fold change in EC_{50} values (FC) was predictive for the change in viral load on Day 14, while the number of protease mutations at baseline (all, PI resistance associated, or primary) was not. Comparing baseline and end-of-treatment phenotypes, no significant change in TMC114 FC was observed.

Pharmacokinetic/pharmacodynamic relationships

n (%)	TMC114 400 mg b.i.d. N = 6[a]	TMC114 800 mg b.i.d. N = 8[b]	TMC114 800 mg t.i.d. N = 6[a]	TMC114 1200 mg t.i.d. N = 4[c]	All TMC114 subjects N = 24[d]
C_{min} above EC_{50} (corrected)	3 (50.0)	7 (87.5)	5 (85.3)	3 (75.0)	18 (75.0)[e]
C_{min} below EC_{50} (corrected)	3 (50.0)	1 (12.5)	1 (16.7)	1 (25.0)	6 (25.0)[f]
C_{min} above EC_{50} (exact corrected)	3 (75.0)	6 (100.0)	4 (100.0)	3 (100.0)	16 (94.1)[g]
C_{min} below EC_{50} (exact corrected)	1 (25.0)	0	0	0	1 (5.9)[h]

- Statistically significant relationship ($p < 0.05$) between change in log_{10} viral load from baseline on Day 14 versus AUC_{24h}: larger decreases in log_{10} viral load with higher values for AUC_{24h}.
- Statistically significant relationships (mostly $p < 0.05$) between change in log_{10} viral load versus corrected and exact corrected IQ C_{min}, higher values for the decrease in viral load DAVG, and nadir of change in log_{10} viral load with higher IQ values.

a N = 4 for EC_{50} (exact corrected)
b N = 6 for EC_{50} (exact corrected)
c N = 3 for EC_{50} (exact corrected)
d N = 17 for EC_{50} (exact corrected)
e 12 (66.7%) and 6 (33.3%) of these subjects had a decrease of ≥ 0.5 and 1.0 log_{10} in viral load from baseline, respectively.
f 1 (16.7%) subject had a decrease of ≥ 0.5 log_{10} in viral load from baseline.
g 9 (56.3%) and 4 (25.0%) of these subjects had a decrease of ≥ 0.5 and 1.0 log_{10} in viral load from baseline, respectively.
h Subject did not have a decrease of ≥ 0.5 log_{10} in viral load from baseline.

Safety					
Adverse events (AEs) during treatment with TMC114					
Most frequently (in > 1 subjects) reported AEs, n (%)	TMC114 400 mg b.i.d. N = 8	TMC114 800 mg b.i.d. N = 8	TMC114 800 mg t.i.d. N = 7	TMC114 1200 mg t.i.d. N = 6	Control N = 5
Abdominal distention	1 (12.5)	1 (12.5)	0	0	0
Diarrhea	2 (25.0)	5 (62.5)	4 (57.1)	5 (83.3)	0
Dyspepsia	1 (12.5)	0	1 (14.3)	1 (16.7)	0
Flatulence	0	1 (12.5)	2 (28.6)	1 (16.7)	0
Nausea	1 (12.5)	0	1 (14.3)	1 (16.7)	0
Fatigue	0	2 (25.0)	0	1 (16.7)	0
Pyrexia	1 (12.5)	0	1 (14.3)	0	0
Herpes simplex	0	1 (12.5)	0	1 (16.7)	0
Increased appetite	1 (12.5)	0	1 (14.3)	0	0
Sensation of heaviness	0	1 (12.5)	0	1 (16.7)	0
Dizziness	0	0	1 (14.3)	2 (33.3)	0
Headache	1 (12.5)	1 (12.5)	3 (42.9)	3 (50.0)	0
Nasopharyngitis	0	1 (12.5)	0	1 (16.7)	0
Pharyngolaringeal pain	2 (25.0)	0	0	0	0
Pruritis	0	0	1 (14.3)	1 (16.7)	0
Hot flush	0	2 (25.0)	1 (14.3)	0	0
n (%) with 1 or more AE	8 (100.0)	7 (87.5)	7 (100.0)	6 (100.0)	1 (20.0)
n (%) with rash	1 (20.0)	0	2 (28.6)	0	0
n (%) of deaths	0	0	0	0	0
n (%) with 1 or more other SAE	0	0	0	0	0
n (%) treatment stopped due to AE	1 (20.0)	0	1(14.3)	1 (16.7)	0
n (%) with 1 or more grade 3 or 4 AEs	1 (20.0)	0	1(14.3)	1 (16.7)	0
Adverse events during the first 2 days of follow-up (Days 14 and 15)					
n (%) with 1 or more AE	1 (20.0)	2 (25.0)	0	0	0
n (%) with 1 or more grade 3 or 4 AEs	0	1 (12.5)	0	0	0
Clinical laboratory	No consistent clinically relevant TMC114 treatment-related changes over time in median laboratory parameters were noted. Most post-dose individual abnormal laboratory results were graded 1 or 2 in severity, and were related to liver function or lipid/glucose metabolism. Three subjects developed 1 or more TMC114 treatment-emergent grade 3 or 4 laboratory abnormalities: increased cholesterol (1 subject, grade 3), increased AST (1 subject, grade 3, reported as AE, premature discontinuation), and increased amylase and increased lipase (1 subject, grade 4, reported as AE, premature discontinuation). Two more subjects developed a laboratory abnormality that was reported as adverse event: increased potassium (hyperkalemia, grade 4, hemolyzed sample pre-dose on Day 1), and increased triglycerides (hyperlipidemia, grade 3, first day of follow-up). There were no consistent or clinically relevant TMC114 treatment-related changes over time for urinalysis.				
Vital signs	There were no consistent or clinically relevant changes over time in vital sign parameters.				
ECG	There were no consistent or clinically relevant changes over time in median ECG parameters. Four subjects had both a treatment-emergent abnormal QTc interval and an abnormal change in QTc; no dose relationship with TMC114 was observed.				

Physical examination	There were no clinically relevant, treatment-related physical examination findings.

Conclusions

- For all 4 dose groups, C_{min}, C_{max}, and AUC_{24h} increased with the total daily dose of TMC114 on Day 14.
- Treatment with TMC114 800 mg b.i.d., 800 mg t.i.d., and 1200 mg t.i.d. for 13 days followed by a single intake on Day 14 resulted in a significant reduction of viral load when compared to the control group. Under treatment with 400 mg b.i.d., the reduction in viral load was smaller but still statistically significant compared to the control group at treatment endpoint. No conclusions could be drawn for CD4+ cell count due to the high variability of the data and the short duration of the trial.
- The baseline TMC114 FC was predictive for the change in viral load on Day 14, while the number of protease mutations at baseline (all, PI resistance associated, or primary) was not.
- Statistically significant larger decreases in $\log_{10}$ viral load were observed with higher values for AUC_{24h} and various measures of IQ. Although the number of subjects was small, the data suggest that the decrease in $\log_{10}$ viral load was smaller for subjects with C_{min} below plasma protein binding corrected EC_{50} than for subjects with C_{min} above plasma protein binding corrected EC_{50}.
- In these HIV-1 infected, PI-experienced subjects, all 4 TMC114 dose regimens were generally safe and well tolerated; in general, the safety and tolerability profile of TMC114 was similar for all 4 dose groups.

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