SYNOPSIS

Trial Identification and Trial Protocol Summary

Company: Tibotec Pharmaceuticals **Nonproprietary Name**: rilpivirine hydrochloride **Indication**: HIV-1 infection	**Drug Substance**: TMC278 **Trial no**.: TMC278-TiDP6-C209 **Clinical Phase**: III
Title: A Phase III, randomized, double-blind trial of TMC278 25 mg q.d. versus efavirenz 600 mg q.d. in combination with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve HIV-1 infected subjects	
Principal Investigator: [redacted], MD, [redacted], France.	**Countries**: 21
Trial Period: Start: 21-Apr-2008 End: 04-Jan-2011 (data cut-off date of Week 96 analysis)	**No. of Investigators**: 112 **No. of Subjects Randomized**: 694 (690 randomized and treated)

Objectives: The primary objective of this trial was to demonstrate non-inferiority of treatment with TMC278 when administered as 25 mg once daily (q.d.) compared with control (efavirenz [EFV] 600 mg q.d.) in regard to the proportion of virologic responders (plasma viral load <50 human immunodeficiency virus [HIV]-1 ribonucleic acid [RNA] copies/mL [hereafter referred to as copies/mL], according to the Time to Loss of Virologic Response [TLOVR] algorithm) at 48 weeks in antiretroviral (ARV) treatment-naïve HIV-1 infected adult subjects, with a maximum allowable difference of 12%.

Secondary objectives were to:

- demonstrate non-inferiority of TMC278 compared with EFV with a maximum allowable difference of 10% at 48 weeks for the primary efficacy parameter
- evaluate superiority in efficacy of TMC278 compared with EFV, in case non-inferiority was established
- evaluate and compare the safety and tolerability of TMC278 when administered as 25 mg q.d. versus (vs.) EFV over 48 and 96 weeks
- evaluate and compare the antiviral activity of TMC278 when administered as 25 mg q.d. vs. EFV over 48 and 96 weeks
- evaluate and compare immunologic changes (as measured by Cluster of Differentiation 4 [$CD4^+$] cell count) in the TMC278 group vs. those in the control group over 48 and 96 weeks
- assess the evolution of the viral genotype and phenotype over 48 and 96 weeks
- evaluate the population pharmacokinetics and the pharmacokinetic/pharmacodynamic relationships for efficacy and safety of TMC278. The influence of covariates on TMC278 pharmacokinetics was also investigated
- assess preference-based health states (measured by version 2 of the Short-Form-36® [SF-36v2®]) and medical resource utilization for use in future economic evaluations (not presented in this report)
- assess treatment adherence as measured by the Modified Medication Adherence Self-Report Inventory (M-MASRI)

Design: TMC278-TiDP6-C209 (C209) is an ongoing, 96-week, randomized, double-blind, double-dummy, active-controlled, international Phase III trial in human immunodeficiency virus (HIV)-1 infected, antiretroviral (ARV) treatment-naïve adult subjects. The trial was designed to evaluate the long-term efficacy, safety and tolerability of TMC278 25 mg once daily (q.d.) compared with efavirenz (EFV) 600 mg q.d. (control). Each of these non-nucleoside reverse transcriptase inhibitors (NNRTIs) is being given in combination with a background regimen containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). Adult subjects with a plasma viral load of ≥5,000 HIV-1 ribonucleic acid (RNA) copies/mL (hereafter referred to as copies/mL), who were ARV treatment-naïve, who had HIV-1 susceptible to the background regimen at screening, and in whom the genotype of HIV-1 exhibited no NNRTI resistance-associated mutations (RAMs) at screening, were eligible for the trial.

Approximately 680 HIV-1 infected subjects were to be randomized in a 1:1 ratio to TMC278 25 mg q.d. or to EFV 600 mg q.d. The trial was designed to consist of a screening period of a maximum of 6 weeks, a 96-week double-blind treatment period, and a post 96-week double-blind treatment period until all subjects, who had not discontinued earlier, had been treated for at least 96 weeks and the Week 96 database had been locked; this period was of a maximum of 36 weeks between the first subject and the last subject reaching the Week 96 visit. After database lock, subjects were unblinded and received open-label treatment until the final/withdrawal visit. This final visit was to take place 6 weeks after database lock for EFV subjects and TMC278 subjects not participating in trial TMC278-TiDP6-C222 (C222) or at the time of roll-over into trial C222 for other TMC278 subjects. A post-treatment follow-up period could take place after the final/withdrawal visit for subjects with ongoing (serious) adverse events ([S]AEs). Subjects who experienced virologic failure and discontinued the trial were invited to participate in an optional, observational, non-interventional data collection period of about 6 months. This required a separate informed consent form (ICF).

The primary objective of this trial was to demonstrate non-inferiority of TMC278 versus (vs.) EFV in regard to the proportion of subjects achieving a confirmed plasma viral load of <50 copies/mL at 48 weeks of treatment (using the time to loss of virologic response [TLOVR] algorithm, referred to as virologic responders), with a maximum allowable difference of 12%. Additionally, the safety, tolerability, durability of antiviral activity, immunologic changes, HIV genotypic and phenotypic characteristics, pharmacokinetics, pharmacokinetic/pharmacodynamic relationships of TMC278 for efficacy and safety, patient-reported outcomes, and medical resource utilization (not presented in this report) were assessed throughout the trial.

This report describes the results of the Week 96 analysis of the trial, which was performed when all subjects had reached Week 96 or had discontinued earlier. The cut-off date for this analysis was 04 January 2011. In addition, since the primary parameter for this trial was at Week 48, data at the Week 48 time point are presented, where appropriate, for comparison purposes.

Subject Selection

Inclusion Criteria

1. Male or female subjects, aged 18 years or older.
2. Subject with documented HIV-1 infection.
3. Subject had signed the ICF voluntarily.
4. Subject could comply with the trial protocol requirements.
5. Subject had never been treated with a therapeutic HIV vaccine or an ARV prior to screening.

Inclusion Criteria, continued

6. Subject's HIV-1 plasma viral load at screening was ≥5,000 copies/mL (assayed by RNA polymerase chain reaction standard specimen procedure).

   Note: Retesting of HIV-1 plasma viral load to reassess eligibility was allowed only once using an unscheduled visit during the screening period.

7. In the judgment of the investigator, it was appropriate to initiate ARV therapy (ART) based on the subject's medical condition and taking into account guidelines for the treatment of HIV-1 infection.

   Note: At the time of the start of the trial, treatment guidelines recommended considering initiation of ART when $CD4^+$ cell counts were <350 cells/μL. However, clinical situations could warrant initiating ART with $CD4^+$ cell counts >350 cells/μL. Examples of such situations included rapidly declining $CD4^+$ cell counts over time, high plasma viral load, history of acquired immunodeficiency syndrome (AIDS)-defining illnesses, or severe symptoms of HIV infection.

8. Subjetc's HIV-1 demonstrated sensitivity to TDF and FTC based on results from the screening virco®TYPE HIV-1 test using the lower clinical cut-off (CCO) (indicated as "Maximal Response") or the biological cut-off (BCO) (indicated as "susceptible") on the screening virco®TYPE HIV-1 result and available historical data.

9. Subject agreed not to start ART before the baseline visit.

10. Subject's general medical condition, in the investigator's opinion, would not interfere with the assessments and the completion of the trial.

Exclusion Criteria

1. Any previous treatment with a therapeutic HIV vaccine or use of ARVs, including use of nevirapine (NVP) for the prevention of vertical HIV transmission.

2. Having documented genotypic evidence of NNRTI resistance at screening or from historical data available in the source documents, i.e., at least 1 of the NNRTI RAMs from the following list (the list was compiled on the basis of the list of International AIDS Society [IAS]-United States of America [USA] NNRTI RAMs, and other relevant publications):

   A098G, E138A, E138G, E138K, E138Q, E138R, F227C, G190A, G190C, G190E, G190Q, G190S, G190T, K101E, K101P, K101Q, K103H, K103N, K103S, K103T, K238N, K238T, L100I, M230I, M230L, P225H, P236L, V106A, V106M, V108I, V179D, V179E, Y181C, Y181I, Y181V, Y188C, Y188H, Y188L, Y318F

3. Previously documented HIV-2 infection.

4. Use of disallowed concomitant therapy from 4 weeks prior to baseline visit.

5. Any condition (including but not limited to alcohol and drug use), which, in the opinion of the investigator, could compromise the subject's safety or adherence to the trial protocol.

6. Life expectancy <6 months.

Exclusion Criteria, continued

7. Subject had any currently active 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:

   - 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 adherence to the trial protocol procedures. If the subject was on maintenance therapy (which may have included human Growth Hormone, appetite stimulants, and anabolic steroids) for previously diagnosed wasting syndrome, he/she was eligible for the trial only if such treatment was not included in the list of disallowed medications;

   - *Pneumocystis carinii* pneumonia (PCP) infection that was considered cured and the acute phase ended at least 30 days previously, and for which currently no therapeutic treatment was required (PCP prophylaxis was allowed, as long as it was not included in the list of disallowed medications);

   - Past occurrence of cryptococcosis that was considered to be fully cured and the acute phase ended at least 30 days previously, and/or for which no therapeutic treatment was required.

   Note: An AIDS-defining illness not clinically stabilized for at least 30 days was to be considered as currently active.

   Note: Primary or secondary prophylaxis for an AIDS-defining illness was allowed in case the medication used was not part of the disallowed medications.

8. Any active clinically significant disease (e.g., pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, clinical suspicion of adrenal insufficiency, hepatic impairment), or findings during screening or medical history or physical examination that, in the investigator's opinion, would have compromised the outcome of the trial.

9. Subject had active tuberculosis and/or was being treated for tuberculosis at screening.

   Note: Subjects who developed tuberculosis during the trial were to be withdrawn from the trial to allow appropriate tuberculosis therapy to be started.

10. Subject had known or suspected acute (primary) HIV-1 infection.

11. Subject had 1 or more of the following risk factors for prolongation of QT interval corrected for heart rate (HR) (QTc):

- A confirmed prolongation of QT/QTc, e.g., repeated demonstration of QT interval corrected for HR using Fridericia's formula (QTcF) >450 ms in the screening electrocardiogram (ECG) (i.e., retesting to reassess eligibility was allowed once using an unscheduled visit during the screening period);
- Pathological Q-waves (defined as Q-wave duration >40 ms or depth >0.4-0.5 mV);
- Evidence of ventricular pre-excitation;
- Electrocardiographic evidence of complete or incomplete left bundle branch block or right bundle branch block;
- Evidence of second or third degree heart block;
- Intraventricular conduction delay with QRS duration >120 ms;
- Bradycardia as defined by sinus rate <50 beats per minute (bpm);
- Personal or family history of long QT syndrome;
- Personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia;
- Syncopal episodes;
- Risk factors for Torsade de Pointes (e.g., heart failure, hypokalemia, hypomagnesemia).

Exclusion Criteria, continued

12. Receipt of any investigational drug or investigational vaccine within 90 days prior to the first study medication administration.
13. Subject enrolled in other clinical trials that included any blood sampling with a volume >50 mL taken over the course of 6 months, specimen collection, or other interventional procedure. Concurrent participation in non-interventional observational trials was allowed as long as there was no impact on the objectives of this trial. Data collected in this trial could be reported in the observational trial.

    Note: Also during the conduct of the trial, subjects were not allowed to participate in any other clinical trial that included any blood sampling with a volume >50 mL taken over the course of 6 months, specimen collection, or other interventional procedure.
14. Previously demonstrated clinically significant allergy or hypersensitivity to any of the components of the investigational medication (TMC278) or to components of EFV or TDF/FTC.
15. Pregnant or breastfeeding female.
16. Female 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 at least 30 days after last intake of study medication.

    Note: Malformations have been observed in fetuses from EFV-treated animals, and also the effects of EFV on hormonal contraceptives are not fully characterized. Therefore, to be eligible for this trial, women of childbearing potential must have agreed to use 1 of the following birth control methods:

    a. a diaphragm or cervical cap and the male partner was to use a condom, or

    b. a hormonal contraceptive or an intra-uterine device (IUD) in combination with a barrier contraceptive (i.e., male condom, diaphragm, cervical cap or female condom), or

    c. be non-heterosexually active, practice sexual abstinence or have a vasectomized partner.

    Note: Women who had been postmenopausal for at least 2 years, women with total hysterectomy, and women who have a bilateral tubal ligation were considered of non-childbearing potential.

    Note: A female condom and a male condom were not to be used together as friction between the 2 can result in failing of either product.

    Note: Spermicides were not to be used as this can potentially increase the rate of HIV-1 transmission.

    Note: A cervical cap is less effective in parous women.
17. Non-vasectomized heterosexually active males without the use of effective birth control methods or not willing to continue practicing these birth control methods from screening onwards until at least 30 days after last intake of study medication.
18. Any grade 3 or 4 laboratory toxicity according to the Division of AIDS (DAIDS) grading table, except for:
    - grade 3 absolute neutrophil count;
    - grade 3 platelets;
    - grade 3 glucose elevation in diabetics;
    - asymptomatic grade 3 pancreatic amylase elevation;
    - asymptomatic grade 3 triglyceride/cholesterol (including low density lipoprotein cholesterol [LDL-C])/glucose elevation;
    - asymptomatic grade 4 triglyceride elevation.
19. Renal impairment: estimated glomerular filtration rate based on creatinine ($eGFR_{creat}$) <50 mL/min.

    Note: The central laboratory calculated $eGFR_{creat}$ using the formula derived from the Modification of Diet for Renal Disease (MDRD) trial.

    Note: Retesting of abnormal screening values that led to exclusion was allowed only once using an unscheduled visit during the screening period (to reassess eligibility).

Treatment	TMC278	EFV
Dosage (per day)	25 mg	600 mg
Active treatment dosage form (F No.)	25 mg tablets (F006)	600 mg tablets (F343 [produced in the USA, debossed and de-inked, then overcoated]), (F344 [produced in the European Union {EU}, debossed and de-inked, then overcoated]) Both sources of EFV were blinded at the same site(s), with the same process (debossed and de-inked, then overcoated) and excipients for coating.
Placebo dosage form (F No.)	Placebo tablets identical to TMC278 in appearance, taste, and smell (F013)	Placebo tablets identical to EFV in appearance, taste, and smell (F335)
Usage	1 x TMC278 25 mg tablet per os (p.o.) with 1 x EFV placebo tablet p.o.	1 x EFV 600 mg tablet p.o. with 1 x TMC278 placebo tablet p.o.
Batch Number	Active TMC278: PD2809, 8BL2H, 9CL1F TMC278 placebo: 0712507, PD2806, PD3020	Active EFV: 0712511, 0712512, JO77004, JO6036, JO78054, JO7Y021, JO7Y053, JO7Z034, JO7Z037, JO81003, JO82017, JO81068, JO81084, JO8X075, JO89027, JO89062, JO89060, JO8Z091, JO91122, JO8Z165, PD2912, JO95130, JO93140, JO94027, JO94086, JO95147, JO9Z149 EFV placebo: PD1933, PD2872, PD3015, JO93144, PD3015
Other ARV Medications	All subjects took a background regimen consisting of TDF (300 mg q.d.) and FTC (200 mg q.d.) administered as 1 Truvada® tablet.	
Dose Regimen	TMC278 25 mg (or placebo) q.d. with food, preferably breakfast, each dose separated by approximately 24 hours, plus EFV 600 mg (or placebo) q.d. on an empty stomach, preferably at bedtime, each dose separated by approximately 24 hours, plus The background regimen, TDF/FTC, was recommended to be taken at the same time as TMC278 (or placebo). ***Note:*** Due to the double-dummy design, subjects receiving active TMC278 also took placebo EFV (and vice versa) in addition to their background regimen.	
Duration of Treatment	96 weeks (excluding screening, post 96-week [double-blind] treatment period, post-treatment follow-up period). After the Week 96 database lock, all subjects were unblinded and received open-label treatment until the final visit. This final visit was to take place 6 weeks after database lock for EFV subjects and TMC278 subjects not participating in the roll-over trial C222 or at the time of roll-over into trial C222 for other TMC278 subjects.	

Treatment, continued	
Duration of Trial	The ongoing C209 trial consisted of a screening period of a maximum of 6 weeks, a 96-week double-blind treatment period, and a post 96-week double-blind treatment period of a maximum of 36 weeks (until all subjects had been treated for 96 weeks or discontinued earlier). A 4-week post-treatment follow-up period could take place after the final/withdrawal for subjects with ongoing (S)AEs at this visit. This report presents the results of the Week 96 analysis (including all data from the double-blind treatment periods prior to the Week 96 database lock). After the Week 96 database lock, all subjects received open-label treatment until the final visit, which was to take place 6 weeks after database lock for EFV subjects and TMC278 subjects not participating in trial C222, or at the time of roll-over into trial C222 for other TMC278 subjects. This open-label treatment period is not part of the Week 96 analysis and is not presented in this report.
Disallowed Medication	From 4 weeks prior to the baseline visit until end of treatment or withdrawal visit: - All investigational drugs - Drugs that can potentiate the activity of ARVs or have intrinsic ARV activity (but no indication for treatment of HIV infection): mycophenolic acid, hydroxyurea, hydroxychloroquine, foscarnet - All disallowed medication as mentioned in the package insert of EFV - All disallowed medication as mentioned in the package insert of TDF/FTC - For any alternative nucleoside/tide reverse transcriptase inhibitors (N[t]RTIs) in the background regimen, the respective package inserts were to be consulted for concomitant use with other medications and for contraindicated medications or medications that were not recommended for concomitant use - Subjects had to cease any ketoconazole treatment at least 4 weeks before the baseline visit - Medications with cytochrome P450 (CYP) 3A4 inhibitory activity were to be used with caution - Potent CYP3A4 inducers were prohibited. From baseline onwards: - Any anti-HIV therapy other than the study medication (TMC278 or EFV) and N(t)RTIs in the background regimen - No vaccines could be given during the first 6 weeks of treatment. After 6 weeks of treatment, approved vaccines were allowed as long as they were given outside the 4-week time frame preceding a plasma viral load measurement. A list of theoretical and established interactions of TMC278 with commonly used co-medications can be found in Section 5.3.13.1 of the trial protocol.

Assessments	
Efficacy	
Plasma Viral Load	Samples for plasma viral load were taken at screening and at every visit throughout the trial, including early withdrawal, as applicable. Samples were also taken at the end of the post 96-week treatment period and 4 weeks after the final/post-Week 96 withdrawal visit, if applicable.
Immunology	Samples were taken at screening and at every visit throughout the trial, including early withdrawal as applicable. Samples were also taken at the end of the post 96-week treatment period.
Resistance Determinations	Samples for phenotypic/genotypic determinations were taken at screening and at every visit throughout the trial, including early withdrawal as applicable. Samples were also taken at the end of the post 96-week treatment period and 4 weeks after the final/post-Week 96 withdrawal visit, if applicable. As standard, genotypic determinations were only performed on samples collected at baseline, at the first visit after confirmed loss of virologic response and at the final/withdrawal visit, while phenotypic determinations were only performed as standard on samples collected at baseline and at the final/withdrawal visit. Other samples were to be analyzed at the discretion of the trial virologist.
Safety	
AEs	Adverse events and HIV-related events were monitored from signing the ICF onwards and at every visit throughout the trial, including early withdrawal as applicable, and were also monitored at the end of the post 96-week treatment period, and 4 weeks after the final/post-Week 96 withdrawal visit, if applicable.
Clinical Laboratory	
Hematology and Biochemistry	Samples were taken after an overnight fast at screening and at every visit throughout the trial, including early withdrawal as applicable. Samples were also taken at the end of the post 96-week treatment period and 4 weeks after the final/post-Week 96 withdrawal visit, if applicable. Additional testing was required in the event of certain graded laboratory abnormalities. The samples collected at baseline, and at Weeks 2 and 24 were also analyzed for cystatin C. Hepatitis A, B, and C tests were performed at baseline. For females of childbearing potential, the samples for biochemistry taken at screening included a serum pregnancy test.
Urinalysis	Urinalysis samples were taken at screening and at every visit throughout the trial, including early withdrawal as applicable. Samples were also taken at the end of the post 96-week treatment period and 4 weeks after the final/ post-Week 96 withdrawal visit, if applicable. A urine pregnancy test was performed at each visit (except at Week 2) for women of childbearing potential.
Pharmacogenomics	Human deoxyribonucleic acid (DNA) and RNA samples were collected at baseline and Week 24.
Proteomics	Plasma samples for exploratory research of plasma proteins on HIV viral disease, antiviral treatment, and potential side effects were collected at baseline and Week 24.

Safety, continued	
Adrenal Safety	Adrenocorticotropic hormone (ACTH) stimulation tests including measurements of cortisol, 17-hydroxy (OH) progesterone and aldosterone before (T0) and 30 (T30) and 60 (T60) minutes after stimulation were performed on Day 1 and at Weeks 48 and 96, including early withdrawal as applicable. In addition, measurements of progesterone, dehydroepiandrosterone sulphate (DHEAS), androstenedione, testosterone and luteinizing hormone (LH) were also performed at these visits. A sample for the determination of basal cortisol was drawn at baseline and at Weeks 4, 12, 24, 48, 72, 96, including early withdrawal as applicable. Samples were also taken 4 weeks after the Week 96/withdrawal visit, if applicable. For subjects with abnormal basal cortisol values or with abnormal ACTH stimulation test results, the need for and timing of a retest were described in Section 5.4.11.1.2.9 of the trial protocol and discussed with the trial physician.
Cardiovascular Safety	Vital signs (pulse and blood pressure [BP]) were measured at screening and at every visit, including early withdrawal as applicable. Measurements were also taken at the end of the post 96-week treatment period and 4 weeks after the final/post-Week 96 withdrawal visit, if applicable. Central ECG readings were performed at screening, and at Weeks 2, 12, 24, 48, 72, and 96, including early withdrawal as applicable. For subjects receiving medication with CYP3A4 inhibitory activity, and for subjects receiving medications associated with a risk of Torsade de Pointes, an unscheduled ECG was to be taken before the start of the co-medication and again 3 to 7 days after initiation of the co-medication, at approximately 4 hours after intake of TMC278/placebo.
Anthropometric Measurements	Anthropometric measurements (weight, body mass index [BMI], waist, hip, breast, and neck circumference, and waist/hip ratio) were performed on Day 1 and at Weeks 24, 48, and 96, including early withdrawal, as applicable.
Physical Examination	A comprehensive physical examination was performed at screening, Day 1, Weeks 12, 24, 48, 72, and 96, including early withdrawal as applicable. Brief physical examinations were performed during the post 96-week treatment period, at the end of the post 96-week treatment period and 4 weeks after the final/post-Week 96 withdrawal visit, if applicable.
Patient-reported Outcomes	
SF-36v2®	Preference-based health states were assessed using the SF-36v2® on Day 1, at Weeks 2, 4, 8, 12, 24, 48, 72, and 96, including early withdrawal as applicable (only reported up to Week 48).
M-MASRI	Self-reported adherence to TMC278, EFV and the background regimen was assessed by an abbreviated version of the published and validated M-MASRI at Weeks 4, 8 12, 16, 24, 32, 40, 48, 60, 72, 84, and 96, including early withdrawal as applicable.

Pharmacokinetics	Sparse samples to determine the TMC278 plasma concentrations were taken at Weeks 4, 8, 12, 24, 48, 72, and 96, including early withdrawal as applicable, and at the end of the post 96-week double-blind treatment period, if applicable. Full pharmacokinetic profiles of TMC278 over a 24-hour period were obtained in a subset of subjects at a time point between at least Week 4 and up to Week 8, in a pharmacokinetic substudy. In addition, samples were to be taken in case a subject started certain co-medications for which additional safety monitoring was required; i.e., just before the start of the co-medication and 3 to 7 days after the start of the co-medication, within 10 minutes after the safety ECG.
Statistical Methods Performed	Intent-to-treat (ITT) and per protocol (PP) populations were analyzed. Descriptive statistics, frequency tabulations, univariate and multivariate logistic regression, Fisher's exact probability test, Wilcoxon rank sum and signed-ranks tests, repeated measures analysis, analysis of covariance (ANCOVA), confidence intervals (CIs) calculated using a normal approximation of the binomial distribution, and using the exact binomial method, stratum-adjusted Mantel-Haenszel analysis, Kaplan-Meier curves, Cox proportional hazards models were performed.

Main Features of the Subjects and Summary of the Results (Week 96 Analysis)

Baseline Disposition and Disease Characteristics	TMC278 N = 346	Control N = 344	All Subjects N = 690
Gender of subjects entered, n (%)			
Male	268 (77.5)	275 (79.9)	543 (78.7)
Female	78 (22.5)	69 (20.1)	147 (21.3)
Age, years			
Median [range]	36.0 [18–78]	36.0 [19–67]	36.0 [18–78]
Time since first positive HIV test, years			
Median [range]	1.2 [0–22]	1.2 [0–25]	1.2 [0–25]
Plasma viral load at baseline, copies/mL			
Median	94,950.0	105,000.0	102,000.0
[range]	[156–3,300,000]	[1010–3,360,000]	[156–3,360,000]
Categorized plasma viral load at baseline, n (%)			
≤100,000 copies/mL	181 (52.3)	163 (47.4)	344 (49.9)
>100,000 to ≤500,000 copies/mL	131 (37.9)	134 (39.0)	265 (38.4)
>500,000 copies/mL	34 (9.8)	47 (13.7)	81 (11.7)
Log_{10} plasma viral load at baseline, copies/mL			
Median [range]	5.0 [2–7]	5.0 [3–7]	5.0 [2–7]
Absolute $CD4^+$ cell count at baseline, cells/µL			
Median [range]	240.0 [1–888]	257.0 [1–757]	245.0 [1–888]
Relative $CD4^+$ cell count at baseline, %			
Median [range]	18.7 [0–42]	17.8 [0–43]	18.3 [0–43]
CDC class, n (%)			
A	248 (71.7)	242 (70.3)	490 (71.0)
B	84 (24.3)	79 (23.0)	163 (23.6)
C	14 (4.0)	23 (6.7)	37 (5.4)
Hepatitis B/C active co-infection, n (%)			
No	313 (94.3)	302 (91.0)	615 (92.6)
Yes	19 (5.7)	30 (9.0)	49 (7.4)
Baseline Resistance			
At baseline, similar proportions of subjects overall (with phenotypic data) were sensitive to TMC278 (99.3%), to EFV (99.3%), and to both their background N(t)RTIs (93.6%).			

Disposition, n (%)			
Completed Week 96	**273 (78.9)**	**277 (80.5)**	**550 (79.7)**
Ongoing in post 96-week double-blind treatment period	270 (78.0)	272 (79.1)	542 (78.6)
Not ongoing in post 96-week double-blind treatment period	3 (0.9)	5 (1.5)	8 (1.2)
Discontinued	**73 (21.1)**	**67 (19.5)**	**140 (20.3)**
AE	11 (3.2)	32 (9.3)	43 (6.2)
Subject reached a virologic endpoint[a]	33 (9.5)	7 (2.0)	40 (5.8)
Subject lost to follow-up	11 (3.2)	10 (2.9)	21 (3.0)
Subject withdrew consent	8 (2.3)	8 (2.3)	16 (2.3)
Subject non-compliant	7 (2.0)	4 (1.2)	11 (1.6)
Other	1 (0.3)[b]	4 (1.2)[c]	5 (0.7)
Sponsor's decision	1 (0.3)[d]	1 (0.3)[e]	2 (0.3)
Subject ineligible to continue the trial	1 (0.3)[f]	1 (0.3)[g]	2 (0.3)

[a] Subjects identified as a virologic failure according to the investigator
[b] Subject [redacted] developed resistance (mutation M184I) to FTC in the background regimen
[c] Subjects [redacted] and [redacted] due to moving out of the country, subject [redacted] due to closure of the trial site, and subject [redacted] due to investigator's decision
[d] Subject [redacted] took disallowed medication while under treatment for Kaposi's sarcoma
[e] Subject [redacted] took a disallowed ARV (Atripla®)
[f] Subject [redacted] was randomized although viral load at screening <5,000 copies/mL
[g] Subject [redacted] took a disallowed ARV (Trizivir®)

>95% Adherence, n (%)	**TMC278 N = 346**	**Control N = 344**	**All Subjects N = 690**
Any M-MASRI adherence data up to and including Week 96, N'	***327***	***322***	***649***
TMC278 (active or placebo)	276 (84.4)	270 (84.1)	546 (84.3)
EFV (active or placebo)	273 (83.7)	265 (82.3)	538 (83.0)
Background regimen	278 (85.3)	271 (84.7)	549 (85.0)
There were small differences in adherence to study medication and background regimen between the TMC278 and control group according to subjects' M-MASRI responses over 96 weeks.			

Efficacy

Primary Parameter

Virologic response at Weeks 48 and 96 (<50 copies/mL, TLOVR), n (%)	**TMC278 N=346**	**Control N=344**	**% Difference [95% CI][a] TMC278-Control**	**Predicted % Difference [95% CI] TMC278-Control[b]**
ITT population				
Week 48	285 (82.4)	286 (83.1)	-0.8 [-6.4, 4.9]	-1.1 [-6.7, 4.4]
Week 96	263 (76.0)	271 (78.8)	-2.8 [-9.0; 3.5]	-3.2 [-9.4; 3.1]
PP population				
Week 48	277 (83.7)	270 (83.9)	-0.2 [-5.8, 5.5]	-0.7 [-6.3, 4.9]
Week 96	257 (77.6)	255 (79.2)	-1.5 [-7.9; 4.8]	-2.0 [-8.3; 4.3]

[a] 95% CI estimated using normal approximation of binomial distribution method.
[b] difference and 95% CI predicted using logistic regression.

A logistic regression model was used to predict the difference (and 95% CI) between the treatment groups in regard to the proportion of subjects in the ITT population achieving plasma viral load <50 copies/mL (TLOVR). At Week 96 this point estimate (95% CI) was -3.2% (-9.4; 3.1) and the lower limit of the 95% CI of the difference between the treatment groups was >-12%, thus demonstrating non-inferiority of TMC278 compared with EFV (at the 12% and 10% margins).

Log_{10} baseline plasma viral load was a statistically significant predictor of virologic response (<50 copies/mL, TLOVR) at Week 96, with higher log_{10} baseline plasma viral load giving a lower chance of virologic response (p=0.0160, odds ratio [95% CI] = 0.69 [0.50; 0.93]).

Although the trial was not powered to detect statistically significant differences in subgroups, at Week 96 in subjects with baseline plasma viral load ≤100,000 copies/mL the proportion of virologic responders (<50 copies/mL, TLOVR) was 82.3% vs. 79.8% (difference [95% CI] = 2.6% [-5.7; 10.9]) in TMC278 and control subjects, respectively, and was 69.1% vs. 77.9% (difference [95% CI] = -8.8% [-18.1; 0.5]), respectively, in subjects with baseline plasma viral load >100,000 copies/mL.

Analysis using the PP population confirmed the result of the ITT analysis of the primary parameter.

The proportion of virologic responders (<50 copies/mL, TLOVR) at Week 96 decreased in both treatment groups with lower adherence (according to subjects' M-MASRI responses up to and including Week 96). The proportion of virologic responders was similar in the TMC278 and control group (80.8% vs. 83.4%, respectively) for subjects who were >95% adherent. The proportion of virologic responders was smaller in the TMC278 group compared with control in subjects who were >90 to ≤95% adherent (65.5% vs. 79.4%, respectively) or who were ≤90% adherent (40.9% vs. 52.2%, respectively).

Efficacy, continued

Secondary Parameters

Virologic response at Week 96	TMC278 N = 346	Control N = 344	% Difference [95% CI][a] TMC278-Control	Predicted % Difference [95% CI] TMC278-Control[b]
Plasma viral load <50 copies/mL (Snapshot)	265 (76.6)	268 (77.9)	-1.3 [-7.6; 4.9]	-1.7 [-8.0; 4.5]
Plasma viral load <400 copies/mL (TLOVR)	273 (78.9)	278 (80.8)	-1.9 [-7.9; 4.1]	-2.3 [-8.3; 3.7]
Plasma viral load <200 copies/mL (TLOVR)	270 (78.0)	278 (80.8)	-2.8 [-8.8; 3.3]	Not calculated

[a] 95% CI estimated using normal approximation of binomial distribution method.
[b] difference and 95% CI predicted using logistic regression.

As was seen for the primary parameter at Week 96, the lower limit of the 95% CI of the difference between the treatment groups predicted by the logistic regression model was consistently >-10% for the Snapshot analysis and for the <400 copies/mL (TLOVR) virologic response definitions at Week 96, hence confirming non-inferiority of TMC278 vs. control at the 12% and 10% margins for these secondary parameters.

At Week 96, there was a smaller proportion of virologic responders (<50 copies/mL) in the TMC278 group compared with control (82.7% vs. 92.2%, respectively; predicted difference [95% CI] = -9.6% [-14.6, -4.7]) using the TLOVR [non-VF censored] analysis, which is based upon the TLOVR algorithm, but excludes (censors) subjects who discontinued prematurely and who were not virologic failures according to the resistance criteria (VF_{res}).

For the TLOVR (non-VF censored) analysis, the proportion of virologic responders (<50 copies/mL) at Week 96 in subjects with baseline plasma viral load ≤100,000 copies/mL was 89.8% in the TMC278 group vs. 92.9% in the control group (difference [95% CI] = -3.1% [-9.5; 3.3]) and was 75.0% vs. 91.6%, respectively, (difference [95% CI] = -16.6% [-24.7; -8.4]) in subjects with baseline plasma viral load >100,000 copies/mL.

Efficacy, Secondary Parameters, continued

Outcome at Weeks 48 and 96 (TLOVR), n (%)	TMC278 N=346		Control N=344	
	Week 48	Week 96	Week 48	Week 96
Virologic response[a]	**285 (82.4)**	**263 (76.0)**	**286 (83.1)**	**271 (78.8)**
Non-responder				
Virologic failure according to efficacy criteria (VF_{eff})[b]	**41 (11.8)**	**45 (13.0)**	**15 (4.4)**	**16 (4.7)**
Rebounder[c]	19 (5.5)	24 (6.9)	9 (2.6)	12 (3.5)
Re-suppressed[d]	*4 (1.2)*	*10 (2.9)*	*3 (0.9)*	*4 (1.2)*
Never suppressed[e]	22 (6.4)	21 (6.1)	6 (1.7)	4 (1.2)
Initial lack of response[f]	*3 (0.9)*	*3 (0.9)*	*1 (0.3)*	*1 (0.3)*
Death	**0**	**0**	**0**	**3 (0.9)**
Discontinued due to AE	**6 (1.7)**	**10 (2.9)**	**25 (7.3)**	**29 (8.4)**
Discontinued due to other reason than AE	**14 (4.0)**	**28 (8.1)**	**18 (5.2)**	**25 (7.3)**

[a] Subjects with 2 consecutive plasma viral load <50 copies/mL (TLOVR).
[b] Subjects who satisfied any of the criteria c-f below were considered VF_{eff}
[c] Subjects with 2 consecutive plasma viral load <50 copies/mL before Week 48/96, and subsequently 2 consecutive plasma viral load ≥50 copies/mL before/at Week 48/96.
[d] Rebounders who subsequently had 2 consecutive plasma viral load <50 copies/mL.
[e] Subjects who never had 2 consecutive plasma viral load <50 copies/mL before Week 48/96.
[f] Subjects who were never suppressed and who never had 2 consecutive plasma viral load showing >1 log_{10} decrease from baseline by Week 12.

At Week 96, the proportion of VF_{eff} was 13.0% vs. 4.7% in the TMC278 and control group, respectively, with rebound being the most common reason for VF_{eff} (6.9% vs. 3.5%, respectively). There were few additional VF_{eff} in the second year of treatment (+1.2% in the TMC278 group and +0.3% in the control group), all of whom were rebounders.

In subjects with baseline plasma viral load ≤100,000 copies/mL, the proportion of VF_{eff} at Week 96 was 7.7% vs. 3.1% in the TMC278 and control group, respectively, while in subjects with baseline plasma viral load >100,000 copies/mL, the proportion of VF_{eff} was 18.8% vs. 6.1%, respectively.

At Week 96, fewer subjects in the TMC278 group (2.9%) discontinued the trial due to an AE than in the control group (8.4%).

Virologic response over time:

The proportion of virologic responders (<50 copies/mL, TLOVR) in the TMC278 and control group increased over time and reached a maximum at Week 32 in the TMC278 group (85.5%) and at Week 24 in the control group (85.5%), after which virologic response rates slowly decreased up to Week 96. The proportion of virologic responders in the TMC278 and control group was 6.4% and 4.3% lower, respectively, at Week 96 than at Week 48.

Time to virologic response:

No clear difference between the treatment groups was noticed from the Kaplan-Meier curves for time to virologic response (<50 copies/mL, TLOVR). Log_{10} baseline plasma viral load was a factor which influenced time to virologic response in the Cox proportional hazards model (p <0.0001, hazard ratio [95%CI] = 0.28 [0.24; 0.33]). In the Cox model, there was a statistically significant slower virologic response in the TMC278 group than the control group (p = 0.0002, hazard ratio TMC278/control [95%CI] = 0.74 [0.63; 0.87]).

Time to failure (treatment [TLOVR] and virologic [TLOVR non-VF censored]):

Log_{10} baseline plasma viral load was a factor which influenced time to treatment failure (p = 0.0121, hazard ratio [95% CI] = 1.41 [1.08; 1.85]) and time to virologic failure (p=0.0002, hazard ratio [95% CI] = 1.90 [1.36; 2.65]) in the Cox proportional hazards model. There was no statistically significant difference between the TMC278 and control group for the time to treatment failure (p = 0.3128; TMC278/control [95%CI] = 1.17 [0.86; 1.60]), but there was a trend for a difference between the treatment groups for time to virologic failure (p=0.0550, TMC278/control [95%CI] = 1.45 [0.99; 2.13]).

Efficacy, Secondary Parameters, continued				
Mean [95% CI] change from baseline at Week 48 and 96 in $CD4^+$ cell count	**TMC278 N=346**		**Control N=344**	
	Week 48	**Week 96**	**Week 48**	**Week 96**
Absolute, cells/µL	195.5 [179.5; 211.6]	220.7 [203.1; 238.4]	181.5 [164.9; 198.2]	226.7 [206.7; 246.7]
Relative, %	8.6 [7.9; 9.2]	10.1 [9.3; 10.9]	8.7 [8.0; 9.3]	10.2 [9.5; 11.0]
There was no statistically significant difference in the mean change from baseline to Week 96 in absolute (p=0.9521) or relative (p = 0.6189) $CD4^+$ cell count between the TMC278 and control group.				

Resistance Determinations, n (%)	**At Failure**	
	TMC278 N = 346	**Control N = 344**
Virologic failure according to resistance criteria (VF_{res})[a]	56 (16.2)	23 (6.7)
VF_{res} with genotypic data	52 (100.0)	18 (100.0)
VF_{res} with ≥1 treatment-emergent RT mutation[b]	43 (82.7)	15 (83.3)
VF_{res} with ≥1 treatment-emergent Extended NNRTI RAMs [b]	29 (55.8)	9 (50.0)
VF_{res} with ≥1 treatment-emergent IAS-USA N(t)RTI RAMs [b]	31 (59.6)	5 (27.8)

[a] Subjects who satisfied any of the criteria below were considered VF_{res} (VF_{res} and VF_{eff} are defined differently. Therefore the numbers for VF_{eff} and VF_{res} are different):
-lack of virologic response (never having had 2 consecutive plasma viral load <50 copies/mL) and plasma viral load increase of ≥0.5 log_{10} copies/mL above nadir (i.e., never suppressed), or
-confirmed loss of virologic response (2 consecutive viral load ≥50 copies/mL after having had 2 consecutive plasma viral load <50 copies/mL; i.e., rebounder), or
-discontinued with a last observed on-treatment plasma viral load ≥50 copies/mL after having had 2 consecutive plasma viral load <50 copies/mL (i.e., stopped treatment while not suppressed [STWNS]).

[b] Denominator for percentages is the number of VF_{res} with genotypic data, i.e., 52 and 18 for TMC278 and control VF_{res}, respectively.

At Week 96, there were 56 (16.2%) VF_{res} (of whom 52 had genotypic data) out of 346 subjects in the TMC278 group and 23 (6.7%) VF_{res} (of whom 18 had genotypic data) out of 344 subjects in the control group. Fewer VF_{res} occurred in the baseline plasma viral load category ≤100,000 copies/mL than in the >100,000 copies/mL category, with the difference between categories more pronounced in the TMC278 group than the control group. At the time VF_{res} occurred (hereafter called 'failure'), the proportion of VF_{res} with ≥1 treatment-emergent NNRTI RAM was 55.8% vs. 50.0% in the TMC278 group and control group, respectively. The proportion of VF_{res} with ≥1 treatment-emergent IAS-USA N(t)RTI RAM was higher in the TMC278 group than the control group (59.6% vs. 27.8%, respectively). The most prevalent NNRTI and N(t)RTI RAMs in TMC278 VF_{res} were E138K and M184I, respectively. For control VF_{res}, the most prevalent NNRTI RAM was K103N and the most prevalent N(t)RTI RAMs were M184I and M184V. None of the NNRTI RAMs emerging in the TMC278 VF_{res} were found in the control VF_{res}, except for K103N. The only new individual mutation present in the Week 96 VF_{res} compared with the Week 48 VF_{res} was E138A, which was present in 1 subject in the TMC278 group at last visit, not at failure.

At Week 96, the proportion of VF_{res} phenotypically resistant to their treatment NNRTI at failure was 44.7% in the TMC278 group and 38.9% in the control group. More than half of TMC278 VF_{res} were resistant to FTC and 3TC (62.5% and 63.0%, respectively). Resistance was also seen in a smaller proportion of control VF_{res} (22.2% for both FTC and 3TC). The majority of TMC278 VF_{res} resistant to TMC278 were also resistant to etravirine (ETR; 90.9%) and EFV (81.8%), while 45.5% were also resistant to NVP. Among the control VF_{res} resistant to EFV, 85.7% were also resistant to NVP, 14.3% to ETR, but none were resistant to TMC278.

Safety data are presented for the Week 96 analysis (cut-off date 04 January 2011)

Safety AEs, n (%)	**TMC278** **N = 346**	**Control** **N = 344**
Any AEs	**309 (89.3)**	**323 (93.9)**
Any grade 1 or 2 AE	**307 (88.7)**	**319 (92.7)**
Grade 1 AE	288 (83.2)	299 (86.9)
Grade 2 AE	188 (54.3)	217 (63.1)
Any grade 3 or 4 AE	**53 (15.3)**	**73 (21.2)**
Grade 3 AE	46 (13.3)	67 (19.5)
Grade 4 AE	15 (4.3)	12 (3.5)
Any treatment-related AE	**150 (43.4)**	**220 (64.0)**
Any treatment-related AE of at least grade 2	**61 (17.6)**	**115 (33.4)**
Death	**0**	**3 (0.9)**
Any SAE	**34 (9.8)**	**41 (11.9)**
AE leading to permanent discontinuation	**11 (3.2)**	**31 (9.0)**
AE leading to temporary discontinuation	**14 (4.0)**	**25 (7.3)**
Any skin event of interest	**68 (19.7)**	**108 (31.4)**
Rash (grouped term)	45 (13.0)	92 (26.7)
Any neuropsychiatric event of interest	**141 (40.8)**	**200 (58.1)**
Neurologic event of interest	85 (24.6)	150 (43.6)
Psychiatric event of interest	98 (28.3)	126 (36.6)
Any hepatic event of interest	**22 (6.4)**	**31 (9.0)**
Any event of interest potentially related to QT interval prolongation	**1 (0.3)**	**4 (1.2)**
Any endocrine event of interest	**24 (6.9)**	**16 (4.7)**
Most frequently reported AEs by preferred term (≥5% in the TMC278 or control group)		
Upper respiratory tract infection	49 (14.2)	46 (13.4)
Diarrhea	48 (13.9)	59 (17.2)
Headache	48 (13.9)	43 (12.5)
Nausea	43 (12.4)	35 (10.2)
Nasopharyngitis	41 (11.8)	44 (12.8)
Insomnia	36 (10.4)	37 (10.8)
Influenza	35 (10.1)	33 (9.6)
Abnormal dreams	29 (8.4)	41 (11.9)
Dizziness	27 (7.8)	91 (26.5)
Rash	26 (7.5)	43 (12.5)
Depression	25 (7.2)	23 (6.7)
Fatigue	20 (5.8)	31 (9.0)
Cough	20 (5.8)	18 (5.2)
Back pain	18 (5.2)	25 (7.3)
Hypertension	18 (5.2)	17 (4.9)
Vomiting	15 (4.3)	20 (5.8)
Somnolence	13 (3.8)	23 (6.7)
Arthralgia	13 (3.8)	19 (5.5)
Anxiety	8 (2.3)	27 (7.8)

Safety, AEs, continued

The majority of subjects experienced at least 1 AE (89.3% of subjects receiving TMC278 and 93.9% of subjects in the control group). At the time of the Week 48 analysis, 1 subject in the control group had died (Burkitt's lymphoma). An additional 2 subjects in the control group had died by the time of the Week 96 analysis (meningococcal sepsis and asphyxia). All 3 fatalities were considered by the investigator to be not related to study medication. Serious AEs were reported in 9.8% and 11.9% of subjects in the TMC278 and control group, respectively. The incidence of AEs leading to permanent discontinuation was 3.2% in the TMC278 group and 9.0% in the control group. Most AEs were grade 1 in severity. The proportion of subjects experiencing grade 3 or 4 AEs was 15.3% in the TMC278 group and 21.2% in the control group. The most frequently reported grade 3 or 4 AEs were in the *investigations* system organ class (SOC), affecting 3.8% of subjects in the TMC278 group and 6.7% in the control group and these were mostly laboratory-related. The most frequently reported grade 3 or 4 AEs in either treatment group were increased blood amylase and depression. No individual grade 3 or 4 AE was reported in more than 1% of subjects in the TMC278 group, except for increased blood amylase (2.0%). The incidence of treatment-related AEs that were at least grade 2 was lower in the TMC278 group (17.6%) compared with the control group (33.4%). The incidence of rash (grouped term) was highly statistically significantly lower in the TMC278 group than in the control group (13.0% vs. 26.7%, respectively; $p < 0.0001$). Neurologic events of interest occurred at a highly statistically significantly lower incidence in the TMC278 group compared with the control group (24.6% vs. 43.6%, respectively; $p<0.0001$). Of these, the incidence of headache was similar in the TMC278 group and control group (13.9% vs. 12.5%, respectively); however, the incidence of dizziness was highly statistically significantly lower in the TMC278 group than in the control group (7.8% vs. 26.5%, respectively; $p<0.0001$). Psychiatric events of interest also occurred in a statistically significantly lower proportion of subjects in the TMC278 group compared with the control group (28.3% vs. 36.6%, respectively; $p=0.0228$). The incidence of events of interest potentially related to QT interval prolongation was low overall (0.3% in the TMC278 group vs. 1.2% in the control group). The incidence of hepatic events of interest (6.4% vs. 9.0%, respectively) and endocrine events of interest (6.9% vs. 4.7%, respectively) was comparable between the TMC278 and control group.

Safety, continued	
Clinical Laboratory Tests	The most frequently reported grade 2-4 laboratory abnormalities in either treatment group were increased total cholesterol (TC) and increased LDL-C. For lipids, only fasted values are discussed. Grade 3 and 4 laboratory abnormalities were reported in 11.6% of subjects in the TMC278 group and 20.6% in the control group: the most frequently reported in either treatment group were increased pancreatic amylase, increased AST, and increased ALT. Mean hemoglobin levels were observed to increase above baseline levels after Week 2 in the TMC278 group and control group before reaching a plateau at approximately Week 16 in the TMC278 group and Week 24 in the control group, after which mean values were maintained at these levels up to Week 96. In general, the mean changes from baseline were similar in the TMC278 group and control group throughout the 96-week treatment period. There was no marked difference in the mean change from baseline over the 96-week treatment period between the treatment groups for transaminases or for pancreatic enzymes. The pattern of mean change from baseline over time for creatinine differed between the treatment groups up to Week 24. In the TMC278 group, there was a small mean increase from baseline at Week 2 followed by a plateau until Week 24. In the control group, the mean creatinine level remained almost unchanged until Week 24. After Week 24, mean values increased slowly at the same rate in both treatment groups up to Week 96. The pattern of mean change from baseline over the 96-week treatment period for $eGFR_{creat}$ differed between the treatment groups, in line with the mean change from baseline in creatinine. In the TMC278 group, a small mean decrease from baseline in $eGFR_{creat}$ was apparent at Week 2 and plateaued until Week 24, while the mean $eGFR_{creat}$ value in the control group remained almost at baseline level until Week 48. After Week 48, $eGFR_{creat}$ values decreased slowly over time in both treatment groups to Week 96. Differences between treatment groups remained relatively constant over the 96-week treatment period. Consistent mean changes from baseline over the 96-week treatment period were observed for the lipid parameters in both treatment groups, however to a lesser extent in the TMC278 group. In the TMC278 group, there was no mean change from baseline at Week 96 for TC and LDL-C, while there was a mean increase from baseline for both parameters in the control group. There was a mean increase from baseline at Week 96 in high density lipoprotein cholesterol (HDL-C) in both treatment groups but to a lesser extent in the TMC278 group. Therefore, mean TC/HDL-C ratio evolved similarly over the 96-week treatment period in both treatment groups. Triglycerides were consistently somewhat lower than baseline in the TMC278 group and somewhat higher than baseline in the control group over the 96-week treatment period. The differences between the treatment groups in mean changes from baseline at Week 96 for TC and LDL-C were highly statistically significantly in favor of TMC278 (both $p<0.001$), and the difference for mean change from baseline in triglycerides was statistically significant ($p=0.011$). The difference for mean change from baseline in HDL-C was highly statistically significantly in favor of control ($p<0.001$).

Safety, continued	
Cardiovascular Safety	There were no consistent or clinically relevant mean changes from baseline in vital signs with TMC278 or control. There was a similar gradual mean increase from baseline in QTcF up to Week 96 in both treatment groups. No notable difference was observed by gender in mean change from baseline in QTcF over the 96-week treatment period. There were no consistent or clinically relevant mean changes from baseline in other ECG parameters. In the TMC278 and control group, 1.5% and 1.8% of subjects, respectively, had increases from baseline >60 ms in QTcF. None of these increases led to an absolute QTcF of >500 ms. Two subjects in the control group were each reported with an AE of grade 3 tachycardia (both not related to study medication), 1 of which was reported as an SAE; 1 subject (control group) was reported with 3 AEs of grade 3 atrial flutter (all doubtfully or not related to study medication); and 1 subject (control group) was reported with grade 3 palpitations (probably related to study medication). No further ECG-related AEs were reported as grade 3 or 4 in severity or were reported as an SAE and none led to discontinuation.
Adrenal Safety	There was no notable mean change from baseline in basal cortisol over the 96-week treatment period in the TMC278 group, compared with a small mean increase from baseline in the control group which was not clinically relevant. There were no consistent or clinically relevant mean changes from baseline for basal 17-OH progesterone and aldosterone, nor for the other endocrine parameters (androstenedione, DHEAS, LH, and testosterone) in either treatment group. The mean increase from baseline for maximum change in cortisol after ACTH stimulation at Week 96 observed in the TMC278 group (3.18 nmol/L) was lower than the mean increase from baseline in the control group (47.76 nmol/L). Similar mean increases from baseline for maximum change in 17-OH progesterone and aldosterone after ACTH stimulation at Week 96 were observed for both treatment groups. Any abnormal cortisol response to ACTH stimulation (i.e., <500 nmol/L) during the 96-week treatment period was reported in 8.5% and 4.1% of subjects in the TMC278 and control group, respectively. Few subjects (2.1% in the TMC278 group vs. 0.4% in the control group) had 2 consecutive abnormal responses to ACTH stimulation, of whom none had signs or symptoms of adrenal insufficiency and all continued treatment.
Anthropometric Measurements	Mean weight and BMI increased over the 96-week treatment period for both treatment groups and the mean increase from baseline was greater in the TMC278 group compared with the control group. Changes in BMI are presumed to reflect the improved general condition of the subjects on treatment. No other clinically relevant changes were observed for other anthropometric measurements.

Noncompartmental Pharmacokinetics (Pharmacokinetic Substudy Performed at Weeks 4-8 Only) Mean (Standard Deviation [SD])	**TMC278 n = 32**
AUC_{24h}, ng.h/mL	2133 (1016)
C_{max}, ng/mL	138.6 (66.7).
C_{trough}, ng/mL	75.8 (37.7)

Population Pharmacokinetics (Week 96 Analysis, Main Trial) Mean (SD)	**TMC278 N = 342**
AUC_{24h}, ng.h/mL	2150.7 (782.90)
C_{trough}, ng/mL	75.0 (32.02)
The mean TMC278 exposure was somewhat higher in female subjects, compared with male subjects, which may be at least partly explained by a difference in bodyweight between the gender subgroups. However, the range of exposures was similar for the different gender subgroups.	

Pharmacokinetic/Pharmacodynamic Relationships

For the evaluation of pharmacokinetic/pharmacodynamic relationships for efficacy, analyses on virologic response parameters were performed on a subpopulation, i.e., excluding (censoring) subjects who discontinued prematurely and who were not VF_{res} (TLOVR [non-VF censored]).

The virologic response rates (<50 copies/mL, TLOVR [non-VF censored]) increased with increasing TMC278 exposure, ranging from 65.8% to 92.7% in the AUC quartiles. Baseline plasma viral load, adherence (subject-reported, M-MASRI), TMC278 exposure, and baseline $CD4^+$cell count were statistically significantly associated with a plasma viral load <50 copies/mL at Week 96 (TLOVR [non-VF censored]).

There were no apparent relationships between the pharmacokinetics of TMC278 and safety parameters (ITT population).

Conclusions

At Week 96, the results for virologic response (76.0% and 78.8% for the TMC278 and control group, respectively [<50 copies/mL TLOVR, ITT population]) and non-inferiority were robust, durable (confirming the results at Week 48), and consistent across different populations and imputation methods, including the PP population and the Snapshot analysis. Virologic response was similar in the TMC278 and control group for subjects with a baseline plasma viral load ≤100,000 copies/mL and it was higher than seen in TMC278-treated subjects with baseline plasma viral load >100,000 copies/mL. There was a greater proportion of VF_{eff} in the TMC278 group than the control group, irrespective of baseline plasma viral load category. In both treatment groups there was a smaller proportion of VF_{eff} with baseline plasma viral load ≤100,000 copies/mL than with >100,000 copies/mL. There were few additional VF_{eff} in the second year of treatment in both treatment groups, all of whom were rebounders.

The virologic response rates in both the treatment groups were similar throughout the 96 weeks of treatment. The time to virologic response was slightly longer and the time to virologic failure tended to be shorter with TMC278, but the time to treatment failure was similar with TMC278 and control.

$CD4^+$ cell count increased over the 96-week treatment period to a similar extent in both treatment groups.

The virologic response rates (<50 copies/mL TLOVR [non-VF censored]) ranged from 65.8% to 92.7% in the AUC quartiles. Baseline plasma viral load, adherence (subject-reported, M-MASRI), TMC278 exposure, and baseline $CD4^+$ cell count were statistically significantly associated with a plasma viral load <50 copies/mL at Week 96 (TLOVR [non-VF censored]).

Analysis of resistance at failure showed that the proportion of TMC278 VF_{res} with ≥1 treatment-emergent NNRTI RAM was somewhat higher compared with control, and a greater proportion of TMC278 than control VF_{res} had ≥1 treatment-emergent IAS-USA N(t)RTI RAM. None of the NNRTI RAMs emerging in the TMC278 VF_{res} were found in the control VF_{res}, except for K103N. The only new individual mutation present in the Week 96 VF_{res} compared with the Week 48 VF_{res} was E138A, in 1 subject in the TMC278 group at last visit, not at failure. A somewhat greater proportion of TMC278 VF_{res} than control VF_{res} were phenotypically resistant to their NNRTI treatment with more than half of TMC278 VF_{res} being resistant to FTC and 3TC. Resistance to N(t)RTIs was also seen in control VF_{res}, although in a smaller proportion of subjects. The majority of TMC278 VF_{res} being resistant to TMC278 were also resistant to ETR and EFV, while a smaller proportion was also resistant to NVP. Of the control VF_{res} resistant to EFV, the majority was also resistant to NVP, a few were also resistant to ETR and none were resistant to TMC278.

Overall, TMC278 was generally safe and well tolerated over 96 weeks of treatment, confirming its favorable safety profile as seen in the Week 48 analysis, with fewer discontinuations due to AEs compared with control. The most common AEs in the TMC278 group, irrespective of severity and causality, were upper respiratory tract infection, headache, diarrhea, and nausea. (Highly) statistically significant differences in the incidence of rash (grouped term), neurologic events of interest (and by PT dizziness) and psychiatric events of interest were observed in favor of TMC278. In general, most laboratory parameters showed no consistent or clinically relevant mean changes from baseline over the 96-week treatment period in either treatment group. Differences between treatment groups in the mean change from baseline remained similar over the 96-week treatment period. Consistent mean changes from baseline over the 96-week treatment period were observed for the lipid parameters in both treatment groups, in favor of TMC278 for TC, LDL-C, and triglycerides, while in favor of control for HDL-C.

Overall, there were no laboratory, cardiovascular, or endocrine signals to suggest safety issues with the use of TMC278 when combined with TDF/FTC.

There were no apparent relationships between the pharmacokinetics of TMC278 and safety parameters.

In conclusion, substantial efficacy of TMC278 as demonstrated at Week 48, as well as non-inferiority compared with control, was maintained to Week 96. TMC278 was shown to be generally safe and well tolerated up to Week 96.