SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. (now Tibotec Pharmaceuticals) **Trade Name**: Intelence™ **Indication**: HIV-1 infection	**Drug Substance**: TMC125 (etravirine) **Trial no**.: TMC125-C216 **Clinical Phase**: III
Title: A Phase III randomized, double-blinded, placebo-controlled trial to investigate the efficacy, tolerability and safety of TMC125 as part of an ART including TMC114/rtv and an investigator-selected OBR in HIV-1 infected subjects with limited to no treatment options. Final (Week 96) Analysis Report.	
Investigator: Prof A. Lazzarin, M.D., Ospedale IRCCS San Raffaele, Divisione di Malattie Infettive, Via Stamira d'Ancona 20, 20127 Milan, Italy	**Country**: Australia, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, The Netherlands, UK, USA
Trial Period: Start: 31-Oct-2005 End: 12-Aug-2008	**No. of Investigators**: 103 **No. of Subjects**: Screened: 954 subjects Randomized and treated: 591 subjects
Objectives: The primary objective of this trial was to show the superiority of TMC125 compared to placebo as part of an ART containing DRV/rtv and an investigator-selected OBR, in the proportion of subjects with undetectable plasma viral load values (< 50 copies/mL) at Week 24 in treatment-experienced HIV-1 infected subjects. Secondary objectives were to compare the antiviral efficacy of TMC125 to placebo in addition to the ART at all time points; to compare the safety and tolerability of TMC125 to placebo; to compare the immunologic changes with TMC125 to placebo; to evaluate changes in HIV-1 genotype and phenotypic drug susceptibility; to evaluate the population pharmacokinetics and the PK/PD relationship of TMC125 and DRV; to evaluate and test HRQL as measured by the Functional Assessment of HIV Infection (FAHI) questionnaire; and to collect medical resource utilization information and use of EuroQoL-5 Dimension (EQ-5D) to calculate utility values, both of which may be used in future economic evaluation models.	
Design: This was a Phase III, randomized, double-blind, placebo-controlled trial to evaluate the long-term efficacy, tolerability, and safety of TMC125 in addition to an antiretroviral therapy (ART) containing darunavir/ritonavir (DRV/rtv), nucleoside reverse transcriptase inhibitor(s) (NRTI[s]) and optional enfuvirtide (ENF) in treatment-experienced HIV-1 infected subjects. In addition, immunologic changes, changes in the HIV-1 genotype, phenotypic drug susceptibility, population pharmacokinetics, and pharmacokinetic/pharmacodynamic (PK/PD) relationships were assessed. A pharmacokinetic substudy was performed at selected sites. To evaluate health-related quality of life (HRQL) and global health status, patient-reported outcomes (PRO) of subjects receiving an ART containing either TMC125 or placebo were assessed. Safety and tolerability were documented throughout the trial. Six hundred HIV-1 infected subjects on a stable but virologically failing regimen were to be included in the trial. Subjects with at least 1 documented non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutation (RAM) (either at Screening or from historical genotype reports), at least 3 documented primary protease inhibitor (PI) mutations, and a HIV-1 plasma viral load > 5000 RNA copies/mL at Screening were eligible. Subjects were randomized in a 1:1 ratio to either TMC125 (200 mg b.i.d.) or to matching placebo; both in combination with DRV/rtv (600/100 mg b.i.d.) and an investigator-selected optimized background regimen (OBR) of at least 2 antiretrovirals (ARVs) consisting of NRTI(s) with or without ENF. The use of ENF was optional and de novo use of ENF was limited to a maximum of 40% of the overall trial population. The trial consisted of a screening period, a 48-week treatment period with optional extension to 96 weeks, and a 4-week follow-up period. For subjects who, in the opinion of the investigator, were deriving clinical benefit from their ART, a possible optional extension immediately followed the 48-week treatment period and continued until the subject was treated for 96 weeks. As long as subjects continued to participate in the trial, they remained on the same ART as started during the initial 48 weeks of treatment. Initially, the optional extension continued in a blinded fashion, however, once the database for the Week 48 Analysis had been locked, the treatment code was broken and subjects continued treatment within the trial in an open-label fashion. This report describes the results of the Final Analysis of the trial which was performed once all subjects had discontinued or completed the trial, including the optional extension period and follow-up visits (if applicable).	

Subject Selection

Inclusion Criteria

1 Male or female, aged 18 years or above.
2 Signed the Informed Consent Form (ICF) voluntarily.
3 Able to comply with the protocol requirements.
4 Documented HIV-1 infection.
5 HIV-1 plasma viral load at screening visit above 5000 HIV-1 RNA copies/mL (assayed by RNA polymerase chain reaction ultrasensitive specimen procedure Roche Amplicor HIV-1 Monitor™).
6 On a stable ART for at least 8 weeks at Screening, and willing to stay on that treatment until Baseline.
7 Documented genotypic evidence of resistance to currently available NNRTIs by having at least 1 NNRTI RAM present (adapted from the IAS-USA list, update November 2005: A98G, L100I, K101E/P/Q, K103H/N/S/T, V106A/M, V108I, E138G/K/Q, V179I/F/G, Y181C/I/V, Y188C/H/L, G190A/E/S, P225H, F227C, M230I/L, P236L, K238N/T, Y318F) on the virco®TYPE HIV-1 report at Screening or from prior genotypic analysis, evidence of which had to be available in the source documents and enrollment of the subject based on these data needed to be agreed upon by the sponsor.
8 Having 3 or more documented primary PI mutations (IAS-USA list, update November 2005) on the virco®TYPE HIV-1 report at Screening.
9 General medical condition, in the investigator's opinion, did not interfere with the assessments and the completion of the trial.

Exclusion Criteria

1 Primary HIV-1 infection.
2 HIV-2 infection.
3 Use of disallowed concomitant therapy.
4 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 protocol.
5 Life expectancy less than 6 months according to the judgment of the investigator.
6 Any currently active AIDS defining illness (Category C conditions according to the Centers for Disease Control [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 period.
   - Wasting syndrome due to HIV infection.

   Note: Primary and secondary prophylaxis for an AIDS defining illness was allowed in case the medication used was not part of the disallowed medication.
7 Any active clinically significant disease (e.g. pancreatitis, cardiac dysfunction) or findings during screening of medical history or physical examination that, in the investigator's opinion, could compromise the outcome of the trial.
8 Acute viral hepatitis including but not limited to A, B, or C.
9 Chronic hepatitis B and/or C with aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN).
   Note: Subjects co-infected with chronic hepatitis B or C were allowed to enter the trial if their condition was clinically stable and was not expected to require treatment during the trial period. Reference was made to the package insert with respect to proper care of hepatitis B co-infection in case tenofovir disoproxyl fumarate (TDF), lamivudine (3TC) and/or emtricitabine (FTC) were included in the OBR.
10 Receipt of an investigational drug within 30 days prior to the trial drug administration, with the exceptions of DRV and tipranavir, TDF, FTC, or Truvada® where these were not yet licensed in a participating country.
11 Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medications administered in this trial.
   Note: DRV is a sulfonamide. Subjects who previously experienced a sulfonamide allergy were allowed to enter the trial. To date, no potential for cross sensitivity between drugs in the sulfonamide class and with DRV had been identified in subjects participating in Phase II trials.
12 Pregnant or breastfeeding female subject.

Exclusion Criteria, Cont'd

13 Female of childbearing potential not using effective birth control methods or not willing to continue practicing these birth control methods during the trial and for at least 30 days after the end of the trial (or after last intake of investigational ARVs);
Note: Hormone-based contraception may not be reliable when taking investigational agents; therefore, to be eligible for this trial, women of childbearing potential were either:
(1) to use a double barrier method to prevent pregnancy (i.e. using a condom with diaphragm or cervical cap), OR
(2) to use hormone-based contraceptive in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap or female condom), OR
(3) to use an intrauterine device (IUD) in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap), OR
(4) not to engage in heterosexual sex, or have a vasectomized partner with confirmed sterility.
Note: Women who were postmenopausal for at least 2 years, women with total hysterectomy, and women who had a tubal ligation were considered of nonchildbearing potential.
Note: Spermacides contain non-oxynol-9 and were not to be used as this could potentially increase the rate of HIV-1 transmission.
Note: Use of an IUD could increase the risk of sexually transmitted infections, including HIV.

14 Heterosexually active male subject not using effective birth control methods or not willing to continue practicing these birth control methods during the trial and until 30 days after the end of the trial (or after last intake of investigational ARVs).

15 Any grade 3 or grade 4 toxicity according to the Division of AIDS (DAIDS) grading scale, except for:
- grade 3 glucose elevation,
- asymptomatic grade 3 pancreatic amylase elevation,
- asymptomatic grade 3 triglyceride/cholesterol elevation,
- asymptomatic grade 4 triglyceride elevation.
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).

16 Clinical or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels (International Normalized Ratio [INR] > 1.5 or albumin < 30 g/L or bilirubin > 2.5 x ULN).
Note: Subject could be included if elevated bilirubin was assessed at the time of Screening as related to an administered ARV and not related to liver disease.

17 Previously received treatment with either TMC125, TMC120, or TMC278 in a previous clinical trial.
Note: Previous use of DRV was allowed.

Criteria for Entering the Optional Extended Treatment Period

1 Completed the entire 48-week treatment period and has voluntarily agreed to participate (i.e. has signed the updated ICF).

2 Willing to continue treatment in a blinded fashion with the same OBR as used during the original 48 weeks of treatment, until the database has been locked for the Week 48 Analysis, after which all subjects will be unblinded and can continue randomized treatment in an open-label fashion.

3 Willing to comply with the protocol requirements and cooperate with the investigator.

Treatment	**TMC125**	**Placebo**	**Darunavir**	**Ritonavir**
Concentration Dosage Form (F No.) Usage	100 mg Tablets (F060) Oral	Not applicable Tablets (F065) Oral	300 mg Tablets (F016) Oral	100 mg Capsules Oral
Batch Numbers	05C17/05C18/05D04/05D05/ 05D21/05D22/05E12/05E16/ 05E17/05E19/05E25/ 05G13/05G14/05G15/ 05G18/05G19/05G20/05G21/ 05H09/05H11/05H12/05H16/ 05H17/05H19/05H22/05J10/ 05J26/05K09/05K10/05K11/ 05K14/05K15/05K16/05K17/ 05K18/05K21/05K23/06A19/ 06A20/06C14/06C15/06C16/ 06C17/06C20/6IL9900/ 6JLBL00/6JLC100/	05J07/05J10/05J19/ 05J20/05J21/05J24/05J25/ 05J26/06B21/06B23/06B24/ 06B27/06B28/06C01/06C02/ 06C03/06C06/06D03/06D04/ 06D05/06D06/06D10/ 06D11/06D12/06D13/06D14/ 06E08/06E09/06E10/06E11/ 06E12/06E15/06E17/06E18/ 06F19/06F22/06F23/06F26/ 06H01/06H03/06H04/06H07/ 06I14/06I19/06I20	PD1508/ PD1587/ PD1591/ PD1595/ PD1818/ PD1822/ PD1826/ PD1830/ PD1838/ 6HG9380-X/ 6HG9382-X/ 6HG9397-X/ 6NG0846-X/ 7DG1989-X	30367VA/2 34391VA/ 36550VA/ 38514VA/ 39680VA/ 258372E21/ 371092E22/ 317092E22/ 389272E21/ 354592E21/ 414202E21/ 42416VA/ 47055VA/ 480192E21/
Dose Regimen	TMC125 200 mg b.i.d. (2 tablets F060 b.i.d.) **or** placebo b.i.d. (2 tablets b.i.d.) + Underlying ART consisting of: DRV/rtv 600/100 mg b.i.d. (2 tablets F016 and 1 capsule ritonavir b.i.d.) + OBR: at least 2 ARV drugs: NRTI(s) with or without ENF			
Duration of Treatment	48 weeks + optional additional 48 weeks			
Duration of Trial	maximum 96 weeks (excluding Screening and Follow-up)			

Disallowed Medication	The following medications were not allowed **from Screening** until completion or the withdrawal visit:
	- Therapeutic HIV vaccines.
	- Other approved vaccines were allowed as long as they are given outside the 4-week time frame preceding a plasma viral load measurement.
	- All investigational drugs were disallowed throughout the trial (except for DRV, Truvada®, TDF, and FTC where these are not licensed yet in a participating country).
	- Cytochrome P450 3A4 inducers:
	  - rifamycins: rifabutin, rifampicin/rifampin; rifapentin;
	  - anticonvulsants: phenobarbital, phenytoin, carbamazepine;
	  - systemic dexamethasone (***Note:*** Local application was allowed);
	  - all products containing *Hypericum perforatum* (St John's Wort) or *Echinacea*.			

Disallowed Medication, Cont'd	The following medications were not allowed **from Baseline** until completion or the withdrawal visit:
	- Cytochrome P450 3A4 inhibitors and inhibitors of transporting proteins:
	  - Systemic azole antifungals: ketoconazole, voriconazole and posaconazole were not allowed. (***Note:*** Itraconazole if not exceeding 200 mg/day and fluconazole were allowed; local application of azoles was allowed.)
	  - Macrolide antibiotics: erythromycin, troleandomycin, and telithromycin. In case there was a need to introduce these drugs during the trial, dosage and regimen had to be discussed in advance with the sponsor. (***Note:*** Clarithromycin was allowed with dose adjustments in subjects with renal impairment).
	- Amphetamines and amphetamine derivatives.
	- Cytochrome P450 3A4 substrates with a small therapeutic index: cisapride, triazolam, midazolam, terfenadine, astemizole, and pimozide.
	- Amiodarone, quinidine, bepridil, flecainide, propafenone, systemic lidocaine, mexilitine, disopyramide.
	- The antimigraine ergotamines, dihydroergotamine, ergonovine, methylergonovine, ergotamine, ergometrine, and other ergot derivatives.
	- The lipid lowering agents simvastatin and lovastatin, pravastatin, cerivastatin. (***Note***: Atorvastatin was allowed with specific dose recommendations).
	- Cyclosporine, tacrolimus, warfarin, digoxin, rapamycin, sirolimus, and meperidine.
	- Calcium channel blockers: amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nifedipine, nicardipine, nimodipine, and verapamil.
	- Warfarin
	- Bone marrow suppressants used in oncology treatment.
	In addition, radiation therapy was not allowed from 28 days prior to first intake of investigational medication to the last intake of investigational medication.
	In case there was a need to administer bone marrow suppressants or radiation therapy during the trial, this had to be discussed in advance with the sponsor.
	Note: if concomitant use of TMC125, DRV/rtv and phosphodiesterase type 5 inhibitors (sildenafil, vardenafil or tadalafil) was indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours was recommended. Alternatively, vardenafil (no more than a single 2.5-mg dose in 72 hours) or tadalafil (no more than a single 10-mg dose in 72 hours) was recommended.
	The following ARV drugs were not allowed **from Baseline** and throughout the trial:
	- any PI other than DRV/rtv.
	- investigational NRTIs (except for TDF, FTC and Truvada® where these are not yet licensed in a participating country) and generic versions of NRTIs not having received a tentative approval by the Food and Drug Administration (FDA).
	- NNRTIs other than TMC125.

Statistical Methods	Intent-to-treat (ITT) analysis, descriptive statistics, frequency tabulations, Breslow-Day test, Cochran-Mantel-Haenszel (CMH) test, Hochberg multiplicity correction, analysis of covariance (ANCOVA), logistic regression, Cox proportional hazards model, Kaplan-Meier curve, Wilcoxon's matched pairs signed ranks test, and Fisher's exact test

Assessments / **Type of Visit**	**Screening** *	**Randomization at Baseline**	**Treatment Period** **									**Final\ Withdrawal Visit**$	**Posttreatment Follow-up Period (30-35 days after Final/ Withdrawal Visit)*****
Time of Visit	**W -6**	**D 1**	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 32**	**W 40**	**W 48**	**W 52**
Informed consent, demographic data, medical & surgical history, concomitant diseases & height	X												
Pregnancy test[a]	X	X		X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X											
Physical examination	X	X				X			X			X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood mononuclear cell (PBMC) sample		X										X	
Hematology & biochemistry (10 h fasting)	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation tests	X	X	X	X	X	X	X	X	X	X	X	X	X
T_3, free T_4, and TSH testing[b]	X	X				X			X			X	
Vital signs (pulse, blood pressure)	X	X	X	X	X	X	X	X	??	X	X	??	X
ECG (central reading)	X	X		X		X			X			X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
TMC125, DRV & ritonavir pharmacokinetics[c]				X	X	X			X			X	
Plasma viral load and samples for phenotype/genotype determinations	X[d]	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X	X[e]	X[e]	X	X[e]
Immunology	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis serology	X												
Dispensation of investigational medication		X	X	X	X	X	X	X	X	X	X		
PRO questionnaires - Compliance questions		X		X		X			X			X	
Observe/Interview for adverse events (AEs) and HIV-1 related events & Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X

* Screening visit had to be performed within 6 weeks prior to randomization at Baseline.

** Unscheduled visits could be performed for safety/tolerability reasons. For confirmation of virologic failure, unscheduled viral load assessments could be performed; however, there had to be a minimum 2-week time interval between such assessments.

*** Not applicable for subjects who continued to receive TMC125 via a Tibotec-sponsored program after Final/Withdrawal visit.

[a] Serum test at Screening for all female subjects, urine test at other visits for female subjects of childbearing potential.

[b] Whenever clinically relevant, extra tests could be done at other visits.

[c] At Week 4, 2 samples were taken. The first sample had to be a trough sample (taken immediately before intake of study medication). The second sample was taken at least 1 hour after intake of study medication. Sampling at Weeks 8, 12, 24, 48, 72, and 96 could be done at any given time point after intake of medication.

[d] At Screening, only genotype determination was performed (virco®TYPE HIV-1).

[e] Samples for phenotype and genotype determinations were taken but analysis was only done if requested by the Protocol Virologist.

$ All subjects who were prematurely withdrawn from the trial were followed for survival until the last follow-up visit of the last subjects in this trial, unless they withdrew consent. Investigators were asked to provide minimal information about the survival of the subjects every 6 months. For any fatal event, investigators were asked to provide information on the cause of death.

Continued

Assessments, Cont'd / **Type of Visit** / **Time of Visit**	**W 48**	**Optional Extended Treatment Period** ** **W 56**	**W 64**	**W 72**	**W 84**	**Final/ Withdrawal Visit$** **W 96**	**Posttreatment Follow-up Period (30-35 days after Final/Withdrawal Visit)**
Informed consent and inclusion criteria extended treatment	X						
Urine pregnancy test, if applicable[a]	X	X	X	X	X	X	X
Physical examination	X			X		X	X
PBMC sample	X					X	
Hematology & biochemistry (10 h fasting) and urinalysis	X	X	X	X	X	X	X
Coagulation tests	X	X	X	X	X	X	X
T_3, free T_4, and TSH testing[b]	X			X		X	
Vital signs (pulse, blood pressure)	X	X	X	X	X	X	X
ECG (central reading)	X			X		X	
Weight	X	X	X	X	X	X	X
TMC125, DRV & ritonavir pharmacokinetics[c]	X			X		X	
Plasma viral load and samples for phenotype/genotype determinations	X	X[d]	X[d]	X[d]	X[d]	X	X[d]
CD4 cell count	X	X	X	X	X	X	X
Dispensation of investigational medication	X	X	X	X	X		
PRO questionnaires - Compliance questions	X			X		X	
Observe/Interview for AEs and HIV-1 related events & Concomitant therapy	X	X	X	X	X	X	X

** Unscheduled visits could be performed for safety/tolerability reasons. For confirmation of virologic failure, unscheduled viral load assessments could be performed; however, there had to be a minimum 2-week time interval between such assessments.

[a] Serum test at Screening for all female subjects, urine test at other visits for female subjects of childbearing potential.

[b] Whenever clinically relevant, extra tests could be done at other visits.

[c] Samples were collected and stored but analysis was only done if requested by the trial pharmacokineticist.

[d] Samples for phenotype and genotype determinations were taken but analysis was only done if requested by the Protocol Virologist.

$ All subjects who were prematurely withdrawn from the trial were followed for survival until the last follow-up visit of the last subjects in this trial, unless they withdrew consent. Investigators were asked to provide minimal information about the survival of the subjects every 6 months. For any fatal event, investigators were asked to provide information on the cause of death.

Main Features of the Subject Sample and Summary of the Results

Note: the previous version of the report described the results of the Week 48 Analysis (dated April 2008), which was performed when all subjects reached Week 48 or discontinued earlier. The present report describes the results of the Final Analysis, which was conducted when all subjects had completed the trial (i.e. were treated for 96 weeks) or discontinued earlier. Caution is advised when comparing the results at Week 48 in this report with the results at Week 48 in the previous report because tabulations are generated from an active database and may change over time as case information is updated (e.g. with follow-up information for a serious adverse event [SAE], confirmation of virologic response < 50 copies/mL at a consecutive visit). This new information can result in slight differences between the results described in the current report and the previous version of the report.

Discontinuations and Treatment Duration	**Placebo N = 296**	**TMC125 N = 295**	**All Subjects N = 591**
Discontinuations - Reason[a], n (%)	***193 (65.2)***	***103 (34.9)***	***296 (50.1)***
Reached virologic endpoint	126 (42.6)	46 (15.6)	172 (29.1)
AE/HIV related event	16 (5.4)	25 (8.5)	41 (6.9)
Withdrew consent	15 (5.1)	9 (3.1)	24 (4.1)
Non-compliant	5 (1.7)	7 (2.4)	12 (2.0)
Lost to follow-up	4 (1.4)	6 (2.0)	10 (1.7)
Sponsor's decision	3 (1.0)	1 (0.3)	4 (0.7)
Ineligible to continue the trial	2 (0.7)	1 (0.3)	3 (0.5)
Other	22 (7.4)	8 (2.7)	30 (5.1)
Completers after 48 weeks of treatment[b]	***2 (0.7)***	***2 (0.7)***	***4 (0.7)***
Completed after 96 weeks of treatment	***101 (34.1)***	***190 (64.4)***	***291 (49.2)***
Duration of Treatment			
Median (range), weeks	71.2 (3-111)	96.0 (3-107)	92.7 (3-111)
Total patient-years of exposure	375.0	434.8	809.8

N = number of subjects, n = number of subjects (in subset)
[a] At any time point.
[b] Subjects who completed the 48-week treatment period and did not continue in the optional extension period.

At Week 96, slightly more subjects in the placebo group (7.4%) discontinued for other reasons than in the TMC125 group (2.7%). After amending the TMC125-C217 protocol (i.e. subjects with at least 48 weeks of treatment in DUET no longer needed to be virologically failing to be included but could roll over if, in the opinion of the investigator, the subject was not responding well to his/her therapy), more subjects rolled over to this open-label trial (especially after unblinding the DUET trials after their Week 48 database lock), resulting in more discontinuations for other reasons in the DUET trials.

Demographic and Baseline Characteristics	**Placebo N = 296**	**TMC125 N = 295**	**All Subjects N = 591**
Demographic Data			
Gender, n (%)			
Male	271 (91.6)	276 (93.6)	547 (92.6)
Female	25 (8.4)	19 (6.4)	44 (7.4)
Age: median (range), years	45.0 (20-69)	46.0 (31-77)	46.0 (20-77)
Weight[a]: median (range), kg	72.0 (45-137)	74.0 (41-115)	72.5 (41-137)
BMI[a]: median (range), kg/m^2	22.9 (15-47)	23.4 (14-34)	23.2 (14-47)
Ethnic origin[b], n (%)			
Caucasian	187 (75.7)	186 (76.5)	373 (76.1)
Black	35 (14.2)	31 (12.8)	66 (13.5)
Hispanic	24 (9.7)	19 (7.8)	43 (8.8)
Asian	0	5 (2.1)	5 (1.0)
Other	1 (0.4)	2 (0.8)	3 (0.6)
Baseline Disease Characteristics			
Viral load[a]: median (range), copies/mL	61450.0 (177-2,110,000)	65300.0 (977-7,030,000)	64500.0 (177-7,030,000)
Log_{10} viral load[a]: median (range), copies/mL	4.79 (2.2-6.3)	4.81 (3.0-6.8)	4.81 (2.2-6.8)
CD4 cell count[a]: median (range), 10^6 cells/L	108.0 (0-912)	100.0 (1-708)	105.0 (0-912)
Duration of known HIV infection[c]: median (range), years	15.1 (5-26)	14.5 (3-25)	14.9 (3-26)
CDC Category[c], n (%)			
Category A	71 (24.0)	57 (19.3)	128 (21.7)
Category B	63 (21.3)	76 (25.8)	139 (23.5)
Category C	162 (54.7)	162 (54.9)	324 (54.8)
Hepatitis B surface antigen (HBsAg) positive, n (%)	19 (6.4)	19 (6.4)	38 (6.4)
Active hepatitis C infection, n (%)	21 (7.4)	20 (7.0)	41 (7.2)
Hepatitis B and/or C co-infection, n (%)	37 (13.1)	38 (13.3)	75 (13.2)

N = number of subjects, n = number of subjects (in subset)

[a] Baseline values were imputed with screening values if no data at Baseline were available.

[b] For ethnic origin: 101 subjects are not included in the denominator for race percentages because local regulations in some countries preclude collection of these data.

[c] At the time of Screening.

Prior ARVs up to Baseline	**Placebo N = 296**	**TMC125 N = 295**	**All Subjects N = 591**
Previous ARV Experience[a], n (%)			
NNRTI			
≥ 1	268 (90.5)	267 (90.5)	535 (90.5)
NRTI			
3 - 5	89 (30.1)	81 (27.5)	170 (28.8)
> 5	201 (67.9)	210 (71.2)	411 (69.5)
PI			
3 - 5	170 (57.4)	169 (57.3)	339 (57.4)
> 5	102 (34.5)	99 (33.6)	201 (34.0)
Fusion Inhibitor[b]			
1	149 (50.3)	144 (48.8)	293 (49.6)
CCR5 Inhibitors			
1	5 (1.7)	9 (3.1)	14 (2.4)
Integrase Inhibitors			
1	3 (1.0)	0	3 (0.5)
ARV Use During Screening, n (%)			
NNRTI	28 (9.5)	28 (9.5)	56 (9.5)
NRTI	291 (98.3)	287 (97.3)	578 (97.8)
Boosted PI	263 (88.9)	253 (85.8)	516 (87.3)
DRV	12 (4.1)	2 (0.7)	14 (2.4)
Unboosted PI	13 (4.4)	24 (8.1)	37 (6.3)
Fusion Inhibitor	64 (21.6)	57 (19.3)	121 (20.5)
Experimental ARVs[c]	1 (0.3)	2 (0.7)	3 (0.5)

N = number of subjects, n = number of subjects with observations

[a] Including ARVs used in the Screening period.

[b] Fusion Inhibitors used up to Baseline: only ENF.

[c] Experimental ARVs at the time of Screening: integrase inhibitors, CCR5 inhibitors and other entry inhibitors.

Baseline Resistance Data	**Placebo N = 296**	**TMC125 N = 295**	**All Subjects N = 591**
Number of Detectable Mutations: median (range)			
IAS-USA NNRTI RAMs[a]	2.0 (0-6)	2.0 (0-5)	2.0 (0-6)
Tibotec NNRTI RAMs[b]	2.0 (0-7)	2.0 (0-6)	2.0 (0-7)
TMC125 RAMs (2007 list)[c]	1.0 (0-5)	1.0 (0-5)	1.0 (0-5)
TMC125 RAMs (2008 list)[d]	1.0 (0-5)	1.0 (0-5)	1.0 (0-5)
TMC125 weighted genotypic score (2008 list)[d]	1.0 (0-8)	1.5 (0-7)	1.5 (0-8)
IAS-USA NRTI RAMs[a]	5.0 (0-9)	5.0 (0-9)	5.0 (0-9)
IAS-USA PI RAMs[a]	13.0 (1-20)	13.0 (5-20)	13.0 (1-20)
IAS-USA primary PI mutations[a]	4.0 (0-8)	4.0 (0-7)	4.0 (0-8)
DRV RAMs[e]	2.0 (0-8)	2.0 (0-7)	2.0 (0-8)
FC for NNRTIs – Antivirogram®: median (range)			
Nevirapine (NVP)	74.3 (0-139)	77.3 (0-139)	74.3 (0-139)
Delavirdine (DLV)	22.0 (0-83)	27.5 (0-88)	23.6 (0-88)
Efavirenz (EFV)	25.0 (0-23773)	39.9 (0-15666)	31.4 (0-23773)
Etravirine (TMC125)	1.6 (0-546)	1.7 (0-3256)	1.6 (0-3256)
TMC125 FC Category, n (%)			
FC $\leq$ 3	194 (66.7)	200 (68.0)	394 (67.4)
3 < FC $\leq$ 13	56 (19.2)	55 (18.7)	111 (19.0)
FC > 13	41 (14.1)	39 (13.3)	80 (13.7)
DRV FC – Antivirogram®: median (range)			
DRV	6.9 (0-610)	6.7 (0-909)	6.8 (0-909)
DRV FC Category, n (%)			
FC $\leq$ 10	183 (62.7)	185 (62.9)	368 (62.8)
10 < FC $\leq$ 40	70 (24.0)	72 (24.5)	142 (24.2)
FC > 40	39 (13.4)	37 (12.6)	76 (13.0)

FC = fold change in EC_{50} value, N = number of subjects, n = number of subjects (in subset)
Baseline values were imputed by last available value of the screening period if no data at Baseline were available.

[a] RAMs and primary mutations are based on the IAS-USA Drug Resistance Mutations Guidelines as published in Johnson VA, et al. Topics in HIV Medicine 2007;15(4):119-125.

[b] List of Tibotec NNRTI RAMs (NPR-TiDP-20060022-VRR, version 5.0, 18 June 2008).

[c] According to Vingerhoets J, et al. Impact of baseline NNRTI mutations on the virologic response to TMC125 in the Phase III clinical trials DUET-1 and DUET-2. Antiviral Therapy 2007;12:S34.

[d] According to Vingerhoets J, et al. An update to the list of NNRTI mutations associated with decreased virologic response to etravirine (ETR): multivariate analyses on the pooled DUET-1 and DUET-2 clinical trial data. Antiviral Therapy 2008;13(suppl3):A26.

[e] According to De Meyer, et al. Identification of mutations predictive of a diminished response to darunavir/ritonavir: analysis of data from treatment-experienced patients in POWER 1, 2, 3 and DUET-1 and DUET-2 (Abstract 54). 6th Eur HIV Drug Resistance Workshop, Budapest, Hungary, March 2008.

Underlying ART During the Treatment Period[a,b]	**Placebo N = 296**	**TMC125 N = 295**	**All Subjects N = 591**
Number of ARVs in Underlying ART, n (%)			
Any ARV			
2	2 (0.7)	0	2 (0.3)
3	85 (28.7)	65 (22.0)	150 (25.4)
4	144 (48.6)	150 (50.8)	294 (49.7)
5	51 (17.2)	65 (22.0)	116 (19.6)
6	13 (4.4)	15 (5.1)	28 (4.7)
7	1 (0.3)	0	1 (0.2)
PI[c,d]			
1	293 (99.0)	290 (98.3)	583 (98.6)
Fusion Inhibitor			
0	141 (47.6)	144 (48.8)	285 (48.2)
1	155 (52.4)	151 (51.2)	306 (51.8)
NRTI			
1	14 (4.7)	13 (4.4)	27 (4.6)
2	159 (53.7)	129 (43.7)	288 (48.7)
3	99 (33.4)	124 (42.0)	223 (37.7)
4	24 (8.1)	28 (9.5)	52 (8.8)
5	0	1 (0.3)	1 (0.2)
Individual ARVs in Underlying ART, n (%)			
PI[c,d]			
DRV/rtv	294 (99.3)	294 (99.7)	588 (99.5)
Fusion Inhibitor			
ENF	155 (52.4)	151 (51.2)	306 (51.8)
De novo	80 (27.0)	79 (26.8)	159 (26.9)
Re-using	75 (25.3)	72 (24.4)	147 (24.9)
NRTI			
Tenofovir (TDF)	194 (65.5)	212 (71.9)	406 (68.7)
Lamivudine (3TC)	149 (50.3)	156 (52.9)	305 (51.6)
Emtricitabine (FTC)	108 (36.5)	102 (34.6)	210 (35.5)
Zidovudine (AZT)	98 (33.1)	107 (36.3)	205 (34.7)
Abacavir (ABC)	77 (26.0)	77 (26.1)	154 (26.1)
Didanosine (ddI)	63 (21.3)	65 (22.0)	128 (21.7)
Stavudine (d4T)	33 (11.1)	41 (13.9)	74 (12.5)
Zalcitabine (ddC)	3 (1.0)	0	3 (0.5)

N = number of subjects, n = number of subjects with observations

[a] TMC125/placebo not included in this tabulation.

[b] Only the initial therapies (i.e. as determined on Day 7) in the underlying ART were considered.

[c] Three subjects did not have DRV recorded as part of their initial therapy because DRV was started after Day 7 of the treatment period (between Days 15 and 28).

[d] Five subjects were protocol violators as they used other PIs in addition to DRV as part of their initial therapy (fosamprenavir [FPV]/rtv, atazanavir [ATV]/rtv, and/or LPV/rtv) for at least 7 days.

Sensitivity of Underlying ARVs During the Treatment Period	**Placebo N = 296**	**TMC125 N = 295**	**All Subjects N = 591**
Number of Sensitive ARVs in Underlying ART[a,b], n (%)			
Any ARV	292	294	586
0	47 (16.1)	49 (16.7)	96 (16.4)
1	123 (42.1)	103 (35.0)	226 (38.6)
2	71 (24.3)	88 (29.9)	159 (27.1)
3	36 (12.3)	45 (15.3)	81 (13.8)
4	14 (4.8)	9 (3.1)	23 (3.9)
5	1 (0.3)	0	1 (0.2)
PI[c]			
DRV/rtv[d]	182 (62.8)	184 (62.8)	366 (62.8)
Fusion Inhibitor			
ENF *de novo* use	80 (27.0)	79 (26.8)	159 (26.9)
NRTI			
0	161 (55.1)	157 (53.4)	318 (54.3)
1	93 (31.8)	91 (31.0)	184 (31.4)
2	33 (11.3)	42 (14.3)	75 (12.8)
3	5 (1.7)	4 (1.4)	9 (1.5)

N = number of subjects, n = number of subjects with observations

[a] TMC125 was not included in the calculation. Sensitivity was based on Antivirogram® (DRV was considered sensitive if the FC was ≤ 10.0), and ENF was counted as sensitive if it had not been used previously. Baseline Antivirogram® data was available for 586 subjects.

[b] Only the initial therapies (i.e. as determined on Day 7) in the underlying ART were considered.

[c] Other (disallowed) PIs (taken by 5 subjects in addition to DRV as part of their initial therapy [FPV/rtv, ATV/rtv, and/or LPV/rtv] for at least 7 days) were not scored as sensitive.

[d] For 3 subjects (not counted here), DRV was not taken on Day 7 of the treatment period.

Efficacy **Primary and Secondary Variables**	**Placebo** **N = 296**	**TMC125** **N = 295**
Primary Variable[a]:		
Virologic Response at Week 24, n (%)		
Viral load < 50 copies/mL	***124 (41.9)***	***186 (63.1)****
De novo ENF	53 (66.3)	58 (73.4)
Not *de novo* ENF[b]	71 (32.9)	128 (59.3)*
Secondary Variables[a]:		
Virologic Response at Week 96, n (%)		
Viral load < 50 copies/mL	***111 (37.5)***	***167 (56.6)****
De novo ENF	46 (57.5)	55 (69.6)
Not *de novo* ENF[b]	65 (30.1)	112 (51.9)*
Non-Response Reason at Week 96, n (%)		
Virologic failure	141 (47.6)	83 (28.1)
Rebound (loss of response)	37 (12.5)	35 (11.9)
Never suppressed (not responding)	104 (35.1)	48 (16.3)
Death	9 (3.0)	6 (2.0)
Discontinuation due to AE	6 (2.0)	19 (6.4)
Discontinuation due to other reasons	29 (9.8)	20 (6.8)
Durability of Virologic Response at Week 96, n (%)		
Viral load < 50 copies/mL at Week 24 and < 50 copies/mL at Week 96	95 (76.6)	150 (80.7)
De novo ENF	43 (81.1)	48 (82.8)
Not *de novo* ENF[b]	52 (73.2)	102 (79.7)

The overall response rate at Week 24 (i.e. the primary endpoint of the trial) in the TMC125 group was 63.1% compared with 41.9% in the placebo group (difference of 21.2%). At Week 24, a significant statistical interaction was noted between ENF use and treatment indicating that the added benefit of TMC125 was different when ENF was used as a *de novo* drug in the ART. Therefore, the primary analysis at Week 24 divided the subjects in the *de novo* ENF users and the not *de novo* ENF users. TMC125 was superior over placebo in the group of subjects who did not use ENF as a *de novo* drug ($p < 0.0001$, CMH test and logistic regression) at Week 24. Furthermore, in the overall trial population across both strata (i.e. either when ENF was used as a *de novo* drug or not), TMC125 showed an additional benefit ($p < 0.0001$, logistic regression) at Week 24.
The overall response rate at Week 96 in the TMC125 group was 56.6% compared with 37.5% in the placebo group (difference of 19.1%). At Week 96, the statistical interaction between ENF use and treatment was no longer significant. The difference between the TMC125 and placebo groups at Week 96 was significant in the overall trial population and the group of subjects not using ENF as a *de novo* drug in the ART ($p < 0.0001$ in favor of TMC125, CMH test), but was not significant in the group of subjects using *de novo* ENF in the ART ($p = 0.1264$, CMH test). When applying the logistic regression model as sensitivity analysis, TMC125 was superior over placebo in the overall trial population and the group of subjects not using ENF as a *de novo* drug in the ART at Week 96.
Virologic response was durable in both treatment groups. In 80.7% of subjects in the TMC125 group and 76.6% of subjects in the placebo group with confirmed virologic response defined as plasma viral load < 50 copies/mL (time to loss of virologic response; TLOVR) at Week 24, the plasma viral load remained undetectable at Week 96.

N = number of subjects, n = number of subjects with observations
Values below the detection limits (< 50 copies/mL) were imputed with 49.

[a] Response criteria are defined according to the TLOVR algorithm given in Appendix B of the FDA Guidance for Industry. According to this TLOVR algorithm, 2 consecutive values below the threshold are required to qualify as a responder. Once a subject was a responder, 2 consecutive values above the threshold needed to be observed in order to be determined a non-responder (rebound). Once a subject was determined as a rebounder, following values below the threshold (re-suppression) were not counted as a response. Intermittent missing values were imputed as response if the preceding value was a response and the missing value was followed by a response value. Subjects who discontinued the trial before Week 48 or for an AE were considered as non-responders after discontinuation. Subjects who discontinued after Week 48 and for reasons other than an AE had their last observation carried forward. Statistical significance in pairwise comparison with placebo (CMH test, for ENF strata only at Week 24, and logistic regression) is indicated with an asterisk (*).

[b] Not *de novo*: combines those subjects re-using ENF and not using ENF.

Efficacy **Secondary Variables**	**Placebo** **N = 296**	**TMC125** **N = 295**
Virologic Response at Week 96[a], n (%)		
Viral load < 400 copies/mL	132 (44.6)	202 (68.5)*
De novo ENF	55 (68.8)	65 (82.3)*
Not *de novo* ENF	77 (35.6)	137 (63.4)*
Viral load decrease > 1 $\log_{10}$ copies/mL	145 (49.0)	210 (71.2)*
De novo ENF	59 (73.8)	66 (83.5)
Not *de novo* ENF	86 (39.8)	144 (66.7)*
Change in Log_{10} Viral Load at Week 96[b]: mean change (SE), copies/mL		
Overall	-1.4 (0.09)	-2.1 (0.09)*
De novo ENF	-2.1 (0.16)	-2.5 (0.15)
Not *de novo* ENF	-1.1 (0.10)	-2.0 (0.10)*
Immunologic Change at Week 96[b]: mean change (SE)		
CD4 cell count (x 10^6 cells/L)	+82.3 (7.31)	+115.0 (7.02)*
De novo ENF	+123.3 (14.3)	+135.2 (13.1)
Not *de novo* ENF	+67.1 (8.30)	+107.6 (8.25)*
CD4 cell count (%)	+3.7 (0.30)	+5.3 (0.31)*
De novo ENF	+5.6 (0.67)	+6.3 (0.60)
Not *de novo* ENF	+3.0 (0.32)	+4.9 (0.36)*

N = number of subjects, n = number of subjects with observations
Values below (/above) the detection limits (< 50 and > 750000 copies/mL) were imputed with 49 (/750001).

[a] Response criteria are defined according to the TLOVR algorithm given in Appendix B of the FDA Guidance for Industry. According to this TLOVR algorithm, 2 consecutive values below the threshold are required to qualify as a responder. Once a subject was a responder, 2 consecutive values above the threshold needed to be observed in order to be determined a non-responder (rebound). Once a subject was determined as a rebounder, following values below the threshold (re-suppression) were not counted as a response. Intermittent missing values were imputed as response if the preceding value was a response and the missing value was followed by a response value. Subjects who discontinued the trial before Week 48 or for an AE were considered as non-responders after discontinuation. Subjects who discontinued after Week 48 and for reasons other than an AE had their last observation carried forward. Statistical significance in pairwise comparison with placebo (CMH test and logistic regression) is indicated with an asterisk (*).

[b] Changes from Baseline are shown. Missing values for non-dropouts were imputed by last observation carried forward (LOCF) up until the final time point. Dropouts before Week 48 and/or for AE reasons are imputed with non-completer equals failure (NC = F; the actual baseline value and thus a change of 0). For subjects dropping out after Week 48 and for reasons other than an AE, the missing values are imputed with LOCF. Statistical significance in pairwise comparison with placebo (ANCOVA) is indicated with an asterisk (*).

Efficacy Secondary Variables, Cont'd	**Placebo N = 296**	**TMC125 N = 295**
Adjudicated Clinical Endpoints[a], n (%)		
New AIDS defining illnesses[b] and/or death	26 (8.8)	22 (7.5)
De novo ENF	3 (3.8)	6 (7.6)
Not *de novo* ENF	23 (10.6)	16 (7.4)
New AIDS defining illnesses[b]	19 (6.4)	18 (6.1)
De novo ENF	1 (1.3)	5 (6.3)
Not *de novo* ENF	18 (8.3)	13 (6.0)
Death	9 (3.0)	7 (2.4)
De novo ENF	2 (2.5)	2 (2.5)
Not *de novo* ENF	7 (3.2)	5 (2.3)
Patient-years adjusted Relative Risk (95% CI) TMC125 vs Placebo		
New AIDS defining illnesses[b] and/or death	*0.73 (0.30; 1.17)*	
New AIDS defining illnesses[b]	*0.82 (0.28; 1.37)*	
Death	*0.68 (0.00; 1.35)*	
Hospitalization[c], n (%)		
All hospitalized subjects	72 (24.3)	75 (25.4)
De novo ENF	20 (25.0)	14 (17.7)
Not *de novo* ENF	52 (24.1)	61 (28.2)
Patient-years adjusted Relative Risk (95% CI) TMC125 vs Placebo		
All hospitalized subjects	*0.90 (0.58; 1.23)*	
De novo ENF	*0.65 (0.16; 1.14)*	
Not de novo ENF	*0.99 (0.58; 1.40)*	
PRO Results at Week 96[d]: mean change (SE)		
FAHI:		
Physical Well-Being	+0.7 (0.41)	+1.8 (0.46)
Functional and Global Well-Being	-0.5 (0.51)	+0.6 (0.54)
Total FAHI	+0.7 (1.31)	+4.1 (1.41)
EQ-5D:		
EQ-Visual Analog Scale (VAS)	+3.9 (1.15)	+6.2 (1.23)
EQ-5D Valuation Index	+0.001 (0.013)	+0.008 (0.012)

N = number of subjects, n = number of subjects with observations

[a] Data after first intake including follow-up. All deaths after first intake are included and there is no distinction made between deaths in treatment or follow-up phase. There were no statistically significant differences in pairwise comparison with placebo (CMH test and logistic regression model) at Week 96.

[b] Confirmed or probable AIDS defining illnesses.

[c] Only hospitalizations with admission date up to and including 96 weeks after first intake are included. No distinction was made between treatment and follow-up data.There were no statistically significant differences in pairwise comparison with placebo (logistic regression model) at Week 96.

[d] Changes from Baseline are shown. Missing values were imputed by LOCF until Week 96. There were no statistically significant differences in pairwise comparison with placebo (ANCOVA) at Week 96.

Efficacy
Subgroup Analyses and Resistance Determinations

Subgroup analyses indicated that use of TMC125 resulted in additional virologic activity regardless of baseline plasma viral load, CD4 cell count, or activity of the underlying PI (DRV/rtv in this trial) as the proportion of subjects with virologic response (viral load < 50 copies/mL TLOVR) at Week 96 in each of the subgroups was always higher in the TMC125 group. Importantly, TMC125 provided additional antiviral efficacy even in the presence of multiple TMC125 RAMs or when used in regimens with no other active agents. Although the virologic response rates increased in both treatment groups as more sensitive ARVs were used in the underlying ART, an added effect of TMC125 was always observed. As expected, the magnitude of the difference between the TMC125 group and the placebo group was larger in subjects who used a lower number of active drugs in the background (including not using *de novo* ENF and/or when the activity of DRV was significantly reduced [FC > 40]).

The most frequently emerging Tibotec NNRTI RAMs observed in at least 5 subjects were V179I, V179F, V108I, Y181C, L100I and K103N.

Safety (n = number of subjects with data)	**Placebo** **N = 296**	**TMC125** **N = 295**
Median Duration of Treatment (range), weeks	***71.2 (3-111)***	***96.0 (3-107)***
Treatment-Emergent AEs (Treatment Period), n (%) Most frequently reported AEs (in > 10% subjects with TMC125)		
Diarrhea	70 (23.6)	62 (21.0)
Injection site reaction	52 (17.6)	50 (16.9)
Nasopharyngitis	37 (12.5)	46 (15.6)
Nausea	34 (11.5)	44 (14.9)
Bronchitis	23 (7.8)	44 (14.9)
Cough	37 (12.5)	39 (13.2)
Headache	37 (12.5)	33 (11.2)
Pyrexia	35 (11.8)	33 (11.2)
Vomiting	22 (7.4)	31 (10.5)
Fatigue	38 (12.8)	30 (10.2)
n (%) with 1 or more AEs	284 (95.9)	284 (96.3)
n (%) of deaths	9 (3.0)	7 (2.4)
n (%) with 1 or more SAEs	71 (24.0)	77 (26.1)
n (%) of treatment discontinued due to AEs	13 (4.4)	25 (8.5)
n (%) with 1 or more grade 3 or 4 AEs	106 (35.8)	130 (44.1)
Treatment-Emergent AEs of Interest (Treatment Period), n (%)		
n (%) with any skin event	56 (18.9)	72 (24.4)
Rash (any type)	35 (11.8)	52 (17.6)
n (%) with any neuropsychiatric event	100 (33.8)	100 (33.9)
Nervous system events	58 (19.6)	54 (18.3)
Psychiatric events	63 (21.3)	62 (21.0)
n (%) with any hepatic event	18 (6.1)	24 (8.1)
Hepatobiliary disorders	11 (3.7)	11 (3.7)
n (%) with any cardiac event	27 (9.1)	32 (10.8)
Coronary artery disorders	6 (2.0)	9 (3.1)
n (%) with any bleeding event	22 (7.4)	21 (7.1)
n (%) with any pancreatic event	13 (4.4)	15 (5.1)
Pancreatitis	2 (0.7)	3 (1.0)

N = number of subjects, n = number of subjects with AEs

During the treatment period, 96.3% of subjects in the TMC125 group reported at least 1 AE, with the most common AEs being diarrhea, rash (any type), injection site reaction (associated with ENF use), nasopharyngitis, nausea and bronchitis. Most AEs were grade 1 or 2 in severity. When adjusted for exposure time, the incidence of subjects with grade 3 or 4 AEs was comparable in both treatment groups (29.9 vs 28.2 per 100 patient-years of exposure), with no consistent pattern of individual grade 3 or 4 AEs. Seven (2.4%) subjects in the TMC125 group and 9 (3.0%) subjects in the placebo group died. No cases of death were considered related to TMC125. The incidence of SAEs was comparable in both treatment groups. Apart from pneumonia (2.4% vs 2.7% for placebo), pyrexia (1.7% vs 1.4%), myocardial infarction (1.7% vs 0.3%), renal failure (1.4% vs 0.3%), *Pneumocystis jiroveci* pneumonia (PJP; 1.0% vs 1.4%) and renal failure acute (1.0% vs 0.7%), all individual SAEs occurred in less than 1.0% of TMC125-treated subjects. The incidence of AEs leading to discontinuation was low in both treatment groups, with the most common AEs being rash (any type, 2.4% vs none in the placebo group), nausea (1.0% vs none) and renal failure (1.0% vs none). Rash (any type) was reported more frequently in the TMC125 group (17.6%) than in the placebo group (11.8%). Most rashes were grade 1 or 2 in severity. Grade 3 rashes occurred in 4 (1.4%) subjects treated with TMC125, and there were no grade 4 rashes with TMC125. Neuropsychiatric events of interest, hepatic events, cardiac events, bleeding events and pancreatic events in the TMC125 group did not show substantial differences with the placebo group.

Safety, Cont'd	**Placebo N = 296**	**TMC125 N = 295**
Clinical Laboratory Tests		
Treatment-emergent laboratory data		
n (%) with any grade 1 abnormality	281 (94.9)	276 (93.6)
n (%) with any grade 2 abnormality	210 (70.9)	227 (76.9)
n (%) with any grade 3/4 abnormality	129 (43.6)	136 (46.1)
n (%) with any grade 3 abnormality	117 (39.5)	127 (43.1)
n (%) with any grade 4 abnormality	32 (10.8)	32 (10.8)

N = number of subjects, n = number of subjects with laboratory abnormalities

Changes over time in the clinical laboratory parameters (including urinalysis), if any, were modest in either treatment group. The differences with placebo were small and considered not clinically relevant. The majority of graded laboratory abnormalities were grade 1 or 2 in severity. The incidence of treatment-emergent grade 3 and 4 laboratory abnormalities was not different between the TMC125 group and placebo group (46.1% vs 43.6% for placebo). The most common treatment-emergent grade 3 or 4 laboratory abnormalities were increases in LDL cholesterol (11.9% vs 10.2% in the placebo group), triglycerides (10.6% vs 7.4%), total cholesterol (9.9% vs 6.1%) and pancreatic amylase (9.6% vs 9.8%) and a decrease in neutrophils (5.5% vs 5.7%). Grade 3 or 4 elevations of hepatic transaminases (AST and ALT) were low (4.4% and 4.1%, respectively, compared to 2.4% each in placebo group).

Cardiovascular Safety

There were no consistent or clinically relevant changes over time in vital signs or ECG parameters including QTc, and no meaningful differences in treatment-emergent abnormalities in cardiovascular parameters between both treatment groups.

Physical Examination and Body Weight

Physical examination findings revealed no relevant differences between TMC125 and placebo. A small gain in body weight from Baseline was observed with no meaningful between-group difference.

Conclusions

TMC125 demonstrated superior efficacy compared to placebo as part of an ART containing DRV/rtv, investigator selected NRTI(s) and optional ENF in subjects with NNRTI resistance as demonstrated by screening or previously documented NNRTI RAMs. At Week 24, 63.1% of treatment-experienced subjects taking TMC125 achieved the primary endpoint of confirmed viral load reduction to < 50 copies/mL compared to 41.9% of placebo subjects. The durable effect of treatment was evidenced by the proportion of responders after 96 weeks of treatment (56.6% in the TMC125 group and 37.5% in the placebo group). In 80.7% of subjects in the TMC125 group and 76.6% of subjects in the placebo group with a confirmed viral load of < 50 copies/mL at Week 24, a sustained virologic response (undetectable viral load) was observed at Week 96. For safety comparisons, the difference in median exposure time between the treatment groups (96.0 vs 71.2 weeks) should be taken into consideration. Except for a higher incidence of rash during TMC125 treatment, safety and tolerability were comparable to the placebo group.

In conclusion, TMC125 demonstrates substantial and durable efficacy over placebo when added to an ART containing DRV/rtv, investigator-selected NRTI(s) and optional ENF in treatment experienced HIV-1 infected subjects, including those with NNRTI RAMs at Baseline, and is generally safe and well tolerated.