SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: - **Indication**: HIV-1 infection	**Drug Substance**: TMC125 **Trial no**.:CR006730 **Clinical Phase**: II
Title: A Phase II, randomized, active controlled, open label trial to investigate the efficacy and tolerability of TMC125 in HIV-1 infected subjects, who are PI-naïve and with documented genotypic evidence of NNRTI resistance from previous NNRTI use.	
Investigator: Assoc. Prof. K. Ruxrungtham, M.D., Thai Red Cross AIDS Research Center, 104 Rajdamri Road, Bangkok 10330, Thailand	**Country**: Multicenter, International
Trial Period: Start: 01-Mar-2005 End: 11-Jul-2006	**No. of Investigators**: 26 **No. of Subjects**: 116

Objectives: The originally defined primary objective of the trial was to evaluate the antiviral activity of TMC125 800 mg b.i.d. (formulation TF035) as part of an ART containing 2 NRTIs, by evaluating the proportion of subjects with plasma HIV 1 RNA levels < 50 copies/mL at 24 weeks (however, due to the premature discontinuation of TMC125 treatment, not all subjects in the TMC125 group had reached Week 24. Therefore, the main focus of the efficacy analyses of the pre therapy switch treatment phase is the change from Baseline in $\log_{10}$ viral load).
The secondary objectives were:
- To evaluate the antiviral activity over the treatment period with TMC125;
- To evaluate safety and tolerability over the treatment period with TMC125;
- To evaluate immunologic changes (as measured by CD4 and CD8 cells) over the treatment period;
- To evaluate changes in viral genotype and drug susceptibility during the trial;
- To evaluate the efficacy, safety and tolerability of TMC125 compared with the active control group over the treatment period;
- To investigate the population pharmacokinetics of TMC125;
- To evaluate the durability of efficacy.

The objective of the pharmacokinetic subtrial was to evaluate the pharmacokinetic profile of TMC125 at Baseline and after 4 weeks of TMC125 treatment when administered in addition to 2 investigator-selected NRTIs.

In November 2005 (approximately 8 months after the first subject was randomized), due to the early identification of suboptimal virologic response in the TMC125 treated subjects, recruitment to the trial was halted and subjects receiving TMC125 were recommended to be switched to an investigator-selected PI-containing ARV treatment regimen. Subjects in the control group were to continue the standard of care regimen consisting of approved ARVs (an investigator selected PI and 2 NRTIs), with only visits at Weeks 12 and 24 from randomization (timing as per the protocol which was in place at the time of the decision to discontinue TMC125 treatment). If a subject in the control group was already beyond 24 weeks of treatment, a Final/Withdrawal Visit was scheduled as soon as possible.
The objectives of the post therapy switch treatment phase were:
- To provide standard of care antiretroviral treatment in the post therapy switch treatment phase to all subjects who were randomized to TMC125 in the pre therapy switch treatment phase;
- To determine the virologic response to an investigator-selected PI-containing ARV recommended regimen after the therapy switch;
- To evaluate the virologic response from the therapy switch compared to the randomized control group from the study start (pre-therapy switch phase).

Design: This was a Phase II, randomized, active controlled, open label, 48 week exploratory trial of TMC125 conducted in HIV-1 infected subjects who were protease inhibitor-naïve (PI-naïve) with documented evidence of resistance to currently available NNRTIs after treatment with a first-line NNRTI regimen, or after treatment with an

NNRTI, either alone or with other ARVs, for the prevention of mother to child transmission (MTCT). The objective of the trial was to evaluate the efficacy, safety and tolerability of TMC125 given at 800 mg b.i.d. (formulation TF035) when added to 2 investigator-selected NRTIs. The control group was treated with an investigator selected PI in combination with 2 investigator selected NRTIs. The subjects were required to be sensitive (by screening virco®TYPE HIV-1) to the selected NRTIs. In the original protocol, it was planned to include 120 subject in the trial, but after discussions with regulatory agencies, the planned number of randomized subjects was increased to 300 subjects, who would be randomized to TMC125 and to active control in a 1:1 ratio, with trial treatment for a maximum of 48 weeks. Plasma viral load levels were used to assess the antiviral efficacy. Immunology, population pharmacokinetics, laboratory and cardiovascular safety were evaluated. In November 2005, an early evaluation of the data showed that there was a difference in the proportion of subjects achieving or maintaining an undetectable viral load (<50 copies/mL) in favor of the control group receiving a PI-based therapy. Based on these data, Tibotec decided to prematurely discontinue treatment with TMC125 and to end enrolment of new subjects. This decision was endorsed by the independent Data Safety Monitoring Board (DSMB). All randomized subjects receiving TMC125 were switched to an investigator-selected ART (a boosted PI-based regimen was recommended) by the end of December 2005, and were followed up for an additional 24 weeks after the treatment switch (in the post therapy switch treatment phase). Subjects in the control group continued the same treatment regimen consisting of approved ARVs (an investigator selected PI and 2 NRTIs), but with only visits at Weeks 12 and 24 from randomization (timing as per protocol in place at the time of decision to discontinue TMC125 treatment). If a subject in the control group was already beyond 24 weeks of treatment, a final/withdrawal visit was scheduled.
A substudy to evaluate the pharmacokinetic profile of TMC125 at Baseline and at Week 4 was conducted in a subset of subjects in the pre therapy switch treatment phase. In addition, blood samples were collected for a population pharmacokinetic analysis of all subjects randomized to TMC125 during the pre therapy switch treatment phase.

Subject Selection

Inclusion Criteria:

1. Voluntarily signed informed consent;
2. Documented HIV-1 infection;
3. Male or female subjects, aged above 18 years;
4. Subject could comply with the protocol requirements;
5. Subject:
   - was on a treatment interruption (minimum duration of 4 weeks) at Screening and agreeing to remain without ART until Baseline; OR
   - was receiving a stable (minimum duration of 12 weeks) NNRTI-containing ART at Screening and agreeing to stay on that ART until Baseline.
     Note: These subjects had to be virologically-failing on this first-line NNRTI-containing regimen as documented by a detectable HIV-1 plasma viral load measurement tested locally, prior to and consecutive with the screening sample; OR
   - has been treated with an NNRTI, either alone or with other ARVs, for prevention of MTCT. *Note*: Subjects treated with an NNRTI-containing regimen for prevention of MTCT were allowed in the trial, however, this subject population was limited to 25% of the total number of subjects.
6. HIV-1 plasma viral load at Screening visit greater than 1000 HIV-1 RNA copies/mL (assayed by RNA polymerase chain reaction ultrasensitive specimen procedure, Cobas Amplicor HIV-1 Monitor™, version 1.5);
7. NNRTI-experienced, with documented genotypic evidence of resistance to currently available NNRTIs either present at Screening or from prior genotypic analysis available in the source documents and after agreement with the sponsor to enroll the subject based on these historical data. A minimum of 1 of the following NNRTI- associated mutations had to be present based on the IAS-USA Drug Resistance Mutation Guidelines.

A98G	L100I	K101E	K101P	K101Q	K103H
K103N	K103S	K103T	V106A	V106M	V108I
Y181C	Y181I	Y181V	Y188C	Y188H	Y188L
G190A	G190E	G190S	P225H	M230L	P236L
K238N	K238T	Y318F			

8. Subject had to be sensitive on the virco®TYPE HIV-1 for the 2 NRTIs to be used in the underlying ART.
9. General medical condition, in the investigator's opinion, did not interfere with the assessments and the completion of the trial.

Exclusion Criteria:

1. Previous treatment with PIs;
2. Previous treatment with a regimen containing only NRTIs. Subjects could have been treated with NRTIs for the prevention of MTCT;
3. Use of disallowed concomitant therapy during the 14 days prior to the start of the treatment period;
4. History of, or currently active, alcohol or drug use that in the investigator's opinion would likely compromise the subject's safety and/or compliance with the trial procedures;
5. Life expectancy less than 6 months;
6. Subject experiencing any active AIDS defining illness at Screening/Baseline [as defined by Category C conditions according to the Centers for Disease Control (CDC) Classification System for HIV Infection 1993] with the following exceptions (to be discussed with the sponsor prior to enrolment):
   - Stable, cutaneous Kaposi's Sarcoma (i.e., no pulmonary or gastrointestinal involvement other than oral lesions) that at Screening was considered unlikely to require any form of systemic therapy during the trial period;
   - Wasting syndrome due to HIV infection if, in the investigator's opinion, it was not actively progressive and its treatment does not require hospitalization or compromise the subject's safety or ability to adhere to the trial protocol procedures. If subjects were on maintenance therapy (which may include human Growth Hormone, appetite stimulants and anabolic steroids) for previously diagnosed wasting, they could be eligible for the trial only if such treatment was not included in the list of disallowed medications.

   Note: Primary and secondary prophylaxis for an AIDS defining illness was allowed if the medication used was not part of the disallowed medication.
7. Any active clinically significant disease (e.g., tuberculosis, cardiac dysfunction) or findings during screening of medical history or physical examination that, in the investigator's opinion, would compromise the outcome of the trial;
8. Receipt of any investigational drug within 30 days prior to the trial drug administration (except for tenofovir and emtricitabine, which were allowed);
9. Previous permanent discontinuation of any NNRTI due to cutaneous events;
10. Previously demonstrated clinically significant allergy or hypersensitivity to any of the components of the investigational medication;
11. Pregnant or breastfeeding female;
12. Female of childbearing potential without the use of effective birth control methods, or not willing to continue practicing these birth control methods during the trial and for at least 14 days after the end of the trial (or after last intake of ART).
    Note: Hormonal contraception may not be reliable when taking TMC125, therefore to be eligible for this trial women of childbearing potential either had to:
    i. use a double barrier method to prevent pregnancy (i.e., using a condom with either spermicidal cream/foam/gel or diaphragm or cervical cap); OR
    ii. Use hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap with spermicide or female condom with spermicide); OR
    iii. Use an intrauterine device (IUD) in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap with spermicide or female condom with spermicide); OR
    iv. Be non-heterosexually active, practice sexual abstinence, or have a vasectomized partner.
    Note: women who were post-menopausal for at least 2 years, women with total hysterectomy and women who have had a tubal ligation were considered of non-childbearing potential.
13. Renal impairment as defined by serum creatinine > 2 x the upper limit of normal (ULN);
14. Any grade 3 or grade 4 toxicity according to the ACTG grading severity list (except for grade 3 glucose, asymptomatic triglyceride/cholesterol grade 3 or 4 elevations, isolated grade 3 increases in gamma-glutamyl transferase [GGT] or isolated grade 3 increases in amylase with no increase in lipase and no history of pancreatitis);
15. Acute hepatitis A, B or C;
16. Chronic hepatitis B or C with aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN;
17. Subjects with clinical or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels (e.g., International Normalized Ratio > 1.3 or albumin < 30 g/l or bilirubin > 2.5 x ULN);
18. Subjects who had been randomized to a TMC125 and/or TMC120 and/or TMC278 (R278474) treatment group in a previous trial.

Re-testing of abnormal screening values that would qualify for exclusion or full re-screening of subjects had to be discussed with the sponsor and was only approved (after discussion, review and approval in writing from the sponsor) in exceptional circumstances.

Treatment	TMC125 Group	Control Group
Pre Therapy Switch Treatment Phase		
Concentration Dosage Form (TF No.) Usage	200 mg Tablets (TF035) Oral	Not applicable Not applicable Not applicable
Batch Number	D04212	Not applicable
Dose Regimen	TMC125 800 mg b.i.d. (4 tablets TF035) + Investigator-selected therapy consisting of 2 NRTIs.	Investigator-selected combination therapy consisting of 1 PI (with or without low-dose ritonavir) and 2 NRTIs.
Duration of Treatment	Planned 48 weeks	
Duration of Trial	Planned 52 weeks	
Post Therapy Switch Treatment Phase: Only for subjects randomized to TMC125 in the pre therapy switch treatment phase		
	Recommended Investigator-selected PI-containing ARV treatment regimen followed up for 24 weeks after the switch from TMC125.	Subjects in the control group who were still in the trial were recommended to be continued on the same treatment regimen, with only visits at Weeks 12 and 24 from randomization (timing as per protocol in place at the time of decision to discontinue TMC125 treatment). Subjects in the control group already beyond 24 weeks of treatment were scheduled for a Final/ Withdrawal Visit.
Disallowed Medication	The prescribing information for all co-administered medications had to be consulted and reviewed carefully. The medications listed in the respective contraindicated, warning and precaution sections had to be followed in order to prevent any potentially serious and/or life threatening drug interactions. The following medications were not allowed from 14 days prior to Baseline until Week 48 or the withdrawal visit: – Therapeutic HIV vaccines; – Other vaccines during the first 6 weeks of treatment; afterwards, approved vaccines were allowed as long as they were given outside the 4-week time frame preceding a plasma viral load measurement; – All investigational drugs were disallowed from 30 days prior to Baseline and throughout the trial, except for tenofovir and emtricitabine where these were not yet licensed in a participating country; – Drugs that can potentiate the activity of antiretroviral drugs or have intrinsic antiretroviral activity (but no indication for treatment of HIV infection): * mycophenolic acid * hydroxyurea * foscarnet; – Cytochrome P450 inducers: * rifamycins: rifabutin, rifampicin/rifampin; rifapentin * anticonvulsants: phenobarbital, phenytoin, carbamazepine * systemic dexamethasone * all products containing *Hypericum perforatum* (St. John's Wort); – Cytochrome P450 inhibitors and inhibitors of transporting proteins: * systemic azole antifungals: ketoconazole and voriconazole were not allowed; itraconazole (if not exceeding 200 mg/day) and fluconazole were allowed; * macrolide antibiotics: erythromycin, clarithromycin and troleandomycin. If there was a need to introduce these drugs during the trial, dosage and regimen had to be discussed in advance with the sponsor.	

<table>
<tr><td>Disallowed Medication, cont'd</td><td colspan="2">– Cytochrome P450 substrates with a small therapeutic index:
* cisapride, triazolam, midazolam, terfenadine, and astemizole;
* Investigators had to be aware that clinically significant interactions have been demonstrated between sildenafil and other ARVs, specifically PIs. Therefore, the administration of these agents and their dose had to take into consideration possible interactions of the phosphodiesterase type 5 (PDE-5) inhibitors and all other medications, including ARVs, being concurrently administered.
– The antiarrhythmics amiodarone and quinidine;
– The antimigraines ergotamine, dihydroergotamine, ergonovine, methylergonovine, ergotaminetartrate and other ergot derivates;
– The lipid-lowering agents simvastatin, lovastatin, cholestyramine and colestipol;
– Cyclosporin, tacrolimus, warfarin and digoxin;
– Immunomodulators: systemic corticosteroids, interleukins and interferons;
– 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.</td></tr>
<tr><td rowspan="2">Disallowed Antiretroviral Medication</td><td>TMC125 Group</td><td>Control Group</td></tr>
<tr><td>- PIs;
- NNRTIs use of any other than TMC125;
- any investigational ARV, except for tenofovir and emtricitabine where these were not yet licensed in a participating country.</td><td>- NNRTIs;
- any investigational ARV, except for TDF, emtricitabine, ATV, fosamprenavir and amprenavir where these were not yet licensed in a participating country.</td></tr>
<tr><td>Statistical Methods</td><td colspan="2">Intent-to-treat (ITT) analysis, descriptive statistics including mean, 95% confidence interval (CI) of the mean, standard deviation (SD), standard error (SE), median, minimum and maximum, frequency tabulations, analysis of covariance (ANCOVA), Fisher's exact test, logistic regression, Wilcoxon matched-pairs signed-ranks test.</td></tr>
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Definition of Data in the 2 Phases:

Pre Therapy Switch Treatment Phase:

- Data of subjects randomized to TMC125 up to the therapy switch treatment visit (switch to an investigator-selected ART; a boosted PI-based regimen was recommended); and
- All data of subjects randomized to the control group (they continued their randomized treatment until the end of the trial).

Post Therapy Switch Treatment Phase (only for subjects initially randomized to TMC125):

- Data of subjects, who were randomized to TMC125 in the pre therapy switch treatment phase, after the therapy switch treatment visit (switch to an investigator-selected ART; a boosted PI-based regimen was recommended) until the end of the trial.

Planned Flowchart of Trial (Pre Therapy Switch Treatment Phase)

Type of Visit	Screen-ing[1]	Randomization and Baseline	Treatment period [2] (For time window see protocol)										Final with-drawal visit	Post-treatment follow-up period	
Time of Visit	Week 4	Day 1	Wk 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 48	Week 49	Week 52
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent, demographic data, height	X														
Antiretroviral therapy history	X														
Serum β-HCG pregnancy test, if applicable	X														
Urine pregnancy test, if applicable		X			X	X	X	X	X	X	X	X	X		X
Inclusion/exclusion criteria	X	X													
Medical and surgical history & concomitant diseases	X														
Complete physical examination	X	X			X		X			X			X		X
Brief physical examination			X[3]	X[3]		X		X	X		X	X		X	
PBMC sample		X								X			X		
Hepatitis A, B and C test [4]	X						X			X			X		
T_3 and T_4 test, reflex to TSH if abnormal [4]		X					X			X			X		
Coagulation test [4]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Hematology and biochemistry (fasting), urinalysis	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (pulse, blood pressure, body temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma viral load	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (central reading)	X	X					X			X			X		
Weight	X	X			X	X	X	X	X	X	X	X	X		X
TMC125 pharmacokinetics [5]					X		X			X			X		
Underlying antiretroviral pharmacokinetics[9]					X		X			X			X		
Samples for phenotype/genotype determinations and sample for protein analysis [6]	X[7]	X	X	X	X	X	X	X	X	X	X	X	X[7]	X	X
Immunology	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dispense investigational medication		X	X	X	X	X	X	X	X	X	X	X			
EQ-5D and side effect questionnaires[8]		X			X										
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance questions			X	X	X	X	X	X	X	X	X	X	X		
Body Image questionnaire [8]		X					X			X			X		
Observe/Interview for AEs and HIV related events		X		X	X	X	X	X	X	X	X	X	X	X	X

[1] Screening visit had to be performed within 4 weeks prior to the start of treatment with investigational medication. The aim was to start the investigational medication approximately 2 weeks after Screening (as soon as the screening virco®TYPE HIV-1 was available).
[2] Unscheduled visits could be performed for safety/tolerability reasons or confirmation of plasma viral load.
[3] Brief physical examination at Weeks 1 and 2 consists of a skin examination only.
[4] Whenever clinically relevant; extra tests could be done at other visits.
[5] Samples were only collected for subjects randomized to TMC125. At Week 4, 2 samples were taken. The first sample had to be a trough sample (taken immediately before intake of investigational medication). The second sample was taken at least 1 hour after intake of investigational medication. Sampling at Weeks 12, 24 and 48 could be done at any given time point after intake of medication; at Week 24, a second sample had tobe taken at any given time point after the first one.
[6] Protein analysis was performed if deemed necessary by the sponsor.
[7] Samples collected at Screening and final/withdrawal visits were tested in real time, and genotypic results provided to investigators. Samples collected at Baseline were analyzed in batches. Samples collected at other intervals could be selected for testing by the Protocol Virologist based on plasma viral load.
[8] Only in selected countries.
[9] Samples were only collected for subjects randomized to TMC125.

Flowcharts After Protocol Amendment IV for Subjects in TMC125 Treatment Group (Post Therapy Switch Treatment Phase)

Type of Visit	Final/Withdrawal Visit	Post Therapy Switch Treatment Phase			
Time of Visit	As soon as possible after communication Nov 28	1-week follow-up	4-week follow-up	12-week follow-up	24-week follow-up
Visit*	13	14	15	-	-
New informed consent for additional follow-up visits**				X	
Urine pregnancy test, if applicable	X		X		
Complete physical examination	X		X		
Brief physical examination		X			
PBMC sample	X				
Hepatitis A, B and C test	X				
T_3 and T_4 test, reflex to TSH if abnormal	X				
Coagulation test	X	X	X		
Hematology and biochemistry (fasting), urinalysis	X	X	X	X	X
Vital signs (pulse, BP, body temperature)	X	X	X		
Plasma viral load	X	X	X	X	X
ECG (central reading)	X				
Weight	X		X		
TMC125 pharmacokinetics [1]	X				
Underlying antiretroviral pharmacokinetics	X				
Samples for phenotype/genotype determinations and for protein analysis [2]	X[3]	X[4]	X[4]	X[3]	X[3]
Immunology	X	X	X	X	X
Concomitant therapy	X	X	X	X	X
Record/Update ART	X	X	X	X	X
Compliance questions	X				
Body Image questionnaire [5]	X				
Observe/Interview for AEs and HIV related events	X	X	X	X	X

* The original visits 13, 14 and 15 of the eCRF could be used. The 12- and 24-week Follow-up Visits were added to the eCRF.

** The investigator informed the subject about the decision of Tibotec to discontinue the trial earlier than planned as soon as possible after the communication on Nov 28, 2005.

[1] Sampling could be done at any given time point.

[2] Protein analysis was performed if deemed necessary by the sponsor.

[3] Samples were tested in real time, and genotypic results provided to investigators.

[4] Samples could be selected by the Protocol Virologist based on plasma viral load.

[5] Only in selected countries.

Flowchart After Protocol Amendment IV for Subjects in Control Group

Type of Visit	Treatment Period	Final/Withdrawal Visit*
Time of Visit	Week 12	Week 24
Visit**	7	13
New informed consent***	X[1]	
Urine pregnancy test, if applicable		X
Complete physical examination		X
PBMC sample		X
Hepatitis A, B and C test		X
T_3 and T_4 test, reflex to TSH if abnormal		X
Coagulation test		X
Hematology and biochemistry (fasting), urinalysis	X	X
Vital signs (pulse, blood pressure, body temperature)		X
Plasma viral load	X	X
ECG (central reading)		X
Weight		X
Samples for phenotype/genotype determinations and sample for protein analysis [2]	X[4]	X[3]
Immunology	X	X
Concomitant therapy	X	X
Compliance questions		X
Body Image questionnaire [5]		X
Observe/Interview for AEs and HIV related events	X	X

* If a subject was beyond Week 24 of treatment in the trial, a Final/Withdrawal Visit was scheduled as soon as possible.
** The original visits 7 and 13 of the eCRF could be used.
*** The investigator informed the subject about the decision of Tibotec to discontinue the trial earlier than planned as soon as possible after the communication on Nov 28, 2005.
[1] If a subject was already beyond the Week 12 visit, the new informed consent was signed at the first following visit.
[2] Protein analysis was performed if deemed necessary by the sponsor.
[3] Samples were tested in real time, and genotypic results provided to investigators.
[4] Samples could be selected by the Protocol Virologist based on plasma viral load.
[5] Only in selected countries.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	Pre Therapy Switch Treatment Phase	
	TMC125 800 mg b.i.d. N = 59	Control N = 57
Demographic Data		
Number of Subjects Entered, M (%) / F (%)	31 (52.5%)/ 28 (47.5%)	28 (49.1%)/ 29 (50.9%)
Age: median (range), yrs	34.0 (23; 50)	36.0 (20; 61)
Weight: median (range), kg	67.6 (39; 91)	69.5 (50; 101)
Ethnic origin, n (%)		
Black	24 (40.7)	23 (40.4)
Caucasian /white	20 (33.9)	21 (36.8)
Asian	10 (16.9)	11 (19.3)
Hispanic	2 (3.4)	1 (1.8)
Other	3 (5.1)	1 (1.8)
Baseline Disease Characteristics		
Log_{10} viral load[a]: median (range), copies/mL	4.31 (2.3; 5.8)	4.33 (2.5; 5.8)
CD4 cell count[a]: median (range), 10^6 cells/L	180.0 (7; 698)	245.0 (9; 527)
CD4 cell count[a]: median (range), %	13.90 (1.3; 35.3)	16.30 (2.6; 31.5)
Duration of known HIV infection at Screening: N	19	24
Median (range), years	3.3 (0.37; 8.64)	3.0 (1.15; 11.16)
CDC Class at Screening, n (%)		
Category A	28 (47.5)	36 (63.2)
Category B	16 (27.1)	10 (17.5)
Category C	15 (25.4)	11 (19.3)
HBsAg, n (%)		
Positive, confirmed	1 (1.7)	2 (3.5)
HCV RNA PCR, n (%)[b]		
Positive	2 (15.4)	1 (20.0)
Baseline Resistance Data Number of mutations, median (range)		
All RT mutations	30 (11; 47)	31 (14; 51)
Tibotec NNRTI RAMs	2 (0; 4)	2 (0; 4)
IAS-USA NNRTI RAMs	1 (0; 3)	1 (0; 4)
IAS-USA NRTI RAMs	2 (0; 6)	1 (0; 7)
NRTI TAM1 mutations	0 (0; 4)	0 (0; 5)
NRTI TAM2 mutations	1 (0; 5)	1 (0; 6)
All protease mutations	10 (3; 14)	10 (4; 18)
IAS-USA PI RAMs	2 (0; 5)	3 (0; 6)
Primary IAS-USA PI mutations	0 (0; 1)	0 (0; 1)
Fold Change in EC_{50} of NNRTIs, median (range)		
Delavirdine	52.8 (0.7; 96.7)	51.3 (0.5; 112.5)
Efavirenz	86.6 (0.6; 12453.4)	126.6 (0.5; 17730.5)
Nevirapine	85.8 (0.8; 139.4)	88.0 (0.4; 129.9)
TMC125	2.0 (0.3; 69.5)	2.1 (0.3; 1074.6)
Previous ARV Experience, n (%)		
Any ARV: ≥ 3	57 (96.9)	55 (96.5)
Any NNRTI: ≥ 1	59 (100)	57 (100)
Any NRTI: ≥ 2	57 (96.9)	55 (96.5)
Any PI: = 1	0	1 (1.8)[c]

[a] Baseline values were imputed by last available value of the screening period if no data at Baseline were available.

[b] Percentage is calculated out of the number of subjects who had a RNA PCR performed.

[c] Subject had previously taken 3 capsules of LPV/rtv (protocol violation).

Baseline Characteristics - Subject Disposition, cont'd		Pre Therapy Switch Treatment Phase	
		TMC125 800 mg b.i.d. N = 59	Control Group N = 57
Individual ARVs in Pre Therapy Switch Treatment Phase			
NRTIs	Abacavir	16 (27.1)	12 (21.1)
	Didanosine	20 (33.9)	16 (28.1)
	Emtricitabine	1 (1.7)	0
	Lamivudine	11 (18.6)	16 (28.1)
	Stavudine	14 (23.7)	12 (21.1)
	Tenofovir	22 (37.3)	30 (52.6)
	Zidovudine	35 (59.3)	29 (50.9)
PIs	Amprenavir	0	1 (1.8)
	Atazanavir	0	18 (31.6)
	Lopinavir	0	36 (63.2)
	Nelfinavir	0	2 (3.5)

		Post Therapy Switch Treatment Phase N = 53
Baseline Disease Characteristics		
Log_{10} viral load [a]: median (range), copies/mL		2.76 (1.7; 5.4)
CD4 cell count[a]: median (range), 10^6 cells/L		229.0 (10.0; 798.0)
CD4 cell count[a]: median (range), %		17.2 (0.8; 35.9)
ARVs in Post Therapy Switch Treatment Phase, n (%)		
Any ARV		44 (83.0)
NRTI + PI		39 (73.6)
NRTI only		2 (3.8)
PI only		3 (5.7)
No ARV		9 (17.0)
Number of ARVs used in Post Therapy Switch Treatment Phase, n (%)		
NRTIs	2	35 (66.0)
	3	6 (11.3)
PIs	1	39 (73.6) [b]
	2	3 (5.7) [c]
Individual ARVs in Post Therapy Switch Treatment Phase, n (%)		
NRTIs	Any	41 (77.4)
	Abacavir	15 (28.3)
	Didanosine	9 (17.0)
	Emtricitabine	2 (3.8)
	Lamivudine	11 (20.8)
	Stavudine	13 (24.5)
	Tenofovir	17 (32.1)
	Zidovudine	21 (39.6)
PIs	Any	42 (79.2)
	Amprenavir	3 (5.7)
	Atazanavir	13 (24.5)
	Indinavir	1 (1.9)
	Lopinavir	27 (50.9)
	Saquinavir	1 (1.9)

[a] Data from therapy switch day, or the data from the immediately preceding time point if this was missing;
[b] 1 subject used single PI and 38 subjects used single PI boosted;
[c] All double PI boosted.

Treatment Duration and Discontinuations	Pre Therapy Switch Treatment Phase	
	TMC125 800 mg b.i.d. N = 59	**Control N = 57**
Duration of Treatment (Weeks)		
Median (range)	14.3 (3.9-32.1)	27.1 (11.1-47.3)
Subject Disposition (n [%])		
Completed	53 (89.8)	53 (93.0)
Total discontinued	6 (10.2%)	4 (7.0%)
Reasons:		
AE/HIV-related event	3 (5.1%)	0
Withdrew consent	1 (1.7%)	1 (1.8%)
Non-compliant	0	2 (3.5%)
Reached virologic endpoint	2 (3.4%)	0
Other	0	1 (1.8%)
	Post Therapy Switch Treatment Phase N = 53	
Duration of Treatment Weeks)		
Median (range)	24.1 (5.0-30.0)	
Subject Disposition (n[%])		
Completed	50 (94.3%)	
Total discontinued	3 (5.7%)	
Reasons:		
Lost to follow-up	1 (1.9%)	
Withdrew consent	1 (1.9%)	
Other	1 (1.9%)	

Efficacy		Pre Therapy Switch Treatment Phase			
		TMC125 800 mg b.i.d. N = 59		**Control N = 57**	
Log_{10} Viral Load (copies/mL)		n	Mean (SD)	n	Mean (SD)
Change from Baseline,	W1	56	-0.88 (0.657)	54	-0.91 (0.411)
	W2	56	-1.26 (0.778)	54	-1.39 (0.603)
	W4	55	-1.50 (0.912)	55	-1.66 (0.697)
	W8	47	-1.57 (1.164)	56	-1.97 (0.661)
	W12	40	-1.39 (1.215)	53	-2.16 (0.902)
	W16	28	-1.13 (1.270)	52	-2.29 (1.034)
	W20	17	-0.99 (1.038)	41	-2.22 (1.106)
	W24	8	-1.51 (0.965)	52	-2.13 (1.244)

Efficacy, cont'd		Pre Therapy Switch Treatment Phase			
		TMC125 800 mg b.i.d. N = 59		Control N = 57	
Virologic response, n (%)					
Viral Load < 50 Copies/mL	W1	1/56 (1.8)		0/54 (0.0)	
	W4	8/55 (14.5)		9/55 (16.4)	
	W8	14/47 (29.8)		16/56 (28.6)	
	W12	10/40 (25.0)		28/53 (52.8)	
	W16	8/28 (28.6)		35/52 (67.3)	
	W24	3/8 (37.5)		33/52 (63.5)	
Viral Load < 400 Copies/mL	W1	10/56 (17.9)		6/54 (11.1)	
	W4	27/55 (49.1)		26/55 (47.3)	
	W8	26/47 (55.3)		39/56 (69.6)	
	W12	19/40 (47.5)		45/53 (84.9)	
	W16	9/28 (32.1)		44/52 (84.6)	
	W24	4/8 (50.0)		41/52 (78.8)	
≥1 Log_{10} Drop in Viral Load	W1				
	W4	38/55 (69.1)		47/55 (85.5)	
	W8				
	W12	24/40 (60.0)		47/53 (88.7)	
	W16				
	W24	6/8 (75.0)		44/52 (84.6)	
CD4+ $x10^6$ cells/L		n	Mean (SD)	n	Mean (SD)
Change from Baseline	W4	53	47.4 (86.9)	51	63.5 (87.5)
	W12	38	41.6 (96.6)	52	78.5 (81.4)
	W24	6	111.8 (119.51)	51	123.5 (121.2)

		Post Therapy Switch Treatment Phase N = 53	
Log_{10} Viral Load (copies/mL)		n	Mean (SD)
Change from Baseline	W4	53	-0.44 (1.30)
	W12	39	-0.56 (1.71)
	W24	49	-0.53 (1.89)

Virologic response cross-tabulation: Post Versus Pre Therapy Switch Treatment Phase at Endpoint n (%)

	Viral Load at Endpoint[a] of Post Therapy Switch Treatment:		
	≥ 50 copies/mL	< 50 copies/mL	Total
Viral Load at Endpoint[a] of Pre Therapy Switch Treatment:			
≥ 50 copies/mL	20 (37.7)	19 (35.8)	39 (73.6)
< 50 copies/mL	3 (5.7)	11 (20.8)	14 (26.4)
Total	23 (43.4)	30 (56.6)	53 (100)

CD4+ $x10^6$ cells/L		n	Mean (SD)
Change from Baseline	W12	39	65.2 (119.5)
	W24	47	35.5 (120.9)

[a] Endpoint: The last time point within the treatment phase of the subject.

Efficacy Conclusions

During the pre therapy switch treatment phase, all virologic response parameters indicated a lower response in the subjects treated with TMC125 compared to the control group.
In the TMC125 group, a mean decrease from Baseline in the log_{10} viral load was observed with -1.50 copies/mL at Week 4, which was maintained up to Week 12 (-1.39 copies/mL). After Week 12, a rebound was observed

(-0.99 copies/mL at Week 20).
In the control group, the mean change from Baseline in $\log_{10}$ viral load was -1.66 copies/mL at Week 4, -2.16 copies/mL at Week 12, and remained the same up to Week 24 (-2.13 copies/mL).
At Week 12, the virologic response was lower in the TMC125 group compared to the control group (< 50 copies/mL: 25.0% vs 52.8%; < 400 copies/mL: 47.5% vs 84.9%; > 1 $\log_{10}$ drop: 60.0% vs 88.7%).
Median baseline CD4 cell counts were 180.0 x 10^6 cells/L in the TMC125 group and 245.0 x 10^6 cells/L in the control group. In both treatment groups, CD4 cell counts increased over time. The mean increase in CD4 cell counts was greater in the control group (Week 12: +41.6 x 10^6 cells/L in the TMC125 group and +78.5 x 10^6 cells/L in the control group; Week 24: +111.8 x 10^6 cells/L in the TMC125 group [N=6]) and +123.5 x 10^6 cells/L for the control group [N=51]).

During the post therapy switch treatment phase, a decrease in mean $\log_{10}$ plasma viral load was observed from the post therapy switch treatment phase Baseline (approximately –0.5 copies/mL at Weeks 12 and 24).
Cross tabulation of the number of subjects with < 50 copies/mL and ≥ 50 copies/mL in the post therapy switch treatment phase versus the pre therapy switch treatment phase at endpoint showed that from the 14 subjects (out of 53 subjects) with a viral load < 50 copies/mL at endpoint of the pre therapy switch treatment phase, 11 subjects retained a viral load < 50 copies/mL and 3 subjects had a viral load ≥ 50 copies/mL at endpoint of the post therapy switch treatment phase.
During the post therapy switch treatment phase, an increase in mean CD4 cell count was observed from the post therapy switch treatment phase Baseline (+65 x 10^6 cells/L at Week 12 and +36 x 10^6 cells/L at Week 24).

Resistance Determinations

Analysis of the resistance data of the TMC125 treatment group in the pre therapy switch treatment phase showed the following trends (note that the numbers of subjects per subgroup were small):

- A lesser viral load response was observed:
  - in all subgroups with 1 or more detectable NNRTI resistance-associated mutations at Baseline compared to the subgroup without detectable NNRTI RAMs at Baseline;
  - in subjects who had the NNRTI mutation Y181C, but not K103N, at Baseline;
  - in subjects with a baseline TMC125 FC ≥ 10;
  - in subjects with a higher number of baseline NRTI RAMs (IAS-USA NRTI RAMs) or TAMs.
- A better viral load response was observed:
  - in subjects using 2 sensitive NRTIs compared with 1 sensitive NRTI in the underlying ART;
  - in subjects with a baseline TMC125 FC < 4.

Emergence of both NNRTI and NRTI mutations was observed in a substantial number of subjects failing or not responding to the TMC125 containing regimen: 57% (17 of 30) of subjects showed additional Tibotec NNRTI RAMs, 27% (8 of 30) of subjects showed additional IAS-USA NRTI RAMs.

Safety	Pre Therapy Switch Treatment Phase	
	TMC125 800 mg b.i.d. N = 59	**Control N = 57**
Most frequently reported AEs (> 5% subjects in either treatment group), n (%)		
Nausea	10 (16.9)	6 (10.5)
Diarrhea	8 (13.6)	16 (28.1)
Headache	8 (13.6)	10 (17.5)
Upper respiratory tract infection	5 (8.5)	10 (17.5)
Lower respiratory tract infection	5 (8.5)	2 (3.5)
Pruritus	5 (8.5)	1 (1.8)
Vomiting	4 (6.8)	2 (3.5)
Dry skin	2 (3.4)	5 (8.8)
Loose stools	2 (3.4)	10 (17.5)
Herpes simplex	1 (1.7)	5 (8.8)
n (%) with 1 or more AEs	48 (81.4)	51 (89.5)
n (%) of deaths	0	0
n (%) with 1 or more other serious AEs	2 (3.4)	2 (3.5)
n (%) of treatment stopped due to AEs	3 (5.1)	0
n (%) with 1 or more grade 3 or 4 AEs	8 (13.6)	10 (17.5)
Laboratory Safety:		
n (%) with 1 or more treatment-emergent lab abnormalities of Grade 3	5 (8.5)	15 (26.3)
Grade 4	3 (5.1)	3 (5.3)
	No clinically meaningful changes over time were observed in the laboratory parameters in both treatment groups.	
Cardiovascular Safety	There were no obvious significant changes or trends over time in any of the cardiovascular safety parameters	

	Post Therapy Switch Treatment Phase N = 53
Most frequently reported AEs (> 5% subjects), n (%)	
Diarrhea	13 (24.5)
Nausea	7 (13.2)
Upper respiratory tract infection	6 (11.3)
Hyperbilirubinemia	4 (7.5)
Loose stools	3 (5.7)
Vomiting	3 (5.7)
n (%) with 1 or more AEs	38 (71.7%)
n (%) of deaths	0
n (%) with 1 or more other serious AEs	2 (3.4)
n (%) of treatment stopped due to AEs	0
n (%) with 1 or more grade 3 or 4 AEs	14 (26.4)
Laboratory Safety:	
n (%) with 1 or more treatment-emergent lab abnormalities of Grade 3	20 (37.7)
Grade 4	6 (11.3)
	There were no obvious significant changes or trends over time in any of the laboratory parameters

Cardiovascular Safety	There were no obvious significant changes or trends over time in any of the cardiovascular safety parameters

Safety Conclusions

In the pre therapy switch treatment phase, 48 (81.4%) subjects reported at least 1 AE in the TMC125 group. In the control group, 51 (89.5%) subjects reported at least 1 AE (note: difference in duration of therapy between the 2 groups).
By preferred term, the most common AEs (incidence ≥10%) were nausea (16.9%), diarrhea (13.6%), and headache (13.6%) in the TMC125 group, and diarrhea (28.1%), loose stools (17.5%), upper respiratory tract infection (17.5%), headache (17.5%), and nausea (10.5%) in the control group.
The majority of events were graded 1 or 2 in severity. Grade 3 or 4 AEs occurred in 8 (13.6%) subjects in the TMC125 group and in 10 (17.5%) subjects in the control group. Grade 3 or 4 AEs were mostly single events and did not occur in more than 2 subjects.
No subjects died during the trial. Two subjects in both the TMC125 and control group had 1 or more SAEs. In the TMC125 group, 1 subject was hospitalized for a blood transfusion (preferred term: anemia) and 1 subject was hospitalized for pulmonary tuberculosis. In the control group, 1 subject was hospitalized for quadriceps adherence surgery and 1 subject was hospitalized for corrective surgery of a nasal septum dysmorphy (preferred term: nasal septum disorder).
Three subjects permanently discontinued TMC125 because of AEs (pulmonary tuberculosis [not related], angioneurotic edema [probably related], and angioneurotic edema [probably related] with maculopapular rash [possibly related]). No subjects in the control group discontinued treatment due to an AE.
No clinically meaningful changes over time were observed in the laboratory parameters in both treatment groups. In total, 7 subjects (11.9%) in the TMC125 group and 16 subjects (28.1%) in the control group had grade 3 or 4 laboratory abnormalities. In the TMC125 group, all grade 3 or 4 abnormalities were single events.

There were no obvious significant changes or trends over time in any of the cardiovascular safety parameters, and there were no other significant safety findings.

Safety Conclusions, cont'd

In the post therapy switch treatment phase (subjects who received TMC125 in the pre therapy switch treatment phase and were switched to an investigator-selected ART), the most common AEs (incidence ≥10%) were diarrhea (24.5%), nausea (13.2%), and upper respiratory tract infection (11.3%). Most AEs were grade 1 or 2 in severity. Grade 3 or 4 AEs were mostly single events and did not occur in more than 2 subjects.
Two subjects had SAEs during the post therapy switch treatment phase, one with anemia (the same subject as in the pre therapy switch treatment phase) and one with increased transaminases (not considered related to treatment).
There were no discontinuations from this phase of the study due to AEs.
There were no obvious significant changes or trends over time in any of the laboratory and cardiovascular safety parameters, and no other significant safety findings.

Pharmacokinetics of TMC125 (Substudy)	**TMC125 800 mg b.i.d.**	
Meaṇ (SD), t_{max}: median (range)	**Day 1 (n =12)**	**Week 4 (n = 11)**
t_{max}, h	4.00 (2.00 - 10.00)	4.00 (0.00 - 10.00)
C_{0h}, ng/mL		384.5 (242.6)
C_{min}, ng/mL		317.8 (199.7)
C_{12h}, ng/mL		377.9 (284.3)
C_{max}, ng/mL	178.7 (213.3)	528.5 (314.2)
AUC_{12h}, ng.h/mL	1148 (1186)	5165 (3238)
$C_{ss, av}$, ng/mL		430.4 (269.9)

FI, %		50.86 (19.12)
Acc. Index		8.366 (8.833)

Pharmacokinetics of TMC125 (Population Pharmacokinetics)

Parameter	N	Mean (SD)	Geometric Mean	Median	Minimum	Maximum
AUC_{12h} (ng.h/mL)	51	4608.8 (2380.56)	3987.2	4521	1129	11068
C_{0h} (ng/mL)	51	275.3 (158.10)	231.2	257.2	61	737
IQ_{C0h}	45	557 (734)				
$IQ_{Css,av}$	45	773 (948)				

Pharmacokinetics

Pharmacokinetic substudy:

Mean plasma concentrations of TMC125 on Day 1 were approximately 100 ng/mL. The mean plasma concentrations in Week 4 lay between 376 ng/mL and 475 ng/mL. At Week 4, morning and evening predose concentrations were comparable (mean values of 385 and 378 ng/mL, respectively). The interindividual variation (%CV) was 119% for C_{max} and 103% for AUC_{12h} on Day 1 compared to 59% for C_{max} and 63% for AUC_{12h} at Week 4.

The mean accumulation index, comparing AUC_{12h} at Week 4 compared that on Day 1, was 8.4, but inter-subject variation in the accumulation index was high. The accumulation index varied between 1.0 and 31.7 with a %CV of 106%. The geometric mean of the accumulation index was 5.7. On Day 1, mean values for C_{max} and AUC_{12h} were 179 ng/mL and 1148 ng.h/mL, respectively. In Week 4, mean values for C_{min}, C_{max} and AUC_{12h} were 318 ng/mL, 529 ng/mL and 5165 ng.h/mL, respectively. The t_{max} at Week 4 showed no time-dependency.

Population pharmacokinetics:

In general, the estimated pharmacokinetic parameters for TMC125 were slightly lower but in the same range as those observed in the pharmacokinetic substudy.

PK/PD Relationships

The mean reduction from Baseline in plasma viral load appeared to be higher in the 2 quartiles with the highest TMC125 exposure.

Subjects with low IQ_{C0h} values had a lesser virologic response than subjects with higher IQ values. Similar results were obtained with analyses for $IQ_{Css,av}$, indicating that the combined effect of pharmacokinetics and TMC125 FC influenced the virologic response.

Graphically, no relationship was observed between TMC125 exposure and occurrence of AEs of interest or maximum change from Baseline in laboratory parameters.

Conclusions

The results of the final analysis of trial TMC125-C227 demonstrated that TMC125-treated subjects, while exhibiting a substantial mean decrease in viral load, had inferior responses compared with the control PI-treated subjects. This was affected in a large part by reduced susceptibility to the NRTI backbone. Additionally, some subjects had reduced susceptibility to TMC125, while, since these subjects were PI-naïve, all of them retained full susceptibility to the PI used in the control group. Since a boosted PI has been shown by itself (in the context of chronic monotherapy) to lead most PI-naïve subjects to undetectability, reduced background NRTI susceptibility had little or no impact in the efficacy of the control arm. Therefore, it is clear that in the context of reduced background efficacy, subjects receiving TMC125 were very likely to have had reduced responses compared to the control arm.

Recent presentations have documented high levels of NRTI and NNRTI resistance in subjects failing first line therapy in the developing world. In hindsight, it was not likely that, in this setting of high NRTI resistance, TMC125 could perform as well as a boosted PI in NNRTI resistant but PI-naïve patients. However, TMC125 retains potent in vitro and in vivo activity against a large subset of NNRTI resistant isolates and with an appropriate

background therapy should constitute a useful active agent in the armamentarium against drug resistant HIV infection. Therefore, the results of this trial should not lead to ascertain the efficacy of TMC125 in subjects with NNRTI resistance, but simply suggest that TMC125 should not be used with 2 NRTIs in subjects failing EFV or NVP and 2 NRTIs, especially in the situation where multiple NNRTI and NRTI mutations have developed. Ongoing Phase III studies will help to better define the role of TMC125 in patients with NNRTI resistant viruses.

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