SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: - **Indication**: HIV-1 Infection	**Drug Substance**: TMC125 **Trial no.**: TMC125-C211 **Clinical Phase**: IIb
Title: An open-label trial of TMC125 in HIV-1 infected subjects who were randomized in any sponsor-selected TMC125 trial to an active control arm and either virologically failed or completed the entire treatment period, or to a placebo arm and were treated for at least 48 weeks.	
Investigator: C. Hicks, Division of Infectious Diseases, Duke University Medical Center, Durham, NC27710, United States	**Country**: United States, Canada, Italy, Belgium, Spain, France, Poland, Portugal.
Trial Period: Start: 27-Sep-2004 End: 20-Mar-2007	**No. of Investigators**: 33 **No. of Subjects**: 43
Objectives: The primary objective of this study was to evaluate the long-term safety and tolerability of TMC125. Secondary objectives were to evaluate the antiviral activity and immunological effect of TMC125 as part of an ARV regimen over time, and to evaluate genotypic and phenotypic changes over time.	
Design: This was a Phase IIb, open-label, rollover trial to evaluate the long-term safety and tolerability of TMC125, administered as part of an individually optimized antiretroviral therapy, in HIV-1 infected subjects. In addition, the antiviral activity and immunological effect of TMC125 as part of an antiretroviral regimen over time, and the evolution of HIV phenotype and genotype were evaluated. Subjects who were randomized to an active control arm of any sponsor-selected TMC125 trial and virologically failed or completed the entire treatment period, or who were randomized in a fully blinded TMC125 trial, being unblinded after treatment for at least 48 weeks and identified as having received placebo and who might have derived benefit from TMC125 treatment as judged by the investigator could be enrolled. TMC125 800 mg b.i.d. (formulation TF035) and, after the formulation switch, 200 mg b.i.d. (formulation F060) was given in combination with an investigator-selected, optimized underlying therapy starting at Baseline and consisting of at least 2 drugs (NRTIs and/or allowed PIs and/or ENF) for 48 weeks. Tolerability and safety were assessed throughout the trial. The efficacy parameters were determined at defined time-points during the trial. The trial involved a screening visit, preferably on the same day as the withdrawal visit of the sponsor-selected trial, a baseline visit, a treatment period of 48 weeks, a final visit and a 4-week follow-up period.	
Subject Selection Inclusion Criteria 1. Subject had signed the Informed Consent Form (ICF) voluntarily; 2. Male or female subject, aged 18 years and above; 3. Subject having previously been randomized to an active control arm of a sponsor-selected TMC125 trial and having completed the entire treatment period or having met the definition of virological failure, as defined in the original protocol, before TMC125-C211 screening or subjects who were randomized in a fully blinded TMC125 trial, being unblinded after treatment for at least 48 weeks and identified as having received placebo; 4. Subject agreed to take TMC125 in combination with the investigator-selected combination therapy consisting of at least 2 drugs (NRTIs and/or allowed PI and/or ENF; low-dose ritonavir [≤ 400 mg daily dose] was not counted as a separate ARV); 5. Subject could comply with the protocol requirements; 6. Subject's general medical condition, in the investigator's opinion, did not interfere with the assessments and the completion of the trial. Exclusion Criteria	

1. Use of disallowed concomitant therapy;
2. History of or currently active alcohol or substance use which in the investigator's opinion would likely have compromised the subject's safety or compliance with the study procedures;
3. Any active clinically significant disease (e.g., tuberculosis, cardiac dysfunction) or findings during physical examination that, in the investigator's opinion, would have compromised the subject's safety;
4. Pregnant or breastfeeding female;
5. Female subject 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 the last intake of investigational medication):
   Note: Hormonal based contraception may not be reliable when taking TMC125, therefore to be eligible for this study, women of childbearing potential had to either:
   (1) use a double barrier method to prevent pregnancy (i.e., using a condom with either spermicidal cream/ foam/ gel or diaphragm or cervical cap), or
   (2) 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
   (3) use an intra-uterine device in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap with spermicide or female condom with spermicide), or
   (4) be non-heterosexually active, practice sexual abstinence or have a vasectomized partner.
   Note: Women who were postmenopausal for at least 2 years, women with total hysterectomy and women who had undergone a tubal ligation were considered of non-childbearing potential;
6. Renal impairment as defined by serum creatinine > 2 x upper limit of normal (ULN);
7. Any grade 3 or grade 4 toxicity according to the ACTG grading severity list (except for grade 3 glucose and asymptomatic triglyceride/cholesterol grade 3 or 4 elevations; or asymptomatic and isolated grade 3 or 4 elevations in gamma-glutamyl transferase [GGT] with all other liver enzymes and bilirubin within normal ranges, or isolated grade 3 elevation in amylase with no increase in lipase and no history of pancreatitis);
8. Subjects with clinical or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels (International Normalized Ratio > 1.3 or albumin < 30 g/L or direct bilirubin > 2.5 x ULN).

Treatment	**TMC125**	
Concentration	800 mg b.i.d. or, after formulation switch, 200 mg b.i.d.	
Dosage Form (TF No.)	200 mg tablets b.i.d. (TF035); 100 mg tablets b.i.d. (F060)	
Usage	Oral	
Batch Number	**Formulation TF035** D03106, D04210, D04255, D04256	**Formulation F060** 05H25, 05E24, 05E03, 05E11, 05E10, 05D26, 05D25, 05D23, 05E02, 05D07, 05D06
Dose Regimen	TMC125 800 mg b.i.d. (4 tablets TF035 b.i.d.) or after formulation switch, TMC125 200 mg b.i.d. (2 tablets F060 b.i.d.) + Underlying ART consisting of: OBR: at least 2 ARV drugs: NRTI(s) and/or allowed PI(s) and/or ENF	
Duration of Treatment	48 weeks	
Duration of Trial	48 weeks (excluding Screening and follow-up)	
Disallowed Medication	**Disallowed Antiretroviral Therapy** The following ARV drugs were not allowed from Baseline and throughout the trial: - PIs: use of PIs other than the combinations of LPV/rtv 400/100 mg b.i.d., SQV/rtv 1000/100 mg b.i.d., ATV/rtv 300/100 mg q.d. and SQV/LPV/rtv 1000/400/100 mg b.i.d. SQV could be administered as Fortovase or Invirase. SQV or ATV was not to be used without low-dose ritonavir when combined with TMC125. - NNRTIs: use of any other than TMC125.	

	Disallowed Concomitant (non-ARV) Therapy
	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 throughout the trial (except for tenofovir, emtricitabine, ENF where these were not yet licensed in a participating country);
	• Drugs that could 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 3A4 inducers:
	  ➢ Rifamycins: rifabutin, rifampicin/rifampin,
	  ➢ Anticonvulsants: phenobarbital, phenytoin, carbamazepine,
	  ➢ Systemic dexamethasone,
	  ➢ All products containing *Hypericum perforatum* (St John's Wort);
	• Cytochrome P450 3A4 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. In the event that there was a need to introduce these drugs during the trial, dosage and regimen had to be discussed in advance with the sponsor;
	• Cytochrome P450 3A4 substrates with a small therapeutic index:
	  ➢ Terfenadine, astemizole, cisapride, triazolam, and midazolam;
	  ➢ Investigators were 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 was 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 antimigraine ergotamines, dihydroergotamine, ergonovine, methylergonovine, ergotaminetartrate and other ergot derivates;
	• The lipid lowering agents simvastatin, lovastatin, cholestyramine and colestipol;
	• Cyclosporin, tacrolimus, warfarin, digoxin;
	• Immunomodulators: systemic corticosteroids, interleukins, 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.

Statistical Methods	Intent to treat (ITT) analysis, descriptive statistics, frequency tabulations Wilcoxon matched-pairs signed-ranks test, Kaplan-Meier curves.

Type of visit	Withdrawal visit previous TMC125 trial	Screening [1]	Baseline [2]	Treatment period [3]									Final\ withdrawal visit	Post treatment follow-up period	
Time of Visit			Day 1	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	Week 1 follow-up visit	Week 4 follow-up visit
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Informed consent		X													
Urine pregnancy test , if applicable	X		X			X	X	X	X	X	X	X	X		X
Inclusion/exclusion criteria		X													
Complete physical examination	X		X				X	X		X			X		X
Brief physical examination				X[4]	X[4]	X			X		X	X			
PBMC sample	X		X							X			X		
Hepatitis A, B and C test [5]	X						X			X			X		
T_3, T_4 and TSH testing[5]	X		X				X	X		X			X		
Coagulation test [8]	X		X		X	**X**	X	X	X	X	X	X	X	X	X
Hematology & biochemistry (10 h fasting) , Urinalysis	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
ECG (central reading)	X		X					X		X			X		
Weight	X		X			X	X	X	X	X	X	X	X		X
TMC125 pharmacokinetics [6]						X		X		X			X		
Samples for phenotype/genotype determinations [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Samples for protein analysis					X	X		X		X			X		
Plasma viral load	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Immunology	X		X		X	X	X	X	X	X	X	X	X		X
Dispensation of investigational medication			X		X	X	X	X	X	X	X	X			
Concomitant therapy	X		X	X	X	X	X	X	X	X	X	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	X

1) Screening visit preferably took place on the same day as the withdrawal visit of the sponsor-selected TMC125 trial. Overlapping assessments from the original trial to the TMC125-211 were only conducted once. In case the original trial was not immediately followed by trial TMC125-C211 all assessments needed to be performed.
2) Baseline visit could be scheduled as soon as results of screening assessments were known, showing the subject to be eligible for inclusion. In case the baseline visit was performed within 14 days of the screening visit only the concomitant therapy and the AE/HIV related events needed checked and the investigational medication was dispensed. ART could be modified at Baseline.
3) Unscheduled visits could be performed for safety / tolerability reasons and for a confirmatory plasma viral load.
4) Only a skin examination was to be performed at Week 1 and Week 2.
5) Whenever clinically relevant, extra tests could be done at other visits.
6) Pharmacokinetic samples were taken and only analyzed upon sponsor specific request. Samples could be taken at any given time point before or after intake of study medication.
7) Samples collected at Screening and Final/withdrawal visits were tested in real time for the determination of the virco®TYPE HIV-1. Screening and Final/withdrawal visit virco®TYPE HIV-1 results were provided to the investigators. Baseline samples were tested in batches; reports were not provided. Samples collected at other intervals could be selected for testing by the Protocol Virologist based on viral load; reports were not provided.
9) Coagulation test consisted of measurement of PT, PTT and calculation of INR.

Main Features of the Subject Sample and Summary of the Results

Subject Dispostion Discontinuations and Treatment Duration	**TMC125 N = 43**
Discontinuations – Reason, n (%)	***14 (32.6)***
Adverse event/HIV related event	6 (14.0)
Subject reached a virologic endpoint	4 (9.3)
Subject lost to follow-up	1 (2.3)
Subject withdrew consent	1 (2.3)
Subject noncompliant	1 (2.3)
Subject ineligible to continue the trial	1 (2.3)
Duration of Treatment	
Median (range), weeks	48.1 (1.7 - 54.4)
Total patient-years of exposure	33.2

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

Baseline Characteristics	**TMC125 N = 43**
Demographic Data	
Gender, n (%)	
Female	3 (7.0)
Male	40 (93.0)
Age: median (range), years	45.0 (18 – 58)
Weight: median (range), kg	76.9 (44 – 157)
BMI: median (range), kg/m^2	24.3 (19 – 50)
Ethnic Origin, n (%)	
Caucasian	32 (74.4)
Black	8 (18.6)
Hispanic	2 (4.7)
Other	1 (2.3)
Baseline Disease Characteristics*	
Viral load: median (range), copies/mL	16630 (49 – 651,220)
Log_{10} viral load: median (range), copies/mL	4.2 (1.7 – 5.8)
CD4+ cell count: median (range), 10^6 cells/L	158.0 (1.0 – 671.0)
Duration of known HIV infection: median (range), years	15.2 (2.9 - 22.9)
CDC Category, n (%)	
Category A	8 (18.6)
Category B	7 (16.3)
Category C	28 (65.1)
HBV – HBsAg Positive, n (%)	2 (4.7)
Active HCV infection , n (%)	2 (4.7)
Hepatitis B and/or C co-infection	3 (7.0)

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

* at Baseline of TMC125-C211 trial

Previous ARV experience, n (%)	**TMC125 N = 43**
NNRTI	
≥ 1	39 (90.7)
NRTI	
≥ 3	42 (97.8)
PI	
≥ 3	36 (83.8)
Fusion Inhibitor	
1	24 (55.8)

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

Baseline Resistance Data	**TMC125 N = 43**
Baseline RT Mutations, median (range)	
Tibotec NNRTI RAMs[a]	2 (0 – 6)
TMC125 RAMs[a]	1 (0 – 4)
IAS – USA NNRTI RAMs[b]	1 (0 – 3)
IAS – USA NRTI RAMs[b]	6 (1 – 11)
Baseline FC NNRTIs, median (range)	
Nevirapine (NVP)	59.7 (0.2 – 153.5)
Delavirdine (DLV)	26.3 (0.4 – 247.7)
Efavirenz (EFV)	12.3 (0.4 – 15693)
TMC125	1.7 (0.1 – 578.4)

N = number of subjects; n = number of subjects with observations.
[a] Based on the Tibotec extended list of mutations[2].
[b] Based on the November 2005 IAS-USA list of mutations[1].

Underlying ART During the Treatment Period	TMC125 N = 43
Number of ARVs in Underlying ART, n (%)	
Any ARV	
2	5 (11.6)
3	16 (37.2)
4	14 (32.6)
5	4 (9.3)
6	3 (7.0)
7	1 (2.3)
NRTI	
0	1 (2.3)[a]
1	5 (11.6)
2	23 (53.5)
3	11 (25.6)
4	2 (4.7)
5	1 (2.3)
PI	
0	12 (27.9)
1	27 (62.8)
2	4 (9.3)
FI	
0	16 (37.2)
1	27 (62.8)
Individual ARVs in Underlying ART, n (%)	
PI	
Lopinavir (LPV)	24 (55.8)
Saquinavir (SQV)	5 (11.6)
Atazanavir (ATV)	2 (4.7)
Tipranavir (TPV)[b]	2 (4.7)
Amprenavir (APV)[b]	1 (2.3)
Indinavir (IDV)[b]	1 (2.3)
NRTI	
Tenofovir (TDF)	31 (72.1)
Lamivudine (3TC)	21 (48.8)
Didanosine (ddI)	14 (32.6)
Emtricitabine (FTC)	12 (27.9)
Stavudine (d4T)	9 (20.9)
Zidovudine (AZT)	5 (11.6)
Abacavir (ABC)	5 (11.6)
FI	
Enfuvirtide (ENF)	27 (62.8)
De novo[c]	7 (16.3)
Re-using	20 (46.5)

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

[a] One subject (211-2402) was a protocol violator as no NRTI was recorded as part of the OBR.

[b] Three subjects used at least one disallowed PI during the treatment period (protocol violators). Subject 211-5601 took IDV for 2 months, subject 211-7012 took DRV for 4 months, TPV for 6 weeks and APV for approximately 4 months and subject 211-7016 took TPV for 16 days.

[c] *De novo* use = ENF not previously used up to Baseline

Only the initial therapies (i.e., as determined on Day 7) were considered

Sensitivity of Underlying ARVs During the Treatment Period[a,b]	**TMC125 N = 43**
Number of Sensitive ARVs (Antivirogram®) in Underlying ART, n (%)	
Any ARV	
0	13 (30.2)
1	14 (32.6)
2	12 (27.9)
3	3 (7.0)
4	1 (2.3)
NRTI	
0	15 (35.7)
1	17 (40.5)
2	9 (21.4)
3	1 (2.4)
PI	
0	23 (79.3)
1	6 (20.7)
FI	
0	20 (74.1)
1	7 (25.9)

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

[a] TMC125 was not included in the calculation. Sensitivity was based on Antivirogram®. ENF was counted as sensitive if it had not been used previously.

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

Safety	**TMC125 N = 43**
Treatment-Emergent AEs (Treatment Period)	
Most frequently reported AEs[a], n (%)	
Nausea	9 (20.9)
Fatigue	7 (16.3)
Diarrhea	6 (14.0)
Injection site reaction	6 (14.0)
Flatulence	5 (11.6)
Upper respiratory tract infection	5 (11.6)
n (%) with 1 or more AEs	42 (97.7)
n (%) of deaths during treatment[b]	2 (4.7)
n (%) with one or more serious AEs	7 (16.3)
n (%) of treatment discontinued due to AEs	6 (14.0)
n (%) with one or more grade 3 or 4 AEs	15 (34.9)
Treatment-Emergent AEs of Interest	
n (%) with any skin event of interest	14 (32.6)
n (%) with rash (any type)	13 (30.2)
n (%) with any neuropsychiatric event of interest	16 (37.2)
n (%) with nervous system event of interest	10 (23.3)
n (%) with psychiatric event	10 (23.3)
n (%) with any hepatic event	4 (9.3)
n (%) with hepatobiliary disorders	2 (4.7)
n (%) with any cardiac event	2 (4.7)
n (%) with any bleeding event	4 (9.3)
n (%) with any pancreatic event	1 (2.3)
n (%) with pancreatitis	1 (2.3)

N = number of subjects; n = number of patients with observations.
[a] Individual preferred terms in at least 10% (rounded %) of subjects.
[b] One additional subject died during follow up

During the 48-week treatment period, 97.7% of subjects reported at least 1 AE, with the most common AEs (individual preferred terms at least 10.0%) being nausea, fatigue, diarrhea, injection site reaction, flatulence and upper respiratory tract infection. Most AEs were grade 1 or 2 in severity. No consistent pattern of individual grade 3 or 4 AEs was seen. Two subjects died during the treatment period and 1 subject died during the follow-up period. None of the deaths were considered related to TMC125. SAEs were reported in 7 subjects (16.3%) during TMC125 treatment. All but one SAE (dehydration, which occurred in 2 subjects) occurred in only 1 subject each. The incidence of SAEs at least possibly related to investigational medication was 4.7% (2 subjects). Six subjects permanently discontinued trial treatment due to AEs with the most common AE (> 1 subject) being abdominal pain upper (2 subjects, 4.7%). Rash (any type, grouped term) was reported in 13 subjects (30.2%). Most rashes were grade 1 or 2 in severity. Grade 3 rash occurred in 1 subject who discontinued TMC125 as a result of this event. Neuropsychiatric events of interest occurred in 16 subjects (37.2%). Hepatic events, cardiac events, bleeding events and pancreatic events were generally low in incidence (< 10%) and of grade 1 or 2 in severity.

Clinical Laboratory Tests	***TMC125 N = 43***
Treatment emergent laboratory data	
n (%) with any grade 1 abnormality	39 (90.7)
n (%) with any grade 2 abnormality	32 (74.4)
n (%) with any grade 3/4 abnormality	14 (32.6)
n (%) with any grade 3 abnormality	14 (32.6)
n (%) with any grade 4 abnormality	3 (7.0)

The overall incidence of laboratory abnormalities was low and no clinically relevant mean changes from Baseline were observed for any laboratory test parameter. The majority of graded laboratory abnormalities was grade 1 or 2 in severity. Treatment-emergent grade 3 laboratory abnormalities occurred in 14 (32.6%) subjects and three (7.0%) subjects had a treatment-emergent grade 4 laboratory abnormality. The most common treatment-emergent grade 3 or 4 laboratory abnormalities were increases in triglycerides experienced in 5 subjects (11.9%) and a decrease in neutrophil count experienced in 3 subjects (7.0%).

Cardiovascular Safety

Small mean changes from Baseline were observed for vital signs or ECG parameters. None of the changes over time or treatment-emergent individual abnormalities were considered clinically relevant.

Other Safety Parameters

There were no clinically relevant changes over time in physical examination findings.

Efficacy

Parameter	**TMC125 N = 43**
Log_{10} viral load: mean change (SE) from Baseline (copies/mL)	
Week 24	-0.64 (0.165)
Week 48	-0.57 (0.145)
Virologic Response Rate (TLOVR), n (%)	
Viral load < 50 copies/mL	
Week 24	12 (27.9)
Week 48	9 (20.9)
Viral load < 400 copies/mL	
Week 24	19 (44.2)
Week 48	16 (37.2)
Viral load decrease ≥ 1.0 log_{10} copies/mL	
Week 24	13 (30.2)
Week 48	10 (23.3)
Immunologic change[a]: mean change (SE)	
CD4+ cell count (x 10^6 cells/L)	
Week 24	+ 25.2 (14.9)
Week 48	+33.4 (16.4)

The efficacy results of this trial showed that treatment with TMC125 as part of an individually optimized ART resulted in a substantial initial mean decrease in plasma viral load from Baseline of approximately -1.1 log_{10} copies/mL after 4 weeks of treatment. The initial response was followed by a subsequent loss of response with gradual rebound towards Baseline (approximately -0.6 log_{10} copies/mL at Week 48). Secondary efficacy parameters were in line with the results for the primary efficacy parameter. The mean imputed CD4+ cell count reached approximately 258 x 10^6 cells/L at Week 32, after which a downward trend was seen. The mean change from Baseline at Week 48 in CD4+ cell count (imputed data) was +33.4 x 10^6 cells/L.

N = number of subjects; n = number of observations; SE = standard error

[a] NC = F.

Conclusions

Trial TMC125-C211 was a rollover trial for subjects not virologically suppressed in the control groups of other Phase II trials, and as such had failed an additional ART compared to subjects in the originating trials. The subjects had high levels of ARV resistance at trial entry. Results confirmed the long-term safety and tolerability of the TMC125 800 mg b.i.d. (TF035) or 200 mg b.i.d (F060) treatment regimens in this patient population. The safety profile was consistent with the safety profile observed in other trials. Most AEs were grade 1 or 2 in severity and infrequently led to discontinuation. No new safety signals were identified. No consistent or clinically relevant changes in laboratory, vital signs or ECG parameters were observed. The antiviral activity of TMC125 in this population was demonstrated by a substantial initial mean decrease in plasma viral load from Baseline. This was followed by a subsequent loss of response. The lack of durability of the response is very likely due to multiple

factors, including a high degree of ARV experience and/or resistance at trial entry and limited activity of the background ARVs in the majority of subjects. These results are consistent with current treatment guidelines that recommend at least 2 active agents in treatment-experienced patients to increase the likelihood of substantial and sustained virologic response.

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