SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: Prezista™ **Indication**: HIV-1 infection	**Drug Substance**: Darunavir **Trial no.**: TMC114-C202 **Clinical Phase**: II
Title: A Phase II, randomized, controlled, partially blinded trial to investigate the efficacy, safety, and dose-response relationship of TMC114/ritonavir in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of TMC114/ritonavir. Analysis with cut-off date of 18 December 2006, at which time all subjects had reached Week 96 or discontinued before.	
Investigator: D. Berger, M.D., Northstar Medical Center, [redacted] USA	**Country**: USA, Argentina
Trial Period: Start: 17-Sep-2003 End: 18-Dec-2006 (cut-off date for LPLV for Week 96 analysis)	**No. of Investigators**: 50 **No. of Subjects**: 319

Objectives:

In the original protocol, the primary objective was to evaluate the dose-response relationship of antiviral activity of the DRV/rtv dose regimens at 24 weeks in order to determine the recommended dose. The selection of the recommended dose was based on the combined interim analyses as defined per amended protocol, which included 150 subjects in each of the two dose-finding trials (TMC114-C202 + TMC114-C213) who reached Weeks 16 and 24 or discontinued earlier.

The amended primary objective of the dose-finding part of this trial was to compare all DRV/rtv dose groups with control at Week 24 (the primary endpoint) by means of the confirmed virologic response (TLOVR), defined as a drop in viral load of at least 1.0 $\log_{10}$ versus baseline. The cut-off date for the primary efficacy analysis was set at February 1, 2005. At that time, 201 of the 278 subjects reached 24 weeks of treatment or discontinued earlier in the TMC114-C202 trial.

Secondary objectives were:

- to evaluate safety and tolerability up to 144 weeks per current protocol;
- to evaluate the durability of the antiviral activity;
- to evaluate the effect of the functional monotherapy with DRV over 2 weeks in different doses;
- to investigate the dose-response by comparing the virologic response and safety parameters at different DRV/rtv doses and exposure.

The objective of this Week 96 analysis is to update earlier analyses to evaluate safety, tolerability and durability of antiviral activity of DRV up to Week 96, and to compare this to the control arm. The primary focus is on subjects who were randomized to DRV/rtv 600/100 mg b.i.d. and control.

Design: The ongoing TMC114-C202 trial consists of 2 parts, a dose-finding and an open-label part. In the initial partially blinded dose-finding part, subjects received either control PI-based treatment (standard of care) or 1 of 4 DRV (TMC114)/rtv dose regimens (400/100 mg q.d., 800/100 mg q.d., 400/100 mg b.i.d., 600/100 mg b.i.d.) in addition to an optimized background regimen (OBR) consisting of NRTIs with or without enfuvirtide (ENF). The safety and efficacy data from this part of trial TMC114-C202 and the similar dose-finding trial TMC114-C213 led to the selection of DRV/rtv 600/100 mg b.i.d. as the recommended dose. The results of the dose-finding part of these trials are described in a separate report (primary efficacy analysis with cut-off date of 1 February 2005). After selection of the recommended dose, all subjects randomized to DRV/rtv were instructed to switch to the recommended dose in the open-label part of the trial, while the subjects in the control group continued their therapy unchanged and will continue to do so until the end of the trial.

This report describes the results of a preplanned interim analysis of TMC114-C202 including data from the start of the trial (17 September 2003) up to the cut-off date of 18 December 2006, at which time all subjects had reached Week 96 or discontinued before.

Subject Selection

Inclusion Criteria

1. Male or female subjects, aged 18 years or older;
2. Subjects with documented HIV-1 infection;
3. Subjects receiving a PI-containing regimen at screening initiated at least 8 weeks prior to screening with plasma HIV-1 RNA > 1000 copies/mL (assayed by RNA PCR Standard specimen procedure);
4. Prior use of more than 1 NRTI for at least 3 months in total;
   Note: Tenofovir counted as an NRTI;
   Note: Treatment with an investigational NRTI for a period of at least 3 months counted as an NRTI treatment;
5. Prior use of one or more NNRTIs (investigational included) as part of a failing regimen;
   Note: Treatment with an investigational NNRTI counted as an NNRTI treatment;
   Note: A regimen could fail virologically or due to intolerance; approved NNRTIs did not have to represent a worthy treatment option;
   Note: Subjects with documented NNRTI resistance were allowed even when previous NNRTI use could not be documented;
6. Subjects having at least 1 primary PI mutation as defined by the IAS guidelines of March 2003 (D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V, L90M);
7. Subjects experienced to at least one PI for a total period of at least 3 months;
8. Subjects voluntarily signed the informed consent form;
9. Subjects who could comply with the protocol requirements;
10. Subjects having a general medical condition that, in the investigator's opinion, did not interfere with the assessments and the completion of the trial.

Re-testing of abnormal screening values that led to exclusion or full re-screening of subjects having completed the Trial Termination Form needed to be discussed with the sponsor and was only approved (after discussion, review and approval in writing from the sponsor) on an exceptional basis.

Exclusion Criteria

1. Presence of any currently active AIDS defining illness (Category C conditions according to the 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.
   - Wasting syndrome due to HIV infection if, in the investigator's opinion, it was not actively progressive and its treatment did not require hospitalization or compromised the subject's safety or compliance to adhere to the study protocol procedures. If subjects were on maintenance therapy (which could 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 in case the medication used was not part of the disallowed medication.
2. Current or past history of alcohol and/or drug use which, in the investigator's opinion, could compromise the subject's safety or compliance to the study protocol procedures;
3. Subjects with an NNRTI in their therapy at screening;
4. Subjects on a treatment interruption at screening;
5. Subjects for whom an investigational ARV was part of the regimen at screening (with the exception of fos-amprenavir), or use of any other non-ARV investigational agents at least 90 days prior to screening;
6. Use of disallowed concomitant therapy;
7. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication (DRV/rtv/placebo);
   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 sulphonamide class and DRV has been identified in subjects participating in Phase II trials.
8. Life expectancy of less than 6 months;
9. Pregnant or breast feeding;

10. Female subject of childbearing potential without use of effective non-hormonal birth control methods or not willing to continue practicing these birth control methods from screening until at least 14 days after the end of the treatment period;

Note: Hormonal based contraception could not be reliable when taking DRV, therefore to be eligible for this study women of childbearing potential either had to:

(1) Use a double barrier method to prevent pregnancy (i.e., using a condom with either diaphragm or cervical cap), or,

(2) use hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom), or,

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

(4) be non-heterosexually active, practice sexual abstinence or have a vasectomized partner (confirmed sterile).

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

11. Subjects with clinical or laboratory evidence of active liver disease, liver impairment/dysfunction or cirrhosis irrespective of liver enzyme levels;

Note: Subjects diagnosed with hepatitis A, B or C had to be excluded.

12. Any active or unstable medical condition (e.g., TB; cardiac dysfunction; acute viral infections) or findings during screening of medical history or physical examination that, in the investigator's opinion, could compromise the subjects safety or outcome of the study;
13. Subjects with the following laboratory abnormalities as defined by ACTG grading scheme (see Protocol, Addendum 5 in Appendix 7.1.1: ACTG grading severity list):
    - Renal impairment: serum creatinine grade 2 or greater (> 1.5 x upper limit of normal [ULN]).
    - Lipase grade 2 or greater (> 1.5 x ULN).
    - Hemoglobin toxicity grade 2 or greater (≤ 7.9 g/dL).
    - Platelet count grade 2 or greater (< 75000/mm³).
    - Absolute neutrophil count grade 2 or greater (≤ 999/mm³).
    - ALT, AST grade 2 or greater (> 2.5 x ULN).
    - Total bilirubin grade 2 or greater (> 1.5 x ULN) unless clinical assessment foresaw an immediate health risk to the subject. For subjects who received indinavir or atazanavir at screening the total bilirubin could not exceed 3 x ULN.
    - Any grade 3 or 4 toxicity with the following exceptions: unless clinical assessment foresaw an immediate health risk to the subject:
        - Subjects with pre-existing diabetes or assessments under non-fasted conditions who experienced a glucose grade 3 or 4;
        - Subjects with triglyceride or cholesterol elevation of grade 3 or 4 under non-fasted conditions;
        - Subjects who experienced asymptomatic triglyceride or cholesterol elevations of grade 3 or 4;
        - Subjects who experienced an asymptomatic and isolated gamma-glutamyltransferase (GGT) grade 3 or 4 elevation with all other liver functions tests (LFTs) and bilirubin within normal ranges.
14. Subjects who had been randomized to a DRV treatment arm in a previous DRV trial.

Re-testing of abnormal screening values that led to exclusion or full re-screening of subjects having completed the Trial Termination Form needed to be discussed with the sponsor and was only approved (after discussion, review and approval in writing from the sponsor) on an exceptional basis.

Treatment	**DRV**			**ritonavir (Norvir®)**
	Dose-finding part		**Open-label part**	
Concentration	200 mg tablet	400 mg tablet	300 mg tablet	100 mg capsules
Dosage Form (TF No.)	F002	F001	F016	
Usage	Oral	Oral	Oral	Oral

Dose Regimen	Dose Finding Part: 400/100 mg DRV/rtv q.d. 800/100 mg DRV/rtv q.d. 400/100 mg DRV/rtv b.i.d. 600/100 mg DRV/rtv b.i.d. Open Label Part: 600/100 mg DRV/rtv b.i.d.
Duration of Treatment	144 weeks
Duration of Trial	screening: max 6 weeks, treatment period: 144 weeks, follow-up (FU): 4 weeks
Disallowed Medication	**Control and DRV/rtv treatment groups** **ARVs:** - **From screening until baseline:** investigational ARVs (except FTC, ENF, ATV and (fos)APV), all approved NNRTIs. - **From baseline until the end of the treatment period:** tipranavir (investigational at time of study initiation), all investigational PIs (with exception of fosamprenavir), abacavir*, investigational NRTIs, all approved and investigational NNRTIs. **Non-ARVs:** - **From screening until baseline:** amphetamines and amphetamine derivatives, all products containing *Hypericum perforatum* (St John's Wort), rifampin, rifapentine, phenobarbital, phenytoin, carbamazepine, modafinil - **From screening until the end of the treatment period:** experimental vaccines (approved vaccines were allowed as long as these were given outside the 4-week time frame preceding a plasma viral load measurement), dexamethasone **DRV/rtv treatment groups** **ARVs:** - **From baseline until the end of the treatment period:** PIs other than DRV/rtv, abacavir*, investigational NRTIs, all approved and investigational NNRTIs **Non-ARVs:** - **From baseline until the end of the treatment period:** amphetamines and amphetamine derivatives, all products containing *Hypericum perforatum* (St John's Wort), rifampin, rifapentine, phenobarbital, phenytoin, carbamazepine, modafinil, systemic use of ketoconazole and itraconazole at > 200 mg/day, amiodarone, bepridil, flecainide, propafenone, quinidine, systemic lidocaine, mexiletine, disopyramide, astemizole, terfenadine, ergot derivatives (dihydroergotamine, ergonovine [ergometrine], ergotamine, methylergonovine), cisapride, pimozide, midazolam, triazolam, clonazepam, lovastatin, simvastatin, pravastatin, cholestyramine and colestipol, telithromycin, cyclosporine, tacrolimus, rapamycin, serolimus, calcium channel blockers (e.g., felodipine, nifedipine, nicardipine, amlodipine, verapamil etc.), meperidine (pethidine). * Abacavir was disallowed during the trial, however, if subjects were receiving abacavir as part of their regimen at screening and had tolerated abacavir (no evidence of hypersensitivity) for at least 8 weeks, then these subjects could continue abacavir as part of their optimized underlying antiretroviral therapy (ART). Subjects could not discontinue abacavir and restart after screening.

Assessments	
Pharmacokinetics	In the pharmacokinetic substudy, subjects underwent a 12-hour (b.i.d. dosing regimens) or 24-hour (q.d. dosing regimens) pharmacokinetic sampling period at Week 4, Week 24 and optionally Week 40. In the pharmacokinetic main study in all subjects; the time points of sample collection were - at baseline and, - at Weeks 2, 4, 8, 12, 24, 48, 72, 96, 120 and 144 (or early withdrawal). One sample was collected (except Week 4) and there were no requirements for the time after intake of study medication. At Week 4, 2 samples were drawn: just before intake of DRV/rtv (trough concentration) and at least 1 hour after drawing of the first sample.
Resistance determinations	Samples for phenotype and genotype determinations were taken - at screening, Day –14, and baseline, - at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144 (or early withdrawal), - at both FU visits (1 and 4 weeks after last study medication intake) Analysis of samples taken at Weeks 1, 4, 8, 12, 16, 20, 32, 40, 60, 72, 84, 108, 120, 132 and at FU (1 and 4 weeks after withdrawal) depended on the judgment of the Protocol Virologist.
Efficacy	
Plasma viral load	Samples for plasma viral load determinations were taken - at screening, Day –14, Day –7, and baseline, - at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144 (or early withdrawal), - at both FU visits.
Immunology	Samples for immunology assessment were taken - at screening, Day –14, and baseline, - at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144 (or early withdrawal).
Safety	
Adverse Events (AEs)	AEs were checked at every visit and reported from screening onwards until the last trial-related activity.
Clinical Laboratory	Samples for hematology, biochemistry (fasted) and coagulation testing were taken at every visit, i.e., - at screening, Day –14, Day –7, and baseline, - at Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144 (or early withdrawal), - at both FU visits. At Weeks 3, 6 and 10, only LFTs and bilirubin (total, indirect, and direct) were assessed. Urinalysis was performed - at screening, Day –14, and baseline, - at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144 (or early withdrawal). A hepatitis A, B and C test was performed at screening, baseline, Week 8, Week 16, and Week 24, and other visits if clinically relevant.
Cardiovascular safety	Vital signs (pulse, blood pressure [BP]) were assessed - at screening, Day –14, Day –7, and baseline, - at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144 (or early withdrawal). Central ECG readings were performed - at screening, Day –14, and baseline, - at Weeks 2, 4, 12, 24, 48, 72, 96, 120 and 144 (or early withdrawal).

Physical Examination	Physical examination was performed - at screening and baseline, - at Weeks 12, 24, 48, 72, 96, 120 and 144 (or early withdrawal).
Anthropometric measurements	Height was measured at screening. Weight and waist and hip circumference were determined - at screening and baseline, - at Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132 and 144 (or early withdrawal).
Questionnaires	The subjects completed a quality of life questionnaire - at baseline - at Weeks 4, 12, 24, 48, 72, 96, 120 and 144 (or early withdrawal). Body image questionnaires were completed at the same time points, except at Weeks 4 and 12.
Statistical Methods	Descriptive statistics, frequency tabulations, intent-to-treat analysis, Wilcoxon (matched-pairs) signed-ranks test, Mann-Withney U test, Kruskal-Wallis test, logistic regression model, Cox proportional hazards model, linear regression, generalized linear mixed effects model, ANOVA, ANCOVA, Cochran-Mantel-Haenszel test.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	DRV/rtv			Control	All subjects
	Total DRV/rtv[a]	Lower dose/ 600/100 mg b.i.d.[b]	600/100 mg b.i.d.[c]		
Number of subjects (M/F) Age: median (range), yrs	258 (238/20) 45 (27;75)	192 (176/16) 45 (28;75)	66 (62/4) 46 (27;73)	61 (54/7) 46 (35;60)	319 (292/27) 45 (27;75)
Plasma viral load: mean (SD), log_{10} copies/mL	4.66 (0.74)	4.67 (0.76)	4.62 (0.68)	4.58 (0.77)	4.64 (0.75)
CD4+ count: median (range), 10^6 cells/L	98.5 (1;819)	93.5 (1;819)	115 (3;776)	113 (3;1274)	104 (1;1274)
Time since HIV infection diagnosis: median (range), years	12.8 (3; 23)	12.8 (4;23)	12.9 (3;22)	14.0 (5;23)	12.9 (3;23)
Previous PI treatment duration median (range), months	64.7 (3;150)	66.8 (3;129)	62.2 (6;150)	59.6 (5;107)	64.1 (3;150)
Number of PI resistance-associated mutations[d], median (range)	11 (2;18)	11 (3;18)	11 (2;16)	12 (2;16)	11 (2;18)
Previous ARV experience, n (%)					
PI: ≥ 2	250 (96.9)	187 (97.4)	63 (95.5)	60 (98.4)	310 (97.2)
NNRTI: ≥ 1	255 (98.8)	190 (99.0)	65 (98.5)	60 (98.4)	315 (98.7)
NRTI: ≥ 4	250 (96.9)	187 (97.4)	63 (95.5)	58 (95.1)	308 (96.6)
Fusion Inhibitor[e]: 1	60 (23.3)	41 (21.4)	19 (28.8)	15 (24.6)	75 (23.5)
Discontinuations - Reason n (%)	**123 (47.7)**	**96 (50.0)**	**27 (40.9)**	**56 (91.8)**	**179 (56.1)**
Subject reached a virologic endpoint	51 (19.8)	42 (21.9)	9 (13.6)	43 (70.5)	94 (29.5)
Adverse event/HIV-related event	36 (14.0)	27 (14.1)	9 (13.6)	3 (4.9)	39 (12.2)
Subject lost to follow-up	13 (5.0)	7 (3.6)	6 (9.1)	1 (1.6)	14 (4.4)
Subject withdrew consent	10 (3.9)	9 (4.7)	1 (1.5)	6 (9.8)	16 (5.0)
Subject non-compliant	7 (2.7)	6 (3.1)	1 (1.5)	2 (3.3)	9 (2.8)
Subject ineligible to continue the trial	2 (0.8)	2 (1.0)	0	1 (1.6)	3 (0.9)
Sponsor's decision	2 (0.8)	2 (1.0)	0	0	2 (0.6)
Other	2 (0.8)	1 (0.5)	1 (1.5)	0	2 (0.6)

[a] The Total DRV/rtv group includes all subjects who received DRV/rtv.

[b] The Lower dose/ 600/100 mg b.i.d. group includes all subjects who started DRV/rtv treatment at 400/100 mg q.d., 800/100 mg q.d., or 400/100 mg b.i.d. and who switched to the recommended dose after February 1, 2005 or discontinued.

[c] The 600/100 mg b.i.d. group includes all subjects who were randomized to the DRV/rtv 600/100 mg b.i.d. group at the start of the trial and therefore received DRV/rtv at the recommended dose from the first drug intake in the trial or discontinued.

[d] Based on the November 2005 IAS-USA list of mutations.

[e] ENF was the only FI used.

Efficacy ITT	Time point	DRV/rtv Total DRV/rtv N = 258	DRV/rtv Lower dose/ 600/100 mg b.i.d. N = 192	DRV/rtv 600/100 mg b.i.d. N = 66	Control N = 61
Primary Variable					
Virologic response[a]: decrease of at least 1.0 log_{10} in VL vs. baseline; n (%)	Week 24	145 (56.2)	103 (53.6)	42 (63.6)	8 (13.1)
	Week 48	128 (49.6)	94 (49.0)	34 (51.5)	6 (9.8)
	Week 96	112 (43.4)	82 (42.7)	30 (45.5)	4 (6.6)
Secondary Variables					
Virologic response[a]: VL below 50 copies/mL; n (%)	Week 24	79 (30.6)	54 (28.1)	25 (37.9)	5 (8.2)
	Week 48	80 (31.0)	57 (29.7)	23 (34.8)	5 (8.2)
	Week 96	77 (29.8)	52 (27.1)	25 (37.9)	3 (4.9)
Virologic response[a]: VL below 400 copies/mL; n (%)	Week 24	121 (46.9)	84 (43.8)	37 (56.1)	7 (11.5)
	Week 48	110 (42.6)	80 (41.7)	30 (45.5)	5 (8.2)
	Week 96	96 (37.2)	69 (35.9)	27 (40.9)	4 (6.6)
Change vs. baseline in log_{10} VL[b] (copies/mL), mean (SD)	Week 24	-1.47 (1.40)	-1.38 (1.40)	-1.72 (1.38)	-0.26 (0.82)
	Week 48	-1.36 (1.38)	-1.33 (1.40)	-1.44 (1.36)	-0.20 (0.59)
	Week 96	-1.26 (1.42)	-1.22 (1.42)	-1.38 (1.42)	-0.14 (0.52)
Change vs. baseline in CD4+ cell count (x 10^6/L)[c], mean (SD)	Week 24	73.3 (89.03)	75.3 (92.31)	67.3 (79.08)	9.7 (92.24)
	Week 48	87.6 (113.96)	91.4 (118.23)	76.7 (100.55)	3.0 (78.98)
	Week 96	113.1 (154.66)	111.6 (152.07)	117.3 (163.07)	7.2 (82.38)

N = total number of subjects with data; VL = viral load.
[a] ITT-TLOVR
[b] NC=F
[c] LOCF

In treatment-experienced HIV-1-infected subjects, significantly greater efficacy was observed with the recommended dose of DRV/rtv (600/100 mg b.i.d.) at Week 24, 48 and 96 when compared to control PIs. The results for the primary efficacy parameter (decrease in viral load versus baseline of ≥ 1.0 log_{10}) were supported by those of the secondary parameters (other virologic responses and increases in CD4+ cell counts). The responses were greater in both the lower dose/600/100 mg b.i.d. and the DRV/rtv 600/100 mg b.i.d. group compared to control at all time points up to Week 96; the differences were statistically significant at Week 24, Week 48 and Week 96 ($p \leq 0.001$).

Safety	To account for the difference in exposure between the DRV/rtv 600/100 mg b.i.d. group and the control group, the treatment period in the analysis of AEs is split up to present AEs separately for the first 24 weeks and after the first 24 weeks of treatment. In the first 24 weeks, AE rates in the DRV/rtv 600/100 mg b.i.d. and the control groups can be compared as the mean exposure and the number of subjects in both groups were similar. In the treatment period after the first 24 weeks, AE rates in the DRV/rtv 600/100 mg b.i.d. and the control group should not be compared because both the mean exposure and the number of subjects in the control group were much lower compared to the DRV/rtv 600/100 b.i.d. group. Furthermore, the population of subjects in the control group who remained in the study beyond Week 24 represent a population with less advanced HIV infected subjects.					
	Week 1 - 24			**Week > 24**		
	Total DRV/rtv	**600/100 b.i.d.**	**Control**	**Total DRV/rtv**	**600/100 b.i.d.**	**Control**
(N = number of subjects with data)	**N = 258**	**N = 66**	**N = 61**	**N = 221**	**N = 59**	**N = 25**
Mean exposure (weeks)	*22.3*	*22.3*	*18.7*	*78.8*	*81.7*	*37.9*
Adverse Events (AEs) During the Treatment Period						
Most frequently reported AEs[a], n (%)						
Injection site reaction[b]	62 (24.0)	15 (22.7)	11 (18.0)	13 (5.9)	3 (5.1)	2 (8.0)
Diarrhea	53 (20.5)	13 (19.7)	15 (24.6)	36 (16.3)	6 (10.2)	5 (20.0)
Nausea	47 (18.2)	13 (19.7)	4 (6.6)	16 (7.2)	5 (8.5)	2 (8.0)
Headache	44 (17.1)	10 (15.2)	10 (16.4)	14 (6.3)	3 (5.1)	0
Fatigue	36 (14.0)	9 (13.6)	10 (16.4)	23 (10.4)	8 (13.6)	3 (12.0)
Upper respiratory tract infection	33 (12.8)	8 (12.1)	7 (11.5)	35 (15.8)	9 (15.3)	2 (8.0)
Sinusitis	10 (3.9)	3 (4.5)	5 (8.2)	23 (10.4)	9 (15.3)	1 (4.0)
Arthralgia	10 (3.9)	1 (1.5)	3 (4.9)	14 (6.3)	6 (10.2)	1 (4.0)
n (%) with 1 or more AEs	242 (93.8)	64 (97.0)	56 (91.8)	201 (91.0)	56 (94.9)	18 (72.0)
n (%) of deaths	6 (2.3)[c]	1 (1.5)	0	11 (5.0)[c,d]	3 (5.1)[d]	0
n (%) with 1 or more SAEs	35 (13.6)	7 (10.6)	6 (9.8)	48 (21.7)	12 (20.3)	3 (12.0)
n (%) with 1 or more AEs leading to treatment discontinuation	17 (6.6)	5 (7.6)	3 (4.9)	16 (7.2)	3 (5.1)	0
n (%) with 1 or more grade 3 AEs	62 (24.0)	18 (27.3)	15 (24.6)	57 (25.8)	11 (18.6)	3 (12.0)
n (%) with 1 or more grade 4 AEs	21 (8.1)	7 (10.6)	2 (3.3)	17 (7.7)	5 (8.5)	0

[a] ≥ 10% subjects in the DRV/rtv 600/100 mg b.i.d. group during either part of the treatment period.
[b] Associated with ENF administration (50% of the subjects used ENF in their initial ARV therapy).
[c] Including two deaths during follow-up.
[d] Including one death reported after subject was lost to follow-up.

Clinical Laboratory Tests	Most graded individual laboratory abnormalities were grade 1 or 2 in severity. No meaningful difference in the incidence of graded and non-graded laboratory abnormalities was observed between the DRV/rtv 600/100 mg b.i.d. group and the control group when taking into account the difference in exposure, except for triglycerides abnormalities. The overall incidence of triglycerides abnormalities was higher in the DRV/rtv than in the control group. The incidence of grade 3 or 4 triglycerides abnormalities was higher in the DRV/rtv 600/100 mg group than in the control group (18% versus 5%). The incidence of grade 2 triglycerides abnormalities, for which clinical intervention is usually considered, was lower in the DRV/rtv 600/100 mg b.i.d. group than in the control group (6% versus 12%). The incidence of AEs related to laboratory parameters in the DRV/rtv groups was similar to that in the control group.
Cardiovascular Safety	For QTc parameters, no relevant and consistent changes over time relative to baseline were observed in the DRV/rtv 600/100 mg b.i.d. group and control group. For vital signs, no consistent differences compared to control in mean changes from baseline were apparent in the DRV/rtv 600/100 mg b.i.d. group. QTc abnormalities were reported with a similar incidence in the DRV/rtv 600/100 mg b.i.d. and control groups. There were no pathologically prolonged QTc values in the DRV/rtv 600/100 mg b.i.d. group or the control group. Increases by > 60 ms were reported by at most 5% of the subjects in the DRV/rtv 600/100 mg b.i.d. group or the control group. Incidence of abnormally high SBP and DBP was higher in the DRV/rtv 600/100 mg b.i.d. group than in the control group, but most of these abnormalities were grade 1 or 2. This higher incidence can partially be explained by the higher mean exposure and the consequently higher number of measurements for the DRV/rtv group compared to the control group.
Other Safety Parameters	At Week 48, an increase in mean body weight was observed in the DRV/rtv 600/100 mg b.i.d. group, while the weight of the control group had remained unchanged. At Week 96, the increase versus baseline in mean body weight was still 3.0 kg in the DRV/rtv 600/100 mg b.i.d. group, while the mean weight in the control group was slightly decreased (-0.9 kg). At Week 48, an increase in mean waist circumference was observed in the DRV/rtv 600/100 mg b.i.d. and control groups. At Week 96, the increase versus baseline in mean waist circumference was still 1.9 cm in the DRV/rtv 600/100 mg b.i.d. group, while the mean waist circumference in the control group had decreased (-1.3 cm). No clinically relevant changes over time in physical examination findings, BMI or hip circumference were noted.

Conclusions

Updated information made available in this report represents a substantial increase in the length of therapy, providing updated efficacy information of DRV for all subjects in the DRV/rtv 600/100 mg b.i.d. group and for control up to Week 96.

The efficacy results indicate a clear clinical sustained benefit of the recommended dose of DRV/rtv (600/100 mg b.i.d.) in combination with an individually OBR in treatment-experienced HIV-1-infected subjects compared to control. The responses were greater in the DRV/rtv 600/100 mg b.i.d. group compared to control at all time points up to at least Week 96; the differences were highly statistically significant at the primary endpoint at Week 24 and remained significant at Week 48 and Week 96.

At Week 96, DRV/rtv treatment (600/100 mg b.i.d.) resulted in the following benefits:

- 45% responders with a decrease compared to baseline of ≥ 1.0 $\log_{10}$ in viral load compared to 7% responders in the control group;
- 38% responders with a viral load < 50 copies/mL compared to 5% responders in the control group;
- a mean decrease in viral load compared to baseline of 1.38 $\log_{10}$ copies/mL compared to a decrease of 0.14 $\log_{10}$ copies/mL in the control group;
- a mean increase in absolute CD4+ cell count compared to baseline of 117 x 10^6 cells/L compared to an increase of 7 x 10^6 cells/L in the control group.

Treatment with DRV/rtv was generally well tolerated. For the first 24 weeks of treatment, the overall incidence of AEs of any severity grade, SAEs and AEs leading to discontinuation was similar in the DRV/rtv 600/100 mg b.i.d. and control group. In addition, the AE profile observed after Week 24 in the DRV/rtv 600/100 mg b.i.d. group did not differ significantly from the AE profile observed during the first 24 weeks of treatment, except for SAEs which were more frequently reported after Week 24 (20%) than during the first 24 weeks (11%). Due to the high discontinuation rate resulting into a lower mean exposure for the control group, a comparison of the incidence is only relevant for the first 24 weeks of treatment. Furthermore, the population of subjects in the control group who remained in the study beyond Week 24 represent a population with less advanced HIV infected subjects.

During the first 24 weeks of treatment, the most frequently reported AEs in the DRV/rtv 600/100 mg b.i.d. group, apart from injection site reaction associated with ENF administration, were diarrhea, nausea, headache, fatigue, and upper respiratory tract infection. After Week 24, the most frequently reported AEs, apart from injection site reaction associated with ENF administration, were sinusitis, upper respiratory tract infection, fatigue, diarrhea, and arthralgia. In addition, the safety data reported to date do not impact the safety conclusions as described in previous reports. The safety profile of DRV/rtv was generally similar to that of commercially available ARVs in the PI class (excluding tipranavir which was not commercially available at the time of enrollment).