SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: Prezista™ **Indication**: HIV-1 infection	**Drug Substance**: Darunavir **Trial no.**: TMC114-C214 **Clinical Phase**: III
Title: A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of TMC114/rtv versus LPV/rtv in treatment-experienced HIV-1 infected subjects. Final comparative analysis with cut-off date 15 January 2008, at which time all subjects had reached Week 96 or discontinued earlier.	
Investigator: J.V. Madruga, Centro de Referencia e Treinamento DST/AIDS-SP, Sao Paulo, Brazil	**Country**: International
Trial Period: Start: 28-Apr-2005 End: 15-Jan-2008	**No. of Investigators**: 147 **No. of Subjects**: 595
Objectives: The primary objective of this final comparative analysis was to compare virologic response defined as a confirmed plasma viral load of less than 400 copies/mL with DRV/rtv 600/100 mg twice daily (b.i.d.) versus LPV/rtv 400/100 mg b.i.d. at Week 96. Secondary objectives were to evaluate other virologic parameters and immunologic parameters, to compare the quality of life, and to evaluate safety and tolerability over time.	
Design: Trial TMC114-C214 was a randomized, controlled (lopinavir [LPV]/ritonavir [rtv]), open-label Phase III trial to determine the efficacy, safety and tolerability of darunavir (DRV, formerly known as TMC114), formulated as an oral tablet, and administered with low-dose ritonavir over a 96-week treatment period. Five hundred treatment-experienced (LPV-, DRV-, tipranavir [TPV], and enfuvirtide [ENF]-naïve), HIV-1 infected subjects with viral load > 1000 HIV-1 RNA copies/mL were to be randomized. Subjects had to be on their current highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. Initially, subjects on a structured treatment interruption (STI) of at least 4 weeks were permitted to be enrolled. When the protocol was subsequently amended, subjects on an STI were no longer allowed to enroll. At baseline, subjects changed their HAART. An optimized background regimen (OBR) consisting of at least 2 antiretrovirals (nucleoside/nucleotide analogue reverse transcriptase inhibitors [NRTIs] with or without non-nucleoside reverse transcriptase inhibitors [NNRTIs]) was started, and the subjects were randomized in a 1:1 ratio to receive a new PI regimen consisting of either DRV/rtv or LPV/rtv. The primary objective of this trial was to demonstrate noninferiority in efficacy of DRV/rtv versus LPV/rtv at 48 weeks, when administered in combination with an individualized OBR. In addition, safety, tolerability, durability of efficacy, quality of life (QoL), and effects of covariates over 96 weeks were assessed. The trial included a screening period of 4 weeks, a 96-week treatment period, and a 4-week follow-up period. Subjects meeting the per protocol defined criteria for virologic failure (DRV/rtv or LPV/rtv group), or who experienced a grade 4 AE or confirmed grade 4 (or specific grade 3) laboratory abnormality considered at least possibly related to LPV/rtv treatment could enter a rollover phase. In regions where DRV was not yet commercially available, subjects who completed the 96 weeks of treatment with DRV/rtv and who continued to benefit from this treatment had the opportunity to continue treatment in the extension phase of the TMC114-C214 trial where they can receive DRV/rtv until DRV is commercially available or until its development is discontinued. The present report describes the results of the final comparative Week 96 analysis.	
Subject Selection ***Inclusion Criteria*** 1. Male or female, aged 18 years or older. 2. Documented HIV-1 infection. 3. Treatment with current HAART regimen for ≥ 12 weeks. *Note*: HAART was defined as potent anti-HIV treatment usually including a combination of ≥ 3 drugs with activity against HIV, whose purpose is to reduce viral load to undetectable. This regimen usually includes treatment with ≥ 2 NRTIs in combination with ≥ 1 additional antiretroviral (ARV) from the NNRTI and/or PI class. *Note*: STI of ≥ 4 weeks at screening was allowed up to the implementation of Protocol Amendment I (28 November 2005).	

4. Prescreening and screening plasma HIV-1 RNA > 1000 copies/mL (assayed by RNA polymerase chain reaction standard specimen procedure) on current HAART regimen.
   Note: If no documented prescreening viral load was available (taken ≥ 12 weeks after starting the current HAART regimen), a prescreening visit had to be scheduled.
5. Voluntarily signed Informed Consent Form.
6. Able to comply with protocol requirements.
7. General medical condition, in the investigator's opinion, not interfering with the assessments and the completion of the trial.

Exclusion Criteria

1. Presence of any currently active AIDS-defining illness (category C conditions according to the Centers for Disease Control and Prevention [CDC] Classification System for HIV Infection 1993) with the following exceptions:
   - stable cutaneous Kaposi's sarcoma (i.e., no internal organ involvement other than oral lesions) that was unlikely to require any form of systemic therapy during the trial time period;
   - wasting syndrome.

   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 alcohol and/or drug use which, in the investigator's opinion, could compromise the subject's safety or adherence to the trial protocol procedures.
3. Subjects for whom an investigational ARV was part of the current regimen, with the following exceptions if applicable (depending on local regulatory approval): tenofovir (TDF), emtricitabine (FTC), atazanavir (ATV), and fosamprenavir (fAPV).
   Note: Participation in observational trials where no treatment was administered was allowed (if approved by the sponsor).
4. Previous or current use of LPV, ENF, TPV, or DRV.
5. Use of any non-ARV investigational agents within 90 days prior to screening.
6. Use of disallowed concomitant therapy.
7. Life expectancy of < 6 months.
8. Pregnant or breastfeeding.
9. Female subject of childbearing potential without use of effective nonhormonal birth control methods or not willing to continue practicing these birth control methods for ≥ 30 days after the end of the treatment period.
   Note: Hormonal based contraception may not be reliable when taking DRV, therefore to be eligible for this trial, women of childbearing potential had to either:
   - use a double barrier method to prevent pregnancy (i.e., use a condom with either diaphragm or cervical cap);
   - use hormonal based contraceptives in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom);
   - use an intrauterine device in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom);
   - be nonheterosexually active, practice sexual abstinence or have a vasectomized partner (confirmed sterile).

   Note: Women who were postmenopausal for ≥ 2 years, women with total hysterectomy and women with tubal ligation were considered of nonchildbearing potential.
10. Subjects with clinical or laboratory evidence of significantly decreased hepatic function or decompensation (i.e., liver insufficiency), irrespective of liver enzyme levels.
    Note: Subjects coinfected with chronic hepatitis B or C were allowed to enter the trial if their condition was clinically stable and not expected to require treatment during the trial period. Subjects diagnosed with acute viral hepatitis at screening were excluded. In case TDF and FTC were included in the OBR, the package insert had to be consulted with respect to proper care of hepatitis B coinfection.
11. Any active clinically significant disease (e.g., tuberculosis, cardiac dysfunction, pancreatitis, acute viral infections) or findings during screening of medical history or physical examination that, in the investigator's opinion, would compromise the subjects safety or outcome of the trial.

12. Subjects with a grade 3 or 4 laboratory abnormality as defined by the DAIDS grading tables, with the following exceptions unless clinical assessment foresaw an immediate health risk to the subject:
    - pre-existing diabetes, or asymptomatic grade 3 or 4 glucose elevations;
    - asymptomatic grade 3 or 4 triglyceride or cholesterol elevations.
13. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication DRV, LPV, or ritonavir.
    Note: DRV is a sulfonamide derivative. Subjects who previously experienced a sulfonamide allergy were allowed to enter the trial. To date, no potential for cross sensitivity between drugs in the sulfonamide class and DRV has been identified in subjects participating in Phase II trials.
14. Participation in other investigational trials without prior approval of the sponsor.

Rollover Criteria

Subjects meeting ≥ 1 of the following criteria were eligible for participation in the rollover phase; they had to confirm their informed consent for rollover.

1. For the DRV/rtv and LPV/rtv groups: discontinuation due to loss or lack of response. The following description applied for lack or loss of treatment response:
    - plasma HIV-1 RNA > 400 copies/mL at or beyond Week 16 that was confirmed by 2 consecutive measurements; confirmation could be obtained by performing an unscheduled visit;
    - 2 consecutive measurements of plasma HIV-1 RNA > 400 copies/mL following confirmed response < 400 copies/mL (rebound).

    Note: If plasma HIV-1 RNA was > 400 copies/mL at Week 12, the subject could roll over if it was confirmed at Week 16, but not prior to Week 16.

    Note: If the investigator wished to reoptimize the OBR for subjects failing on DRV/rtv, and continue treatment with DRV/rtv, the subject had to continue in the rollover phase of the trial.
2. For the LPV/rtv group only, subjects who discontinued due to a grade 4 AE or confirmed grade 4 (or specific grade 3) laboratory abnormality that was considered at least possibly related to LPV/rtv.
    Note: A temporary treatment interruption of all components of the regimen had to be respected to allow the severity to decrease to ≤ grade 2 before starting intake of DRV/rtv. During follow-up, the abnormality had to be monitored according to the toxicity management guidelines described in the protocol and unscheduled visits could be used to assess resolution of the abnormality.

Criteria for Participation in the Extension Phase After Week 96

Subjects had to confirm their informed consent for participation in the extension phase.

– Subjects who completed the 96 weeks of treatment with DRV/rtv and who continued to benefit from this treatment, but who were living in a region where DRV was not yet commercially available, were eligible for the extension phase.
– For subjects on LPV/rtv, the trial stopped at Week 96 as these subjects did not fulfill the entry criteria of the rollover or the extension phase.

Treatment	**DRV**	**Ritonavir (Norvir®)**	**LPV/rtv (Kaletra®)**
Formulation	300-mg tablet	100-mg capsule	133.3/33.3-mg capsule or 200/50-mg tablet
Dosage Form (TF No.)	F016	-	-
Usage	oral	oral	oral
Dose Regimen	DRV/rtv 600/100 mg b.i.d.		LPV/rtv 400/100 mg b.i.d.
Duration of Treatment	96 weeks		
Duration of Trial	Screening period: maximum 4 weeks; treatment period: maximum 96 weeks; follow-up period: 4 weeks.		
Disallowed Medication	***Disallowed for all subjects from screening until the end of the treatment period:*** *Non-ARVs:* - investigational agents (from 90 days before screening onwards); - experimental vaccines; approved vaccines were allowed if they were given ≥ 4 weeks before a viral load measurement.		

	Disallowed for all subjects from screening until baseline: *ARVs:* - Investigational ARVs (except TDF, FTC, ATV, fAPV); - LPV/rtv, ENF, TPV, DRV. *Non-ARVs:* - herbal supplements: all products containing *Hypericum perforatum* (St John's Wort); - antibiotics: rifampin, rifapentine; - anticonvulsants: phenobarbital, phenytoin, carbamezepine, modafinil; - steroids: systemic dexamethasone (topical formulations were allowed). ***Disallowed for all subjects from baseline until the end of the treatment period:*** *ARVs:* - all PIs other than DRV (for the DRV/rtv group) or LPV (for the LPV/rtv group); - investigational NRTIs (except TDF and FTC); - delavirdine, investigational NNRTIs; - ENF (except for DRV/rtv-treated subjects in the extension phase). ***Disallowed for all DRV/rtv subjects from baseline until the end of the treatment period:*** *Non-ARVs:* - stimulants: amphetamines, amphetamine derivatives; - herbal supplements: all products containing *Hypericum perforatum* (St John's Wort); - antibiotics: rifampin, rifapentine, telithromycin; - steroids: systemic dexamethasone (topical formulations were allowed); - anticonvulsants: phenobarbital, phenytoin, carbamezepine, modafinil; - antiarrhythmics: bepridil, flecainide, propafenone, systemic lidocaine, quinidine, mexilitine, disopyramide, amiodarone; - immunosuppressants: cyclosporin, rapamycin, tacrolimus, sirolimus; - antihistamines: astemizole, terfenadine; - gastroprokinetic: cisapride - antipsychotics: pimozide; - ergot derivatives: dihydroergotamine, ergonovine, ergometrine, ergotamine, methylergonovine; - benzodiazepines: midazolam, triazolam; - narcotic analgesics: meperidine (pethidine); - lipid lowering agents and HMG-CoA reductase inhibitors: pravastatin, lovastatin, simvastatin; - antifungals: systemic use of ketaconazole, or itraconazole at > 200 mg/day.
Assessments	
Efficacy	
Plasma Viral Load	Samples for plasma viral load determinations: - prescreening, screening, baseline; - Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 (or early withdrawal); - first follow-up visit. In the extension phase: - Week 108 and every 12 weeks thereafter up to and including the final/withdrawal visit.
Immunology	Samples for immunology assessment: - prescreening, screening, baseline; - Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 (or early withdrawal); - the first follow-up visit. In the extension phase: - Week 108 and every 12 weeks thereafter up to and including the final/withdrawal visit.

Resistance Determinations	Samples for pheno- and genotype determinations: - screening, baseline; - Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 (or early withdrawal); - both follow-up visits. Samples taken at Weeks 4, 8, 12, 16, 36, 60, 84, and both follow-up visits were only analyzed when judged appropriate by the Protocol Virologist. Peripheral blood mononuclear cells (PBMC) sample: - baseline; - Week 96 (or early withdrawal).
Questionnaires	Only if validated translated versions were available and not for rollover subjects: Quality of Life questionnaire: - baseline; - Weeks 4, 12, 24, 48, 72, and 96 (or early withdrawal). Body image questionnaire: - baseline; - Weeks 24, 48, 72, and 96 (or early withdrawal).
Safety	
Adverse Events	AEs and HIV-related events were checked at every visit and reported from signing of informed consent onwards until the last trial-related activity.
Clinical Laboratory	Samples for hematology, biochemistry (fasted): - screening, baseline; - Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 (or early withdrawal); - both follow-up visits. Coagulation testing: - baseline; - Weeks 24, 48, 96 (or early withdrawal); - at other visits if suspected liver dysfunction. Pregnancy test for female subjects: - serum test: screening; - urine test: baseline, Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 (or early withdrawal). - In the extension phase: Week 108 and every 12 weeks thereafter up to and including the final/withdrawal visit. Urinalysis: - screening, baseline; - Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 (or early withdrawal). Hepatitis A, B and C test: - screening; - other visits: only if diagnosis was suspected.
Cardiovascular Safety	Vital signs (pulse, blood pressure): - screening, baseline; - Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 (or early withdrawal). Electrocardiogram (ECG) readings: - screening, baseline; - Weeks 12, 24, 48, 72, and 96 (or early withdrawal).
Physical Examination	Physical examination: - screening, baseline; - Weeks 12, 24, 48, 72, and 96 (or early withdrawal).
Anthropometric Measurements	Height: baseline. Weight, waist and hip circumference: - baseline; - Weeks 12, 24, 48, 72, and 96 (or early withdrawal).

Pharmacokinetics	Pharmacokinetic samples for DRV/rtv and LPV/rtv: - Weeks 4, 8, 24, 48, 72, and 96 (or early withdrawal); One sample was collected (except on Weeks 4 and 24) with no requirements for the time after the intake of trial medication. At Weeks 4 and 24, 2 samples were drawn: just before intake of DRV/rtv or LPV/rtv and ≥ 1 hour after drawing the first sample. No updated pharmacokinetics analysis was performed.
Statistical Methods	Descriptive statistics, frequency tabulations, intent-to-treat and on-protocol analysis, sensitivity analysis, logistic regression model, Cox proportional hazards model, general linear longitudinal model, Kaplan-Meier curves, ANCOVA, Wilcoxon matched-pairs signed-ranks test, Mann-Whitney U-test, graphical analysis.

Main Features of the Subject Sample and Summary of the Results (96-Week Treatment Period)

Baseline Characteristics - Subject Disposition	**DRV/rtv**	**LPV/rtv**	**All Subjects**
Number of Subjects Entered (M/F), n	298 (229/69)	297 (241/56)	595 (470/125)
Age: median (range), yrs	40.0 (18.0; 68.0)	41.0 (22.0; 76.0)	40.0 (18.0; 76.0)
Log_{10} plasma viral load (copies/mL), mean (SD)	4.33 (0.785)	4.28 (0.808)	4.30 (0.796)
CD4+ cell count (x 10^6/L), median (range)	235 (3; 831)	230 (2; 1096)	232 (2; 1096)
Known duration of HIV infection (years), median (range)	9.1 (0.68; 22.61)	9.1 (0.23; 23.48)	9.1 (0.23; 23.48)
DRV FC, median (range)	0.60 (0.10; 37.40)	0.60 (0.10; 43.80)	0.60 (0.10; 43.80)
LPV FC, median (range)	0.70 (0.40; 74.40)	0.80 (0.30; 74.50)	0.75 (0.30; 74.50)
Primary PI mutations[a], median (range)	0.0 (0; 6)	0.0 (0; 6)	0.0 (0; 6)
PI RAMs[a], median (range)	4.0 (0; 17)	4.0 (0; 14)	4.0 (0; 17)
DRV RAMs[b], median (range)	0.0 (0; 4)	0.0 (0; 4)	0.0 (0; 4)
LPV RAMs[a], median (range)	1.0 (0; 11)	1.0 (0; 9)	1.0 (0; 11)
Subject Disposition			
Discontinuations - Reason	81[c] (27.2)	110 (37.0)	191 (32.1)
Adverse event/HIV related event	23[c] (7.7)	24 (8.1)	47 (7.9)
Subject reached a virologic endpoint	8 (2.7)	43 (14.5)	51 (8.6)
Subject lost to follow-up	13 (4.4)	13 (4.4)	26 (4.4)
Subject withdrew consent	10 (3.4)	12 (4.0)	22 (3.7)
Subject noncompliant	16 (5.4)	7 (2.4)	23 (3.9)
Other	4 (1.3)	7 (2.4)	11 (1.8)
Subject ineligible to continue the trial	5 (1.7)	2 (0.7)	7 (1.2)
Sponsor's decision	1 (0.3)	2 (0.7)	3 (0.5)
Subject did not fulfill all in-/exclusion criteria	1 (0.3)	0	1 (0.2)

n = number of observations, M/F = male/female, SD = standard deviation

[a] Based on the 2007 IAS-USA list of mutations

[b] Based on the 2007 list of DRV RAMs

[c] Not including subject 214-0231 who discontinued during the extension phase due to an AE (lipohypertrophy) that started during the treatment phase

Efficacy
The efficacy results of this trial demonstrated noninferiority in virologic response defined as a confirmed plasma viral load of < 400 copies/mL (primary efficacy parameter) at Week 96 with DRV/rtv 600/100 mg b.i.d. when compared to LPV/rtv 400/100 mg b.i.d. (both in combination with an individualized OBR). Superiority for efficacy of DRV/rtv 600/100 mg b.i.d. versus LPV/rtv 400/100 mg b.i.d. was demonstrated for the primary parameter (viral load of < 400 copies/mL). Although the criterion for superiority was not met for the secondary efficacy parameter viral load < 50 copies/mL at Week 96, there remains a trend of a higher response for DRVrtv versus LPV/rtv for this parameter. A possible explanation for the loss of superiority (viral load < 50 copies/mL) includes the fact that more DRV/rtv subjects than LPV/rtv subjects discontinued the trial for reasons other than reaching a virologic endpoint.

Parameter, at Week 96	DRV/rtv		LPV/rtv		Difference [95% CI]
Primary Variable	**N**		**N**		
OP[a] - Viral load < 400 copies/mL, n (%)	280	189 (67.5)	294	175 (59.5)	8.0 [0.1 ; 15.8]
ITT[a] - Viral load < 400 copies/mL, n (%)	298	199 (66.8)	297	175 (58.9)	7.9 [0.1 ; 15.6]
Secondary Variables	**N**		**N**		
ITT[a] - Viral load < 50 copies/mL, n (%)	298	180 (60.4)	297	164 (55.2)	5.2 [-2.8 ; 13.1]
ITT[b] - Change in log_{10} viral load from baseline (copies/mL), mean (SE)	298	-1.71 (0.075)	297	-1.52 (0.080)	-0.19 [-0.40 ; 0.03]
ITT[b] - Change in CD4+ cell count from baseline (x 10^6/L), mean (SE)	294	115 (9.4)	295	132 (10.6)	-16 [-44 ; 11]

N = number of subjects; n = number of observations; CI = confidence interval; SE = standard error
Populations: ITT = intent-to-treat; OP = on-protocol
[a] time to loss of virologic response (TLOVR)
[b] NC = F

Resistance Determinations

Virologic response at Week 96 (viral load < 400 copies/mL) was higher with DRV/rtv than with LPV/rtv, regardless of the number of baseline DRV RAMs or LPV RAMs, or the baseline LPV FC.

The number of virologic failures was lower in the DRV/rtv group (41 subjects, 13.8%) compared to the LPV/rtv group (76 subjects, 25.6%). Fewer virologic failures treated with DRV/rtv than with LPV/rtv developed additional mutations during the treatment period: 15.4% versus 22.2% DRV RAMs, 28.2% versus 40.3% IAS-USA LPV RAMs, 17.9% versus 34.7% primary PI mutations, 38.5% versus 51.4% IAS-USA PI RAMs and 10.3% versus 27.8% IAS-USA NRTI RAMs, respectively. Fewer virologic failures treated with DRV/rtv than with LPV/rtv lost susceptibility to PIs or NRTIs after treatment. Nineteen percent (7/37) of subjects in the DRV/rtv group lost susceptibility to a PI after treatment compared to 36.2% (25/69) of subjects in the LPV/rtv group. After treatment, only 8.3% (3/36) of virologic failures in the DRV/rtv group lost susceptibility to DRV (FC > 10), whereas 30.9% (17/55) of virologic failures in the LPV/rtv group lost susceptibility to LPV (FC > 10). After treatment, 18.4% (7/38) of DRV/rtv-treated subjects versus 40.9% (27/66) of LPV/rtv-treated subjects lost susceptibility to a NRTI, and 11.4% (4/35) versus 36.4% (20/55) of subjects, respectively, lost susceptibility to the NRTI(s) used in the OBR. Fewer virologic failures treated with DRV/rtv than with LPV/rtv lost susceptibility to other PIs than the studied PI. Most of the DRV/rtv virologic failures retained susceptibility to all PIs.

Quality of Life

	N	DRV/rtv	N	LPV/rtv
ITT[a] - Change in Total FAHI Imputed Score from baseline, mean (SE)	233	0.8 (1.56)	220	0.9 (1.55)
ITT[a] - Clinically meaningful difference in Total FAHI Imputed Score from baseline[b], n (%)	233	60 (25.8)	220	59 (26.8)

N = number of subjects; n = number of observations; ITT = intent-to-treat population
[a] LOCF
[b] Relative increase of 10%

Safety (n = number of subjects with data)	**DRV/rtv** **N = 298**	**LPV/rtv** **N =297**
Mean Exposure (weeks)	***80.71***	***76.36***
Adverse Events		
≥ 1 AE	281 (94.3)	281 (94.6)
Most common AEs[a]		
Diarrhea	105 (35.2)	138 (46.5)
Nausea	58 (19.5)	65 (21.9)
Nasopharyngitis	46 (15.4)	39 (13.1)
Upper respiratory tract infection	45 (15.1)	32 (10.8)
Headache	36 (12.1)	26 (8.8)
Abdominal pain	35 (11.7)	24 (8.1)
Vomiting	31 (10.4)	23 (7.7)
Bronchitis	30 (10.1)	28 (9.4)
Hypertriglyceridemia	24 (8.1)	32 (10.8)
Deaths	3[b] (1.0)	4 (1.3)
≥ 1 SAE	41 (13.8)	49 (16.5)
≥ 1 AE leading to permanent stop	24 (8.1)	24 (8.1)
≥ 1 grade 3 or 4 AE	92 (30.9)	106 (35.7)
Most common AEs of interest (grouped term)[a]		
GI-Related AEs	166 (55.7)	174 (58.6)
Lipid-related AEs	66 (22.1)	72 (24.2)
Rash-Related AEs	59 (19.8)	27 (9.1)
Lipodystrophy-Related AEs	30 (10.1)	30 (10.1)
Liver-Related AEs[c]	30 (10.1)	24 (8.1)

N = number of subjects; n = number of observations

[a] In ≥ 10% (rounded %) of subjects in any treatment group

[b] One subject died under DRV/rtv treatment during the extension phase.

[c] The grouped term 'liver-related AEs' includes liver-related AEs concerning clinical terms and liver-related AEs concerning laboratory test-related terms.

Clinical Laboratory	The majority of graded laboratory abnormalities was grade 1 or 2 in severity. Grade 3 or 4 liver-related abnormalities were observed with similar frequency in both treatment groups: in 3.1% and 3.4% of subjects in the DRV/rtv and LPV/rtv groups for AST, 3.4% and 4.1% of subjects for ALT, and 0.6% versus 0.3% of subjects for hyperbilirubinemia. Grade 3 or 4 increases in triglycerides were observed less frequently in the DRV/rtv group than in the LPV/rtv group (10.0% versus 15.9%). Grade 3 increased total cholesterol was observed in 9.7% versus 13.5%, grade 3 increases in LDL in 7.7% versus 9.3%, and grade 3 or 4 hyperglycemia in 1.7% versus 0.3% of subjects in the DRV/rtv and LPV/rtv groups, respectively. Grade 3 increased amylase was observed in 6.6% versus 2.8% of subjects in the DRV/rtv and LPV/rtv groups, and grade 3 or 4 increased lipase in 2.4% versus 0.3%; the incidence of amylase and lipase abnormalities reported as an AE was similar for both treatment groups; only 1 abnormality in each group (pancreatitis and increased blood amylase) was reported as an SAE. The incidence of grade 3 or 4 hematology-related abnormalities was low for both treatment groups with 0% versus 1.1% for PT, 1.1% versus 1.4% for PTT, 0% versus 1.0% for hemoglobin, 0.3% versus 0% for WBC count, 0.3% versus 1.0% for platelet count, and 0.7% versus 2.4% for neutrophils in the DRV/rtv and LPV/rtv groups, respectively. Grade 3 or 4 increases in ALT and AST were less frequent in DRV/rtv-treated subjects with hepatitis B or C coinfection (12.2% and 10.2%, respectively) than in LPV/rtv-treated subjects with coinfection (25.0% and 22.2%, respectively).

Cardiovascular Safety	None of the observed mean changes from baseline in vital signs parameters and no between-group differences were considered clinically relevant. The incidence of the individual abnormalities for vital signs parameters was generally comparable for both treatment groups. The most common vital signs abnormalities were abnormally high blood pressure values. Grade 3 abnormally high standing DBP occurred in 3.8% of subjects in the DRV/rtv group and 1.7% of subjects in the LPV/rtv group; all other grade 3 abnormalities for vital signs parameters occurred in ≤ 3% of subjects in either treatment group. At Week 96, the ECG analysis showed mean changes from baseline of 2.8 ms for QTcF in both groups and 0 ms and –2.2 ms for QTcB in the DRV/rtv and LPV/rtv groups. For PR interval, a mean increase versus baseline up to 1.9 ms was observed for the DRV/rtv group, compared to a mean increase up to 7.6 ms for the LPV/rtv group. The incidence of the individual abnormalities for ECG parameters was generally comparable for both treatment groups. QTcF values of > 500 ms were not observed. Increases in QTcF of > 60 ms were observed in 2.1% and 1.8% of subjects in the DRV/rtv and LPV/rtv group, respectively.
Other Safety Parameters	There were no clinically relevant changes over time in physical examination findings or anthropometric measurements. The incidence of AEs related to anthropometric measurements was low.

Conclusions

The efficacy analysis after 96 weeks of treatment in this well-controlled, Phase III trial showed sustained noninferiority and superiority in virologic response (viral load < 400 copies/mL) of DRV/rtv 600/100 mg b.i.d. in comparison with LPV/rtv 400/100 mg b.i.d., both administered with an individualized OBR in this ARV treatment-experienced, LPV/rtv naïve, HIV-1 infected population. Noninferiority at Week 96was also observed for the secondary efficacy parameter viral load < 50 copies/mL. The number of virologic failures was lower in the DRV/rtv group than in the LPV/rtv group. Fewer virologic failures treated with DRV/rtv than with LPV/rtv developed resistance to PIs or NRTIs. Most of the DRV/rtv virologic failures retained susceptibility to all PIs.

The safety data confirmed that treatment with DRV/rtv 600/100 mg b.i.d. was generally safe and well tolerated when administered for a period of 96 weeks. Compared to the analysis at Week 48, no relevant new safety findings were identified after 96 weeks of treatment. No remarkable differences in safety were observed between the 2 treatment groups, except for a lower incidence of diarrhea and grade 3 or 4 increases in triglycerides, and a higher incidence of rash-related AEs with DRV/rtv than with LPV/rtv.

Disclaimer

Disclaimer Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.