SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. **Trade Name**: Prezista™ **Indication**: HIV-1 infection	**Drug Substance**: darunavir **Trial no**.: TMC114-C211 **Clinical Phase**: III
Title: A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of darunavir/rtv versus lopinavir/rtv in treatment-naïve HIV-1 infected subjects. Week 48 Primary efficacy analysis.	
Investigator: R. Ortiz, Orlando Immunology Center, 1701 N Mills Ave, Orlando 32803, USA	**Country**: Multicenter
Trial Period: Start: 15-Jul-2005 End: 13-Jun-2007 (cut-off date of Week-48 primary efficacy analysis)	**No. of Investigators**: 117 **No. of Subjects**: 689
Objectives: The primary objective of this Week-48 analysis was to demonstrate non-inferiority in virologic response (time to loss of virologic response [TLOVR]), defined as a confirmed plasma viral load of < 50 copies/mL, with DRV/rtv (800 mg/100 mg q.d.) versus LPV/rtv (800 mg/200 mg total daily dose) at 48 weeks, when administered in combination with a fixed background regimen, consisting of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in a treatment-naïve, HIV-1 infected population with a predefined delta of non-inferiority of 12%. Secondary objectives were to evaluate other virologic parameters and immunologic parameters, to compare the quality of life, to assess pharmacokinetics, resistance characteristics, pharmacokinetic/pharmacodynamic relationships, and to evaluate safety and tolerability over time.	
Design: This trial TMC114-C211 is a randomized, controlled [lopinavir (LPV)/ritonavir (rtv)], open-label Phase III trial to determine the efficacy, safety and tolerability of darunavir (DRV, also known as TMC114) 800 mg, formulated as an oral tablet, and administered with a 100 mg dose of ritonavir and other antiretroviral drugs (ARVs) over a 192-week treatment period. Six hundred and sixty treatment naïve, HIV-1 infected subjects with viral load > 5000 HIV-1 RNA copies/mL were to be randomized. At baseline, eligible trial subjects started their antiretroviral therapy consisting of a protease inhibitor (randomized in a 1:1 ratio to 800/100 mg DRV/rtv q.d. or a daily dose of 800/200 mg LPV/rtv) combined with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine. Virologic parameters, safety, tolerability, durability of efficacy, resistance characteristics, pharmacokinetics, pharmacokinetic-pharmacodynamic relationships, subject-reported side effects and symptoms and adherence, medical resources utilization, health related quality of life and the monitoring of potential body changes through anthropometric measurements were assessed. The trial included a screening period of approximately 14 to 28 days, and a 192 week treatment period followed by a 4-week follow-up period. Subjects meeting the per protocol defined criteria for virologic failure (DRV/rtv or LPV/rtv) or who experienced a grade 4 adverse event (AE) or confirmed grade 4 (or specific grade 3) laboratory abnormality considered at least possibly related to DRV/rtv or LPV/rtv, could enter the 96-week rollover phase of the trial. In the rollover phase, subjects received subsequent antiretroviral therapy with DRV/rtv or LPV/rtv in combination with an optimized background regimen consisting of at least 2 investigator-selected ARVs. The present report describes the results of the primary efficacy analysis. The cut-off date for this analysis was 13 June 2007, at which time all subjects had reached Week 48 of treatment or discontinued earlier.	
Subject Selection ***Inclusion Criteria*** 1. Male or female, aged 18 years or older. 2. Documented HIV-1 infection. 3. Screening plasma HIV-1 RNA ≥ 5000 copies/mL. 4. Subjects qualified for treatment initiation based on the investigator's assessments and/or according to treatment guidelines. *Note*: Most current treatment guidelines recommend considering initiation of ART when CD4+ cell counts are below 350 cells/µL. However, clinical situations may warrant initiating ART with CD4+ cell counts above 350 cells/µL. Examples of such situations would include rapidly declining CD4+ cell counts over time, high plasma viral load, history of AIDS-defining illnesses or severe symptoms of HIV infection. 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 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: An AIDS defining illness not clinically stabilized for at least 30 days was considered as currently active.

   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. Any condition (including but not limited to 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. Previous or current use of ARVs (including both investigational as well as commercially available ARVs indicated for the treatment of HIV-infection and ARVs for treatment of hepatitis B infection with anti-HIV activity (e.g., adefovir, lamivudine, emtricitabine)).

   Note: Women who used a single dose of 200 mg of nevirapine to prevent mother-to-child transmission (MTCT) were allowed in the trial, as long as they had never received other ARVs. Women who had used zidovudine to prevent MTCT were not allowed as this could have resulted in reduced susceptibility to the fixed background regimen.

   Note: Subjects treated for postexposure prophylaxis were not allowed.
4. Primary HIV infection.

   Note: Primary or acute HIV infection is the first phase of HIV disease, occurring in the weeks immediately following infection by HIV and lasting for approximately 3 to 6 months. A viral load test at this stage will usually show extremely high levels of HIV in the blood - often higher than at any other stage of HIV infection, and may therefore not be reliable when evaluating the need for initiating antiretroviral therapy.
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 intra uterine 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 not allowed.

11. Any active clinically significant disease (e.g., cardiac dysfunction, pancreatitis, acute viral infection) 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. Subjects with calculated creatinine clearance (CL_{Cr}) < 70 mL/min.
14. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the investigational medication (DRV) or to LPV, ritonavir, TDF or FTC.
    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.
15. 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:
    - Drop in viral load < 1.0 $\log_{10}$ at Week 12 that was confirmed by 2 consecutive measurements. Confirmation could be obtained by performing an unscheduled visit;
    - Plasma HIV-1 RNA > 50 copies/mL at or beyond Week 24 that was confirmed by 2 consecutive measurements. Confirmation could be obtained by performing an unscheduled visit.

    Note: Subjects rolling over due to virologic failure had to have participated in the trial for at least 12 weeks. Subjects who discontinued treatment due to virologic failure prior to Week 12, were not eligible to participate in the rollover phase unless they also experienced treatment-limiting toxicity.

    Note: Subjects experiencing virologic failure only, could remain on their current regimen or undergo a temporary treatment interruption until the baseline visit of the rollover phase.
2. Treatment-limiting toxicities including at least one of the following specific AEs/confirmed laboratory abnormalities:
    - a grade 3 or 4 cutaneous reaction/rash (according to the DAIDS scale).
    - a confirmed lipase elevation of grade 3 or 4, which persisted after 14 days following the interruption of all trial medications, or if the toxicity recurred more than twice
    - a confirmed recurrence of grade 3 or 4 increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) after trial medication interruption because of a confirmed grade 3 increase in ALT or AST.
    - a grade 4 AE or confirmed grade 4 laboratory abnormality considered at least possibly related to DRV/rtv or LPV/rtv. Exceptions were, unless clinical assessment foresaw an immediate health risk to the subject:
        - subjects with pre-existing diabetes or with non-fasted or asymptomatic glucose grade 4 elevations
        - subjects with non-fasted or asymptomatic triglyceride elevations of grade 4.

      Note: A temporary treatment interruption of all components of the regimen was to be respected to allow resolution or that the severity decreased to grade 2 or below before starting intake of DRV/rtv or LPV/rtv. During follow-up of the abnormality, the abnormality had to be monitored and unscheduled visits could be used to assess resolution of the abnormality.

      Note: TDF/FTC was to be continued if toxicity was unrelated to the fixed background regimen, unless virologic failure was observed and optimization of background regimen was needed.

      Note: The dose of DRV/rtv was to be determined by reason for failure.

Treatment	**DRV**	**Ritonavir (Norvir®)**	**LPV/rtv (Kaletra®)**
Concentration	400-mg tablet	100-mg capsule	capsule, 133.3/33.3 mg or tablet, 200/50 mg
Formulation	F021	-	-
Usage	Oral	Oral	Oral
Dose Regimen	DRV/rtv 800/100 mg q.d.		LPV/rtv 800/200 mg q.d. (or 400/100 mg b.i.d. where once daily dosing was not approved).
Duration of Treatment	max. 192 weeks		
Duration of Trial	Screening period: maximum 4 weeks; treatment period: maximum 192 weeks; follow-up period: 4 weeks		
Disallowed Medication	*Disallowed for all subjects from screening until the end of the treatment period:* - 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. - all ARVs other than the trial medication with the fixed background regimen (TDF/FTC) *Disallowed for all subjects from screening until baseline:* - herbal supplements: all products containing *Hypericum perforatum* (St John's Wort); - antibiotics: rifampin, rifapentine; - anticonvulsants: phenobarbital, phenytoin, carbamezepine, modafenil; - steroids: systemic dexamethasone (topical formulations were allowed). *Disallowed for all DRV/rtv subjects from baseline until the end of the treatment period:* - 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, carbamazepine, modafenil; - antiarrhythmics: bepridil, flecainide, propafenone, systemic lidocaine, quinidine, mexilitine, disopyramide, amiodarone; - immunosuppressants: cyclosporin, rapamycin, tacrolimus, sirolimus; - antihistamines: astemizole, terfenadine; - prokinetic: 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 ketoconazole, or itraconazole at > 200 mg/day		

Assessments	
Efficacy	
Plasma Viral Load	Samples for plasma viral load determinations: - prescreening, screening, baseline; - Weeks 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180 and 192 (or early withdrawal); - first and second follow-up visits.
Immunology	Samples for immunology assessment: - prescreening, screening, baseline; - Weeks 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180 and 192 (or early withdrawal); - the first and second follow-up visits.
Resistance Determinations	Samples for pheno- and genotype determinations: - screening, baseline; - Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180 and 192 (or early withdrawal); - both follow-up visits. Samples taken at Weeks 4, 8, 12, 16, 36, 60, 84, 108, 132, 156 and 180 and both follow-up visits were only analyzed when judged appropriate by the Protocol Virologist. Peripheral blood mononuclear cells (PBMC) sample for characterization of archived viral resistance: - baseline; - Week 96 (or early withdrawal).
Questionnaires	Only if validated translated versions were available and not for rollover subjects: FAHI QoL questionnaire: - baseline; - Weeks 4, 12, 24, 48, 72, 96, 120, 144, 168 and 192 (or early withdrawal). EQ-5D questionnaire: - baseline; - Weeks 48, 96, 144 and 192 (or early withdrawal). M-MAS-SF questionnaire: - baseline; - Weeks 4, 12, 24, 48, 72, 96, 120, 144, 168 and 192 (or early withdrawal). M-MASRI questionnaire: - Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180 and 192 (or early withdrawal).
Safety	
Adverse Events	AEs and HIV-related events were checked at every visit and reported from screening onwards until the last trial-related activity.

Clinical Laboratory	Samples for hematology, biochemistry (fasted): - screening, baseline; - Weeks 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180 and 192 (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 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180 and 192 (or early withdrawal). Urinalysis: - screening, baseline; - Weeks 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180 and 192 (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 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180 and 192 (or early withdrawal). ECG readings: - screening, baseline; - Weeks 4, 24, 48, 72, 96 and 192 (or early withdrawal).
Physical Examination	Physical examination: - screening, baseline; - Weeks 12, 24, 48, 72, 96, 120, 144, 168 and 192 (or early withdrawal).
Anthropometric Measurements	Height: - screening, baseline Weight, waist and hip circumference: - screening (weight only), baseline; - Weeks 24, 48, 72, 96, 120, 144, 168 and 192 (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.
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, Kruskal-Wallis test, Mann-Whitney U-test.

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics	**DRV/rtv**	**LPV/rtv**	**All Subjects**
Number of Subjects (M/F)	343 (239/104)	346 (241/105)	689 (480/209)
Age (years), median (range)	34.0 (18; 70)	33.0 (19; 68)	34.0 (18; 70)
Race	342	344	686
Caucasian	137 (40.1)	153 (44.5)	290 (42.3)
Black	80 (23.4)	71 (20.6)	151 (22.0)
Hispanic	77 (22.5)	77 (22.4)	154 (22.4)
Oriental/Asian	44 (12.9)	38 (11.0)	82 (12.0)
Other	4 (1.2)	5 (1.5)	9 (1.3)
Log_{10} plasma viral load (copies/mL), mean (SD)	4.86 (0.638)	4.84 (0.604)	4.85 (0.621)
CD4+ cell count (x 10^6/L), median (range)	228 (4; 750)	218 (2; 714)	225 (2; 750)
Known duration HIV infection (years), median (range)	1.1 (0; 22)	1.2 (0; 21)	1.1 (0; 22)
Clinical stage of HIV infection, n (%),			
A	226 (65.9)	217 (62.7)	443 (64.3)
B	91 (26.5)	95 (27.5)	186 (27.0)
C	26 (7.6)	34 (9.8)	60 (8.7)
Subject Disposition			
Discontinuations - Reason	40 (11.8)	56 (16.2)	96 (14.0)
Adverse event/HIV related event[a]	11 (3.2)	24 (6.9)	35 (5.1)
Subject reached a virologic endpoint[a]	2 (0.6)	6 (1.7)	8 (1.2)
Subject lost to follow-up	14 (4.1)	10 (2.9)	24 (3.5)
Subject withdrew consent	4 (1.2)	5 (1.4)	9 (1.3)
Subject noncompliant	2 (0.6)	5 (1.4)	7 (1.0)
Other	0	2 (0.6)	2 (0.3)
Subject ineligible to continue the trial	1 (0.3)	1 (0.3)	2 (0.3)
Sponsor's decision	1 (0.3)	0	1 (0.1)
Subject was pregnant	5 (1.5)	3 (0.9)	8 (1.2)

n = number of observations.

[a] Including subjects starting the rollover phase

Efficacy

The efficacy results of this trial demonstrated noninferiority in virologic response defined as a confirmed plasma viral load of < 50 copies/mL at Week 48 (primary efficacy parameter) with DRV/rtv 800/100 mg q.d. when compared to a daily dose of LPV/rtv 800/200 mg (both in combination with a fixed background regimen of TDF/FTC). The results for the primary efficacy parameter were supported by those for the secondary virologic parameters.

Parameter, at Week 48	DRV/rtv 800/100 mg q.d.		LPV/rtv 800/200 mg daily dose		Difference [95% CI] in Response
Primary Variable	**N**		**N**		
OP[a] - Viral load < 50 copies/mL, n (%)	340	285 (83.8)	346	271 (78.3)	5.5 [-0.4; 11.4]
ITT[a] - Viral load < 50 copies/mL, n (%)	343	287 (83.7)	346	271 (78.3)	5.3 [-0.5; 11.2]
Secondary Variables	**N**		**N**		
ITT[a] - Viral load < 400 copies/mL, n (%)	343	301 (87.8)	346	295 (85.3)	2.5 [-2.6; 7.6]
ITT[a] - Viral load decrease ≥ 2.0 $\log_{10}$ copies/mL from baseline, n (%)	343	294 (85.7)	346	293 (84.7)	1.0 [-4.3; 6.3]
ITT[b] - Change in $\log_{10}$ viral load from baseline (copies/mL), mean (SE)	343	-2.77 (0.064)	346	-2.65 (0.068)	-0.11 [-0.30; 0.07]
ITT[b] - Change in CD4+ cell count from baseline (x 10^6/L), mean (SE)	342	154 (7.4)	345	161 (7.1)	-7 [-27; 13]

N = number of subjects; n = number of observations; CI = confidence interval
Populations: ITT = intent-to-treat; OP = on-protocol.
[a] TLOVR.
[b] NC = F.

Resistance Determination

The percentage of virologic failures, (rebounders and subjects who were never suppressed using the TLOVR [non-VF censored algorithm] defined as loss of or never achieving a plasma viral load < 50 copies/mL, respectively), was lower in the DRV/rtv group than in the LPV/rtv group. Of the 343 DRV/rtv subjects, 34 (9.9%) experienced virologic failure versus 49 of 346 (14.2%) LPV/rtv subjects. In the DRV/rtv group, 8 (2.3%) subjects were rebounders and 26 (7.6%) subjects were never suppressed. In the LPV/rtv group, 10 (2.9%) subjects were rebounders and 39 (11.3%) subjects were never suppressed. Development of resistance was assessed in the virologic failures for which matching baseline/endpoint genotypic profiles were available, 10 and 18 subjects in the DRV/rtv and LPV/rtv group, respectively. In the virologic failures of the DRV/rtv group, there were no emerging PI-RAMs identified. In one subject of the LPV/rtv group, 2 PI RAMs emerged by endpoint. In 1 subject of the DRV/rtv group and 2 subjects of the LPV/rtv group, 1 developing NRTI RAM was identified at endpoint, which was associated with a decreased susceptibility to FTC included in the background regimen.

FAHI Questionnaire	DRV/rtv 800/100 mg q.d.		LPV/rtv 800/200 mg daily dose	
	N		**N**	
ITT[a] – Change in Total FAHI Imputed Score from baseline, mean (SE)	298	9.4[c] (1.33)	291	11.7 (1.45)
ITT[a] – Clinically meaningful difference in Total FAHI Imputed Score from baseline[b], n (%)	298	119[c] (40)	291	124 (43)

N = number of subjects; n = number of observations; ITT = intent-to-treat population.
[a] LOCF.
[b] Relative increase of 10%.
[c] Not statistically significant in pairwise comparison with LPV/rtv.

EQ-5D Questionnaire	DRV/rtv 800/100 mg q.d.		LPV/rtv 800/200 mg daily dose	
	N		N	
ITT[a] – Change in EQ-5D Imputed Valuation Index from baseline, mean (SE)	296	0.03[b] (0.01)	291	0.06 (0.01)
ITT[a] – Change in EQ-5D VAS from baseline, n (%)	294	7.6[b] (0.96)	292	9.5 (1.09)

N = number of subjects; n = number of observations; ITT = intent-to-treat population.
[a] LOCF.
[b] Not statistically significant in pairwise comparison with LPV/rtv.

Safety, n (%)	DRV/rtv 800/100 mg q.d. N = 343	LPV/rtv 800/200 mg daily dose N = 346
Mean Exposure (weeks)	***54.8***	***53.3***
Adverse Events, n (%)		
≥ 1 AE	309 (90.1)	328 (94.8)
Most common AEs[a]		
Diarrhea	115 (33.5)	180 (52.0)
Nausea	55 (16.0)	99 (28.6)
Headache	60 (17.5)	50 (14.5)
Upper respiratory tract infection	53 (15.5)	49 (14.2)
Nasopharyngitis	43 (12.5)	37 (10.7)
Abdominal pain	32 (9.3)	42 (12.1)
Vomiting	21 (6.1)	38 (11.0)
Cough	19 (5.5)	36 (10.4)
Deaths	1 (0.3)	3 (0.9)
≥ 1 SAE	25 (7.3)	41 (11.8)
≥ 1 SAE at least possibly related[b]	3 (0.9)	9 (2.6)
≥ 1 AE at least possibly related[b]	172 (50.1)	241 (69.7)
≥ 1 AE leading to permanent stop	16 (4.7)	27 (7.8)
≥ 1 AE leading to permanent stop and at least possibly related[b]	6 (1.7)	12 (3.5)
≥ 1 grade 3 or 4 AE	64 (18.7)	75 (21.7)
≥ 1 grade 3 or 4 AE at least possibly related[b]	21 (6.1)	33 (9.5)
Adverse Events of Interest, n (%)		
Any rash-related AE	50 (14.6)	46 (13.3)
Any cardiac-related AE	17 (5.0)	10 (2.9)
Any gastrointestinal-related AE	176 (51.3)	245 (70.8)
Any liver-related AE	16 (4.7)	31 (9.0)
Any lipid-related AE	19 (5.5)	43 (12.4)
Any glucose-related AE	6 (1.7)	2 (0.6)

N = number of subjects; n = number of patients with observations.
[a] In ≥ 10% (rounded %) of subjects of any treatment group.
[b] In the opinion of the investigator

Clinical Laboratory	The majority of graded laboratory abnormalities was grade 1 or 2 in severity. Grade 2-4 abnormalities were observed in 8.5% and 10.2% of subjects in the DRV/rtv and LPV/rtv groups, respectively for ALT, and 9.4% and 9.1% of subjects in the DRV/rtv and LPV/rtv groups, respectively, for AST. Grade 2-4 increases in triglycerides were observed less frequently in the DRV/rtv group (2.9%) than in the LPV/rtv group (11.1%). Furthermore, grade 2-4 increases in total cholesterol were also observed less frequently with DRV/rtv (12.8%) than with LPV/rtv (22.7%). The overall incidence of other laboratory abnormalities was low and generally comparable for the DRV/rtv and LPV/rtv treatment groups.
Cardiovascular Safety	Small median changes from baseline were observed for vital signs parameters in both treatment groups. None of the observed mean changes from baseline and no between-group differences for any of the vital signs parameters were considered clinically relevant. The QTcF abnormalities observed were generally transient occurrences, which resolved with continued dosing.
Other Safety Parameters	There were no clinically relevant changes over time in physical examination findings. For anthropometric measurements, an increase in mean weight from baseline to Week 48 was seen in both treatment groups, which was more pronounced in the DRV/rtv group; mean weight increase versus baseline was 2.9 kg in the DRV/rtv group and 1.3 kg in the LPV/rtv group.

Pharmacokinetics of DRV 800 mg q.d., median (range)	**DRV/rtv N = 335**
AUC_{24h}, ng.h/mL	87854 (45000; 219240)
C_{0h}, ng/mL	2041.2 (368.1; 7241.6)
All subjects had trough concentrations that were above the protein binding corrected EC_{50} value of 55 ng/mL. Age and weight did not appear to influence the DRV AUC_{24h} or C_{0h} values. Higher baseline AAG levels were associated with higher values for AUC_{24h} and C_{0h}. Female subjects had an approximately 10% (N = 102) higher exposure compared to males (N = 233). There was an approximately 13% lower exposure in Asian subjects (N = 44) compared to Caucasian subjects (N = 135). These differences in exposure had no clinical impact/relevance.	

N = number of subjects with data.

Pharmacokinetic/Pharmacodynamic Relationships
No relevant relationships were observed between the DRV pharmacokinetics and efficacy parameters at Week 48 and no apparent relationships were observed between DRV pharmacokinetics and safety.

Conclusions

The efficacy response (83.7% for < 50 copies/mL at Week 48) observed in subjects receiving DRV/rtv 800/100 mg q.d. provides evidence of the potency of a DRV-containing regimen in this patient population. Noninferiority in virologic response (viral load < 50 copies/mL) compared to treatment with LPV/rtv 800/200 mg total daily dose was demonstrated. Furthermore, absolute responses observed for subjects receiving LPV/rtv (78.3% achieving < 50 copies/mL at Week 48) are among the highest reported for LPV in a phase III study in naïve patients and validate the comparator chosen. The trial included a diverse population of ART-naïve subjects representative of different ethnic backgrounds, gender and geographic regions. Results are robust in view of the low discontinuation rates in each treatment group and the high overall response rates in both groups (up to 84% for DRV/rtv) in comparison with other trials in treatment naïve, HIV-1 infected subjects.

The safety data confirmed that treatment with DRV/rtv 800/100 mg q.d. was generally safe and well tolerated with a similar incidence of rash-related events but a more favorable overall safety profile compared with LPV/rtv (800/200 mg total daily dose) with respect to gastrointestinal disorders and lipid-related disorders.

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