SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals, formerly Tibotec Pharmaceuticals Ltd **Trade Name**: Prezista® **Indication**: HIV-1 Infection	**Drug Substance**: Darunavir (TMC114) **Trial no**.: TMC114-C211 **Clinical Phase**: III
Title: A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1 infected subjects. Week-192 analysis. This trial is referred to as ARTEMIS.	
Investigator: R. Ortiz, Orlando Immunology Center, 1701 N Mills Avenue, Orlando FL, 32803 US	**Country**: Multicenter
Trial Period: Start: 15-Jul-2005 End: 29-Mar-2010 (cut-off for the Week-192 analysis)	**No. of Investigators**: 117 **No. of Subjects**: 689

Objectives

Main Phase

The primary objective of the trial was to demonstrate noninferiority in virologic response (time to loss of virologic response, TLOVR), defined as confirmed plasma viral load < 50 copies/mL, with DRV/rtv versus LPV/rtv at 48 weeks, when administered in combination with a fixed background regimen, consisting of TDF and FTC.

Secondary objectives of the trial were:

- to evaluate the durability of virologic response over 192 weeks;
- to evaluate the superiority for virologic response in case DRV is noninferior;
- to compare the immunologic response;
- to evaluate the resistance characteristics;
- to determine and compare the subject-reported adherence to the ARV medication in subjects treated with DRV/rtv and LPV/rtv, in combination with TDF/FTC;
- to evaluate safety and tolerability over 192 weeks;
- to monitor potential body changes through anthropometric measurements;
- to assess the population pharmacokinetics of DRV in this treatment-naïve population;
- to evaluate the pharmacokinetic/pharmacodynamic relationship.

Extension Phase

The objective was to provide DRV/rtv access to subjects living in a region where DRV was not yet commercially available, not yet reimbursed by the public and/or private health system, or could not be accessed from another source (e.g., access program, government program).

Design: This was a randomized, controlled (lopinavir [LPV]/ritonavir [rtv]), open-label Phase III trial to determine the efficacy, safety and tolerability of darunavir (DRV, formerly TMC114), formulated as an oral tablet, and administered with a 100-mg dose of rtv and other antiretroviral (ARV) drugs over a 192-week treatment period. Six hundred and sixty HIV-1 infected subjects who never received treatment with an ARV were to be randomized.

At baseline, the eligible subjects started ARV therapy that consisted of a protease inhibitor (PI) (randomized in a 1:1 ratio to DRV/rtv 800/100 mg q.d., or LPV/rtv 800/200 mg daily dose) combined with a fixed background regimen consisting of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC).

This trial included a screening period of approximately 14 to 28 days, and a 192-week treatment period. In case a subject had an ongoing adverse event (AE) at withdrawal, there was a 4-week follow-up period. In the original Protocol, subjects from both the DRV/rtv or LPV/rtv treatment groups meeting the per protocol defined criteriafor virologic failure or who experienced treatment-limiting toxicity, and who -based on the investigator's assessment- might have benefited from a change from DRV/rtv to LPV/rtv-based therapy or vice versa, could participate in a rollover phase (in which they received DRV/rtv q.d. or b.i.d., depending on their reason for switch). After Protocol Amendment TMC114-C211-CTPA-GEN-III, this rollover phase was no longer available. In regions where DRV was was not yet commercially available or not yet reimbursed by the public and/or private health system, subjects who completed 192 weeks of treatment with DRV/rtv q.d. in the main phase of the trial (or, if applicable, who received treatment with DRV/rtv q.d. or b.i.d. in the rollover phase) and who continued to benefit

from this treatment, had the opportunity to continue the same DRV/rtv treatment in the extension phase of this trial. In addition, subjects randomized to LPV/rtv in the main phase of the trial, who met the virologic failure criteria or who experienced intolerance, could enter the extension phase by switching to a DRV/rtv-containing regimen (q.d. or b.i.d., depending on their reason for switch). Subjects had access to DRV/rtv in the extension phase until DRV was commercially available, reimbursed or could be accessed from another source (e.g., access program, government program).

Subject Selection

Main Phase

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 qualifed 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 < 350 cells/μL. However, clinical situations may warrant initiating ART with CD4+ cell counts > 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. Subjects had voluntarily signed the ICF.
6. Subjects could comply with the protocol requirements.
7. General medical condition, in the investigator's opinion, did not interfere 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 ≥ 30 days was considered as currently active.
   Note: Primary and secondary prophylaxis for an AIDS-defining illness was allowed in case the medication used is not part of the disallowed medication.
2. Any condition (including but not limited to alcohol and drug use), which, in the opinion of the investigator, could compromise the subject's safety or adherence to the trial protocol.
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, FTC]).
   Note: Women who (had) 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 result 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 usually shows 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 ART.
5. Use of any 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 (IUD) in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom),
   - be non-heterosexually 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 in the trial.
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 were expected to compromise the subject's safety or outcome in the trial.
12. Subjects with a grade 3 or 4 laboratory abnormality as defined by DAIDS grading table with the following exceptions unless clinical assessment foresaw an immediate health risk to the subject:
    - subjects with pre-existing diabetes or with asymptomatic glucose grade 3 or 4 elevations;
    - subjects with asymptomatic triglyceride or cholesterol elevations of grade 3 or 4.
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 rtv, LPV, TDF or FTC.
    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 sulfonamide class and DRV has been identified in subjects participating in Phase II trials.
15. Participation in other investigational or cohort trials without prior approval of the sponsor.

Extension Phase

Only for subjects who were living in a region where DRV was not yet commercially available by the public and/or private health system:

1. Subjects who completed 192 weeks of treatment with DRV/rtv in the main phase of the trial (or who received treatment with DRV/rtv in the rollover phase, if applicable) and who continued to benefit from this treatment.
2. Subjects randomized to LPV/rtv in the main phase of the trial, who met the virologic failure criteria or who experienced intolerance (treament-limiting toxicity), could switch to a DRV/rtv-based therapy.

- Lack or loss of treatment response was defined as:
  - decrease 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.
- Treatment-limiting toxicities included ≥ 1 of the following specific AEs/confirmed laboratory abnormalities:
  - a grade 3 or 4 cutaneous reaction/rash (according to the DAIDS grading table);
  - 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 LPV/rtv. Exceptions were, unless clinical assessment foresaw an immediate health risk to the subject:
    - subjects with pre-existing diabetes or with nonfasted or asymptomatic glucose grade 4 elevations;
    - subjects with nonfasted or asymptomatic triglyceride elevations of grade 4.

Treatment			
	DRV + rtv (Norvir®) (Main Phase and Extension)	**DRV + rtv (Norvir®) (Extension)**	**LPV/rtv (Kaletra®) (Main Phase)**
Concentration	400-mg tablet + 100-mg capsule	300-mg tablet + 100-mg capsule[a]	133.3/33.3-mg capsule, or 200/50-mg tablet
DRV Dosage Form	F021	F016	-
Usage	Oral	Oral	Oral
Dose Regimens	DRV/rtv 800/100 mg q.d. + TDF/FTC 300/200 mg q.d. as fixed background regimen (main phase), or investigator-selected background regimen (extension phase)	DRV/rtv 600/100 mg b.i.d.[a] + Investigator-selected background regimen [a] *For subjects who used this regimen in the stopped rollover phase.*	LPV/rtv 800/200 mg q.d., or 400/100 mg b.i.d. + TDF/FTC 300/200 mg q.d. as fixed background regimen
Duration of Treatment	Maximum 192 weeks		
Duration of Trial	Screening maximum 4 weeks; treatment maximum 192 weeks, follow-up 4 weeks (in case a subject had an ongoing AE at withdrawal), and if applicable, extension		
Disallowed Medication	**ARV Medication** No ARVs other than the trial medication and the fixed background regimen (TDF/FTC) were allowed during the main phase of the trial, although, in the context of prespecified AEs, the fixed background regimen could be changed. **Non-ARV Medication** Not permitted *from screening until the end of the treatment period*: - investigational agents (from 90 days before screening onwards); - experimental vaccines (approved vaccines were allowed if given ≥ 4 weeks before a viral load measurement). Not permitted *from screening until baseline*: - all products containing *Hypericum perforatum*; - phenobarbital, phenytoin, carbamazepine, modafinil; - rifampin, rifapentine; - systemic dexamethasone (topical formulations were allowed). Not permitted *from baseline until the end of the treatment period* (DRV/rtv only): - antiarrhythmics: bepridil, flecainide, propafenone, systemic lidocaine, quinidine, mexilitine, disopyramide, amiodarone; - antibiotics: rifampin, rifapentine, telithromycin; - anticonvulsants: phenobarbital, phenytoin, carbamazepine, modafinil; - antifungals: systemic use of ketoconazole, or itraconazole at > 200 mg/day. - antihistamines: astemizole, terfenadine; - antipsychotics: pimozide; - benzodiazepines: midazolam, triazolam; - ergot derivatives: dihydroergotamine, ergonovine, ergometrine, ergotamine, methylergonovine; - gastroprokinetics: cisapride - herbal supplements: all products containing *Hypericum perforatum*; - immunosuppressants: cyclosporin, rapamycin, tacrolimus, sirolimus; - lipid lowering agents & HMG-CoA reductase inhibitors: pravastatin, lovastatin, simvastatin;narcotic analgesics: meperidine (pethidine); - steroids: systemic dexamethasone (topical formulations were allowed); - stimulants: amphetamines, amphetamine derivatives.		

Assessments – Main Phase	
Pharmacokinetics	- Samples at: Weeks 4, 8, 24, 48, 72, 96, and withdrawal
Efficacy Plasma Viral Load Immunologic Change	 - Samples at: 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 withdrawal, and Week-4 follow-up
Resistance Determinations	- Samples for pheno- and genotype determinations at: screening, baseline, Weeks 24, 48, 72, 96, 120, 144, 168, and 192, or withdrawal - Samples taken at Weeks 4, 8, 12, 16, 36, 60, 84, 108, 132, 156, and 180: analyzed when judged appropriate by the Protocol Virologist based on HIV-1 pasma viral load - PBMC samples at: baseline, Week 192, or withdrawal
M-MASRI Questionnaire	- At Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, and 192, or withdrawal
Safety Adverse Events Clinical Laboratory	 AEs, HIV-related events, AIDS-defining illnessess, and dermatologic events checked at every visit and reported from signing the Informed Consent Form onwards until the last trial-related activity. - Samples for <u>hematology, biochemistry (fasted), and coagulation</u> at: 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 withdrawal, and Week-4 follow-up - <u>Urinalysis</u> at: 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 withdrawal - <u>Pregnancy testing</u> at: 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 withdrawal, and DRV switch/extension visit - <u>Hepatitis serology/viremia</u> at: screening, and at other visits only if diagnosis was suspected
Cardiovascular Safety	- <u>Vital signs</u> at: screeing, baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, and at 192, or withdrawal - <u>ECG</u> at: screening, baseline, Weeks 4 (following second pharmacokinetic blood draw), 24, 48, 72, 96, and 192 or withdrawal if deemed appropriate by the investigator
Physical Examination	- Screening, baseline, Weeks 12, 24, 48, 72, 96, 120, 144, 168, 192, or withdrawal
Anthropometric Measurements	- Screening, baseline, Weeks 24, 48, 72, 96, 120, 144, 168, 192, or withdrawal
Assessments – Extension Phase	
Adverse Events	Checked and recorded at every visit: - AEs at least possibly related to DRV/rtv; - AEs leading to discontinuation; - SAEs and pregnancies.
Clinical Laboratory	A urine pregnancy test for females of childbearing potential at every visit. Other tests could be performed by local laboratories.
Statistical Methods	
Main Phase	Intent-to-treat (ITT) and on-protocol (OP) analyses, descriptive statistics, frequency tabulations, intent-to-treat and on-protocol 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, Pearson's chi square test, Fischer's exact test.
Extension Phase	Frequency tabulations

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics	DRV/rtv 800/100 mg q.d.	LPV/rtv 800/200 mg Daily	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, N, n (%)	343	346	689
Black	80 (23.4)	71 (20.6)	151 (22.0)
Caucasian/White	137 (40.1)	153 (44.5)	290 (42.3)
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 of HIV infection (yrs), 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)
Number of mutations[a], median (range)			
Primary PI mutations	0.0 (0; 3)	0.0 (0; 2)	0.0 (0; 3)
PI RAMs	4.0 (0; 11)	3.5 (0; 8)	4.0 (0; 11)
DRV RAMs	0.0 (0; 2)	0.0 (0; 1)	0.0 (0; 2)
LPV RAMS	1.0 (0; 6)	1.0 (0; 3)	1.0 (0; 6)
Subject Disposition			
Discontinuations – Reason, n (%)	85 (24.8)	114 (32.9)	199 (28.9)
Adverse event/HIV related event[b]	16 (4.7)[c,d]	44 (12.7)[c]	60 (8.7)[e]
Subject lost to follow-up	21 (6.1)	17 (4.9)	38 (5.5)
Subject withdrew consent	19 (5.5)	18 (5.2)	37 (5.4)
Subject noncompliant	7 (2.0)	8 (2.3)	15 (2.2)
Subject is pregnant	9 (2.6)	6 (1.7)	15 (2.2)
Other	2 (0.6)	8 (2.3)	10 (1.5)
Subject ineligible to continue the trial	5 (1.5)	3 (0.9)	8 (1.2)
Subject reached a virologic endpoint[e]	5 (1.5)[e]	9 (2.6)[e]	14 (2.0)[e]
Sponsor's decision	1 (0.3)	1 (0.3)	2 (0.3)

N = number of subjects, n = number of observations

[a] IAS-USA 2009 list

[b] As assessed by the investigator.

[c] Including 3 and 5 subjects with DRV/rtv and LPV/rtv, respectively, who rolled over due to an AE.

[d] Not including Subject 211-0837, who discontinued due to an AE in the follow-up phase.

[e] Including 2 and 7 subjects with DRV/rtv and LPV/rtv, respectively, who rolled over due to virologic failure.

Efficacy

Consistent with the results of the Week-48 and Week-96 analyses, the Week-192 efficacy results of this trial demonstrated noninferiority in confirmed virologic response (plasma viral load of < 50 copies/mL, ITT- TLOVR) at Week 192 for DRV/rtv 800/100 mg q.d. (68.8%) when compared to LPV/rtv 800/200 mg total daily dose (57.2%), both in combination with a fixed background regimen of TDF/FTC, in view of the predefined delta of noninferiority of 12%. Furthermore, statistically significant superiority of DRV/rtv over LPV/rtv at Week 192 could be demonstrated. The results for the primary efficacy parameter with respect to noninferiority of DRV/rtv versus LPV/rtv were supported by those for the secondary virologic parameters. Virologic response was well sustained in both treatment groups, and the percentage of subjects with a confirmed virologic response of < 50 copies/mL (undetectable) at Week 48 who remained undetectable at Week 192 was higher with DRV/rtv group (81.3%) compared with LPV/rtv (68.5%).

Parameter at Week 192	**DRV/rtv 800/100 mg q.d.**		**LPV/rtv 800/200 mg Daily**		**Difference in Response [95% CI]**
Primary Variable	**N**		**N**		
ITT[a b] - Viral load < 50 copies/mL, n (%)	343	236 (68.8)	346	198 (57.2)	11.6 (4.4; 18.8)
OP[a] - Viral load < 50 copies/mL, n (%)	340	235 (69.1)	345	197 (57.1)	12.0 (4.8; 19.2)
Secondary Variables	**N**		**N**		
ITT[a] - Viral load < 400 copies/mL, n (%)	343	258 (75.2)	346	225 (65.0)	10.2 (3.4; 17.0)
ITT[c] - Change in $\log_{10}$ Viral Load From Baseline (copies/mL), mean (SE)	343	-2.35 (0.079)	346	-2.03 (0.084)	-0.32 (-0.55 ; -0.09)
ITT[c] - Change in CD4+ Cell Count From Baseline (x 10^6/L), mean (SE)	343	266 (11.9)	346	269 (13.6)	-3 (-38; 33)

N = number of subjects; n = number of observations; CI = confidence interval; SE = standard error; TLOVR = time to loss of virologic response; NC = F = non-completing is failure

[a] TLOVR

[b] Primary parameter

[c] NC = F

Outcome Table as per FDA Guidance (Snapshot Analysis)

n (%)	**DRV/rtv N = 343**	**LPV/rtv N = 346**
Virologic success (< 50 copies/mL) at Week 192	235 (68.5)	207 (59.8)
Virologic failure[b]	42 (12.2)	52 (15.0)
No virologic data at Week 192 - Discontinued due to AE/death[c]	16 (4.7)	44 (12.7)
No virologic data at Week 192 - Discontinued for other reasons[d]	49 (14.3)	43 (12.4)
No virologic data at Week 192 - On trial	1 (0.3)	0

N = number of subjects; n = number of observations

[a] Visit window is between Week 186 and Week 198.

[b] Includes 1) subjects who had ≥ 50 copies/mL in the 192-week window, 2) subjects who discontinued prior to Week 192 for lack or loss of efficacy, 3) subjects who had a switch in their OBR that was not permitted by the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of study medication), 4) subjects who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was detectable)

[c] Includes subjects who discontinued due to AE or death at any time point from Day 1 through the 192-week time window if this resulted in no virologic data on treatment during the specified window (provided the earliest AE leading to permanent stop was not preceeded by a switch in the OBR that was not permitted by the protocol)

[d] Includes subjects who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was undetectable)

Resistance Determinations
Consistent with the results of the Week-48 and Week-96 analyses, the percentage of virologic failures (rebounders and subjects who were never suppressed, defined as, respectively, loss of or never achieving a plasma viral load < 50 copies/mL [TLOVR non-VF censored]), was lower in the DRV/rtv group than in the LPV/rtv group. Of the 343 DRV/rtv subjects, 55 (16.0%) experienced virologic failure versus 71 out of 346 (20.5%) LPV/rtv subjects. In the DRV/rtv group, 39 (11.4%) subjects were rebounders and 16 (4.7%) subjects were never suppressed. In the LPV/rtv group, 49 (14.2%) subjects were rebounders and 22 (6.4%) subjects were never suppressed. Development of mutations was assessed in the virologic failures with paired baseline/endpoint genotypic profiles (43 and 57 subjects in the DRV/rtv and LPV/rtv group, respectively; genotype was determined on samples with viral load ≥ 50 copies/mL). Four (9.3%) DRV/rtv subjects and 9 (15.8%) LPV/rtv subjects with developing PI RAMs at endpoint were identified. None of the developing PI RAMs were primary (major) PI mutations. All DRV/rtv and LPV/rtv virologic failures, for which paired baseline/endpoint phenotypes were available (39 and 52 subjects in the DRV/rtv and LPV/rtv group, respectively), remained susceptible to DRV, LPV, amprenavir, atazanavir, indinavir, saquinavir, and tipranavir.

Safety, n (%)	**DRV/rtv 800/100 mg q.d. N = 343**	**LPV/rtv 800/200 mg Daily N = 346**
Mean Exposure (weeks)	***162.5***	***153.5***
Adverse Events		
≥ 1 AE	326 (95.0)	333 (96.2)
Most common AEs[a]		
Diarrhea	135 (39.4)	190 (54.9)
Upper respiratory tract infection	84 (24.5)	80 (23.1)
Headache	77 (22.4)	61 (17.6)
Nausea	63 (18.4)	105 (30.3)
Nasopharyngitis	59 (17.2)	50 (14.5)
Abdominal pain	44 (12.8)	50 (14.5)
Cough	42 (12.2)	51 (14.7)
Bronchitis	38 (11.1)	41 (11.8)
Back pain	38 (11.1)	28 (8.1)
Rash	35 (10.2)	30 (8.7)
Influenza	30 (8.7)	44 (12.7)
Fatigue	30 (8.7)	37 (10.7)
Vomiting	28 (8.2)	46 (13.3)
≥ 1 grade 3 or 4 AE	103 (30.0)	110 (31.8)
≥ 1 AE at least possibly related to the PI	194 (56.6)	259 (74.9)
≥ 1 ≥ grade 2 AE at least possibly related to the PI	96 (28.0)	124 (35.8)
≥ 1 ≥ grade 3 AE at least possibly related to the PI	38 (11.1)	42 (12.1)
Deaths	4 (1.2)	7 (2.0)
≥ 1 SAE	55 (16.0)	72 (20.8)
≥ 1 SAE at least possibly related to the PI	3 (0.9)	10 (2.9)
≥ 1 AE leading to permanent discontinuation	26 (7.6)[b,c]	50 (14.5)[b]
≥ 1 AE leading to permanent discontinuation and at least possibly related to the PI	6 (1.7)	23 (6.6)
Adverse Events of Interest, n (%)		
Any rash-related AE	74 (21.6)	57 (16.5)
Any cardiac AE	20 (5.8)	21 (6.1)
Any GI AE	188 (54.8)	240 (69.4)
Any pancreatic AE	11 (3.2)	13 (3.8)
Any liver-related AE	26 (7.6)	50 (14.5)
Any lipid-related AE	43 (12.5)	66 (19.1)
Any glucose-related AE	18 (5.2)	9 (2.6)

There were no new clinically relevant AE findings compared to the known AE profile of DRV/rtv. There was a lower incidence of discontinuations due to AEs, SAEs and AEs at least possibly related to the PI with DRV/rtv 800/100 mg q.d. than with LPV/rtv 800/200 mg daily. There was also a clinically relevant lower incidence of the GI AEs diarrhea, nausea, vomiting, and liver-, and lipid-related AEs. Rash-related AEs were more frequent with DRV/rtv compared to LPV/rtv.

N = number of subjects; n = number of patients with observations.
[a] In ≥ 10% of subjects of either treatment group.
[b] Also including pregnancies (9 and 6 subjects with DRV/rtv and LPV/rtv, respectively).
[c] Including Subject 211-0837, who discontinued due to an AE in the follow-up phase.

Clinical Laboratory	The majority of graded laboratory abnormalities was grade 1 or 2 in severity. Grade 2-4 liver-related abnormalities were observed in 12.6% and 15.8 % of subjects in the DRV/rtv and LPV/rtv groups, respectively for ALT, and 12.9% and 14.9% of subjects in the DRV/rtv and LPV/rtv groups, respectively, for AST. Grade 2 or 3 hyperbilirubinemia was observed in 4 (1.2%) DRV/rtv subjects and 19 (5.5%) LPV/rtv subjects (there was no grade 4 hyperbilirubinemia). Grade 2-4 increases in triglycerides were observed less frequently in the DRV/rtv group (5.9%) than in the LPV/rtv group (16.0%). Furthermore, grade 2-3 increases in total cholesterol were observed less frequently with DRV/rtv (24.3%) than with LPV/rtv (32.7%). Grade 2-3 increases in LDLc cholesterol were observed in 22.9% with DRV/rtv and 18.4% with LPV/rtv. The overall incidence of other laboratory abnormalities was generally low and comparable for the DRV/rtv and LPV/rtv treatment groups.
Cardiovascular Safety	ECG assessments were routinely performed up to Week 96. After Week 96, an ECG was only performed locally at Week 192, if deemed necessary by the investigator. The data assessment did not identify clinically relevant trends over time. None of the observed individual QTcF abnormalities were sustained or led to treatment discontinuation. 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.
Other Safety Parameters	There were no clinically relevant changes over time in physical examination findings. An increase in mean weight from baseline to Week 192 was seen in both treatment groups: 4.2 kg in the DRV/rtv group and 3.5 kg in the LPV/rtv group. The incidence of AEs related to anthropometric measurements was low.

Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Relationships
No updated pharmacokinetic, or pharmacokinetic/pharmacodynamic analyses were performed at Week 192.

Conclusions [The conclusions section of this document was removed before posting to ClinicalTrials.gov]

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