tibotec

Clinical Research Report

Project no:	TMC114
Department:	Clinical R&D **Nonproprietary name:** Darunavir
Status:	Approved **Issued Date:** 11-Oct-2010
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.
Author(s):	S. Spinosa-Guzman, T. Van De Casteele, E. Lathouwers
Trial no:	TMC114-C211 **Clinical Phase:** III
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). The primary objective of this trial was to demonstrate noninferiority in efficacy (defined as confirmed plasma viral load of < 50 copies/mL) of DRV/rtv versus LPV/rtv at 48 weeks, each administered in combination with TDF and FTC. Additionally, the safety, tolerability, durability of efficacy, resistance characteristics, pharmacokinetics, subject-reported adherence, and the monitoring of potential body changes through anthropometric measurements was assessed throughout the trial.

GCP STATEMENT

The study was performed in compliance with Good Clinical Practices, including the archiving of essential documents.

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply to all future information supplied to you which is indicated as privileged or confidential.

	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 regions where DRV 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/tv in the main phase of the trial (or who received treatment with DRV/rtv in a rollover phase, if applicable) and who continued to benefit from this treatment, had the opportunity to continue 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. 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).
Indication:	HIV-1 Infection
Trial Dates:	Start: 15-Jul-2005 / End: 29-Mar-2010 (cut-off for the Week-192 analysis)
Sponsor's Signatory:	S. Spinosa-Guzman
Coordinating Investigator:	R. Ortiz, Orlando Immunology Center, 1701 N Mills Avenue, Orlando FL, 32803 US

Document History TMC114-C211-CRR		
Document Type and *File Name*	**Document Date**	**Comments**
Clinical Research Report TMC114-C211-W48-CRR	15 October 2007	Clinical research report describing data of the primary analysis with cut-off date 13 June 2007 (when all subjects had reached Week 48 or discontinued before)
Clinical Research Report TMC114-C211-W96-CRR	14 November 2008	Clinical research report describing data of the interim analysis with cut-off date 08 May 2008 (when all subjects had reached Week 96 or discontinued before)
Clinical Research Report (this document) TMC114-C211-W192-CRR		Clinical research report describing data of the analysis with cut-off date 29 March 2010 (when all subjects had reached Week 192 or discontinued before)

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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 Cardiovascular Safety Physical Examination Anthropometric Measurements	 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 hematology, biochemistry (fasted), and coagulation 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 - Urinalysis 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 - Pregnancy testing 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 - Hepatitis serology/viremia at: screening, and at other visits only if diagnosis was suspected - Vital signs 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 - ECG at: screening, baseline, Weeks 4 (following second pharmacokinetic blood draw), 24, 48, 72, 96, and 192 or withdrawal if deemed appropriate by the investigator - Screening, baseline, Weeks 12, 24, 48, 72, 96, 120, 144, 168, 192, or withdrawal - 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)[c]
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 $\geq$ 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

Consistent with the results of the analyses at 48 and 96 weeks, the Week-192 analysis demonstrated noninferiority in confirmed virologic response (plasma viral load < 50 copies/mL, ITT - TLOVR) for DRV/rtv 800/100 mg q.d. (68.8%) when compared to LPV/rtv 800/200 mg total daily dose (57.2%). Statistical superiority for DRV/rtv over LPV/rtv in virologic response rates for the efficacy parameter viral load < 50 copies/mL at Week 192 was demonstrated. Virologic response over 192 weeks was sustained to a greater degree in the DRV/rtv group than in the LPV/rtv group. The efficacy response observed in subjects receiving DRV/rtv 800/100 mg q.d. provides further evidence of the durable potency of a DRV/rtv-containing regimen in the treatment-naïve population. The results of this trial are robust in view of the low discontinuation rates and the high overall response rates in both groups. The virologic failure rate was lower in the DRV/rtv group (16.0%) than in the LPV/rtv group (20.5%). There were no developing primary PI mutations identified in the virologic failures of both treatment groups. All virologic failures remained susceptible to DRV, LPV, amprenavir, atazanavir, indinavir, saquinavir, and tipranavir.
The safety data confirmed that treatment with DRV/rtv 800/100 mg q.d. was generally safe and well tolerated with no new clinically relevant safety findings compared with the currently known safety profile of DRV. The incidence of gastrointestinal disorders (diarrhea, nausea, vomiting) and lipid abnormalities (triglycerides and total cholesterol) was lower with DRV/rtv than with LPV/rtv. Rash was more frequent with DRV/rtv than with LPV/rtv.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAG	alpha-1 acid glycoprotein
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apo	apolipoprotein
ARV	antiretroviral
ART	antiretroviral therapy
AST	aspartate aminotransferase
b.i.d.	twice daily
BMI	body mass index
bpm	beats per minute
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL_{Cr}	creatinine clearance
C_{min}	minimum plasma concentration
CRR	Clinical Research Report
DAIDS	Division of AIDS
DBP	diastolic blood pressure
DCPW	discontinuation due to patient wish
DRV	darunavir
DSMB	Data and Safety Monitoring Board
EC_{50}	50% effective concentration in cell-based assays
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQoL-5 Dimension (questionnaire)
FAHI	Functional Assessment of HIV Infection (questionnaire)
FC	fold change in EC_{50}
FDA	Food and Drug Administration
FTC	emtricitabine
GCP	Good Clinical Practice
GI	gastrointestinal
HAART	highly active antiretroviral therapy
HCD	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus - type 1
HQoL	health-related quality of life
HSA	human serum albumin

IAS	International AIDS Society
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	immunoglobulin
IQ	inhibitory quotient
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intra-uterine device
IVRS	interactive voice response system
LOCF	last observation carried forward
LDL	low-density lipoprotein
LPV	lopinavir
LS_{mean}	least square mean
MCV	mean corpuscular volume
M-MASRI	Modified - Medication Adherence Self Report Inventory (questionnaire)
M-MSAS-SF	Modified - Memorial Symptom Assessement Scale - Short Form (questionnaire)
MTCT	mother-to-child transmission
N	number of subjects
n	number of observations
NC = F	noncompleting is failure
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside/nucleotide reverse transcriptase inhibitors
OBR	optimized background regimen
OP	on protocol
PBMC	peripheral blood mononuclear cells
pH	measure of the acidity or basicity of a solution
PI	protease inhibitor
PR	protease
PRO	patient reported outcome
PT	prothrombin time
PTT	activated partial thromboplastin time
q.d.	once daily
QoL	quality of life
RAM	resistance-associated mutation
RBC	red blood cell
RNA	ribonucleic acid
RT	reverse transcriptase
rtv	low-dose ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SE	standard error
SOC	system organ class
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response

VAS	visual analogue scale
VF	virologic failure
WBC	white blood cell

Definitions of Terms

QTcB	QT interval corrected for HR using Bazett's formula[1]: $QTc = QT \times (1000/RR)^b$ where b = 1/2
QTcF	QT interval corrected for HR using Fridericia's formula[2]: $QTc = QT \times (1000/RR)^b$ where b = 1/3

ETHICS

Independent Ethics Committee/Institutional Review Board

The final protocol and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) according to specifications outlined in the applicable regulations (e.g., ICH-GCP, US Code of Federal Regulations [CFR]). The IEC/IRB membership lists or verification of appropriate constitution are available in the Trial Master File.

Ethical Conduct of the Trial

The trial was performed in accordance with the principles of Good Clinical Practice as outlined in 21 CFR Parts 50, 56 and 312 and the declaration of Helsinki and its subsequent revisions, and the European Union Clinical Trials Directive.

Subject Information and Consent

All subjects gave their written consent prior to any trial-related procedure. They were informed about the nature and purpose of the trial, participation and termination conditions, and risks and benefits. It was explained to all subjects that their participation was voluntary and that refusal to participate or wish to withdraw before completion of the trial would not have any effect on their potential future medical care. A copy of the subject information sheet was given to the subject. The IEC/IRB-approved consent form is included in Appendix 8.1.3.

TRIAL ADMINISTRATIVE STRUCTURE

Coordinating Investigator (Multicenter, see Appendix 8.1.4)

R. Ortiz, Orlando Immunology Center, 1701 N Mills Ave, Orlando FL, 32803 USA

Sponsor's Responsible

Medical Leader: S. Spinosa-Guzman

Clinical Development Leader: A. Hendrickx

Global Trial Manager: A. Gause

Clinical Pharmacokineticist: V. Sekar

Virologist: E. Lathouwers

Data Manager: T. Pootemans

Clinical Statistician: T. Van De Casteele

Medical Writer: I. Wuyts

Committees

The Data and Safety Monitoring Board (DSMB) consisted of 4 independent HIV clinicians, a representative of the subject community and an independent statistician. The Tibotec Medical Leader (or representative) and the Tibotec Head Biometrics acted as observers in the DSMB. For further information, refer to Addendum 2 of the Protocol in Appendix 8.1.1.

Central Clinical Laboratory

Virco Business Unit, Generaal De Wittelaan L11 b4, 2800 Mechelen, Belgium

Covance CLS, 7 rue Moise-Marcinhes, 1217 Meyrin, Geneva, Switzerland

BMS, European Headquarters, Waverse Steenweg 1945, 1160 Brussels, Belgium

Contract Research Organization and Level of Involvement

Quintiles, Limited, Station House, Market Street, Bracknell, Berkshire, RG12 1HX, United Kingdom: trial conduct

GCO, Moscow Rep Office, 17/2, Krylatskaya Street, Moscow 121614, Russia: trial conduct (Russia only)

SGS Belgium NV, Life Science Services, Generaal De Wittelaan 19A b5, 2800 Mechelen, Belgium: HA applicant, pharmacovigilance, insurance, data management, data review, statistics

1 INTRODUCTION

Current treatment options for the treatment of human immunodeficiency virus (HIV-1) infected subjects consist of nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs), PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), an integrase inhibitor, and an entry inhibitor. NRTIs, NNRTIs, entry inhibitors, and integrase inhibitors act at an early stage in the HIV life cycle, while PIs act at a later stage of viral replication. As yet, no single drug or combination drug therapy is able to infallibly stop the progression of HIV-1 disease. A triple regimen is considered standard of care[3-6] and when effective, results in suppression of the virus below the detection limits of the current tests, thereby strongly reducing the emergence of resistance.

The use of PIs has been a major breakthrough in the therapy for HIV-1 infection, substantially reducing morbidity and mortality in infected individuals, when used in combination with other ARVs. Their long-term use, however, is hampered by different factors, including high pill burden, food restrictions, and side effects (e.g., gastrointestinal [GI] intolerance, metabolic abnormalities). These factors can negatively impact quality of life (QoL), as well as adherence to the medication regimen. Among other reasons (e.g., drug interactions), poor adherence is associated with the emergence of resistant virus that is no longer inhibited by the drugs currently being used, and commonly, by other ARVs (due to a high degree of crossresistance within each class).

There has been an increasing impetus to assess the burden of HIV using patient-reported outcomes (PROs) such as health-related-QoL (HRQL) instruments, particularly in the clinical trial setting. HRQL is a multidimensional construct defined as the subjective understanding of the impact a disease and its treatment have on physical, social, emotional, functional and global well-being and cognitive functioning[7]. As more effective therapeutic options for HIV infection are being developed, interest in HQoL outcomes is further increasing[8]. Also, as body changes most often observed in HIV-1 infected subjects receiving antiretroviral therapy (ART) may be considered stigmatizing, the monitoring of the onset of these events and their potential impact on QoL through questionnaires, clinical examination and anthropometric measurements are increasingly common in clinical trials.

The current trial is conducted with DRV (formerly TMC114). This compound was identified in the course of lead optimization on the basis of favorable pharmacokinetics in animals and a potent activity profile against HIV strains resistant to all currently approved PIs.

For information on the pharmacologic and toxicologic properties of the compound as well as early development data, refer to the trial Protocol in Appendix 8.1.1 and the Investigator's Brochure[9].

In the Phase IIb trials TMC114-C202 and TMC114-C213 conducted in a population with advanced HIV infection and with limited to no treatment options, DRV was formulated as oral tablets and coadministered with low-dose rtv. The dose-finding part of these trials, included 4 different DRV/regimens (400/100 mg q.d., 800/100 mg q.d., 400/100 mg b.i.d., and 600/100 mg b.i.d.) and a control group (individually optimized background [OBR] regimens + PIs, selected by the investigator).

A combined Week-24 interim analysis was performed when 150 subjects in each trial were treated for ≥ 24 weeks[10]. The results demonstrated that all selected dose regimens of DRV coadministered with 100 mg rtv exhibited superior ARV efficacy when compared with individually optimized ARV regimens used in the control group. All dose regimens of DRV/rtv were generally safe and showed an AE profile comparable to the control group. No dose-related trends in the incidence of AEs, laboratory abnormalities, or abnormal investigations were apparent.

Based on these interim results, DRV/rtv 600/100 mg b.i.d. was selected as the recommended dose for treatment-experienced HIV-1 infected subjects with inadequate virologic suppression.

This dose of DRV/rtv 600/100 mg b.i.d. together with an OBR has subsequently been shown to be highly effective therapy in treatment-experienced, LPV/rtv naïve, HIV-1 infected subjects in trial TMC114-C214, where noninferiority in virologic response (viral load < 400 copies/mL) compared to treatment with LPV/rtv 400/100 mg b.i.d. was demonstrated. Furthermore, in the analysis, DRV/rtv 600/100 mg b.i.d. was also proven superior to LPV/rtv 400/100 mg b.i.d.[11].

In the current trial, TMC114-C211, the long-term antiviral efficacy of DRV, formulated as an oral tablet, coadministered with low-dose rtv as part of a highly active antiretroviral therapy (HAART) in treatment-naïve HIV-1 infected subjects has been evaluated. Based on the combined Week-24 interim analysis of the Phase IIb dose-finding trials TMC114-C202 and TMC114-C213, the comparable safety profile among all DRV dose groups and the control group, and the potential to provide an effective once daily regimen, the dose of 800/100 mg q.d. of DRV/rtv was selected for the treatment period of this trial.

The results of the Week-48 primary efficacy and safety analysis, and the Week-96 analysis of this trial have been described in earlier reports[12,13]. The current report describes the results of the Week-192 efficacy and safety analyses of this trial, when all subjects had reached Week 192 or discontinued earlier.

2 OBJECTIVES

2.1 MAIN PHASE

The primary objective of the trial was to demonstrate noninferiority in virologic response (time to loss of virologic response, TLOVR), defined as a confirmed plasma viral load of < 50 copies/mL, with DRV/rtv versus LPV/rtv treatment 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.

2.2 EXTENSION PHASE

The primary objective of the extension phase 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).

Subjects who completed the 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, had the opportunity to continue DRV/rtv treatment in the extension phase. In addition, subjects randomized to LPV/rtv in the main phase of the trial, who met the virologic failure criteria, or who experienced intolerance on LPV/rtv could also enter the extension phase of the trial to switch to a DRV/rtv-containing regimen.

3 METHODS

3.1 STUDY DESIGN

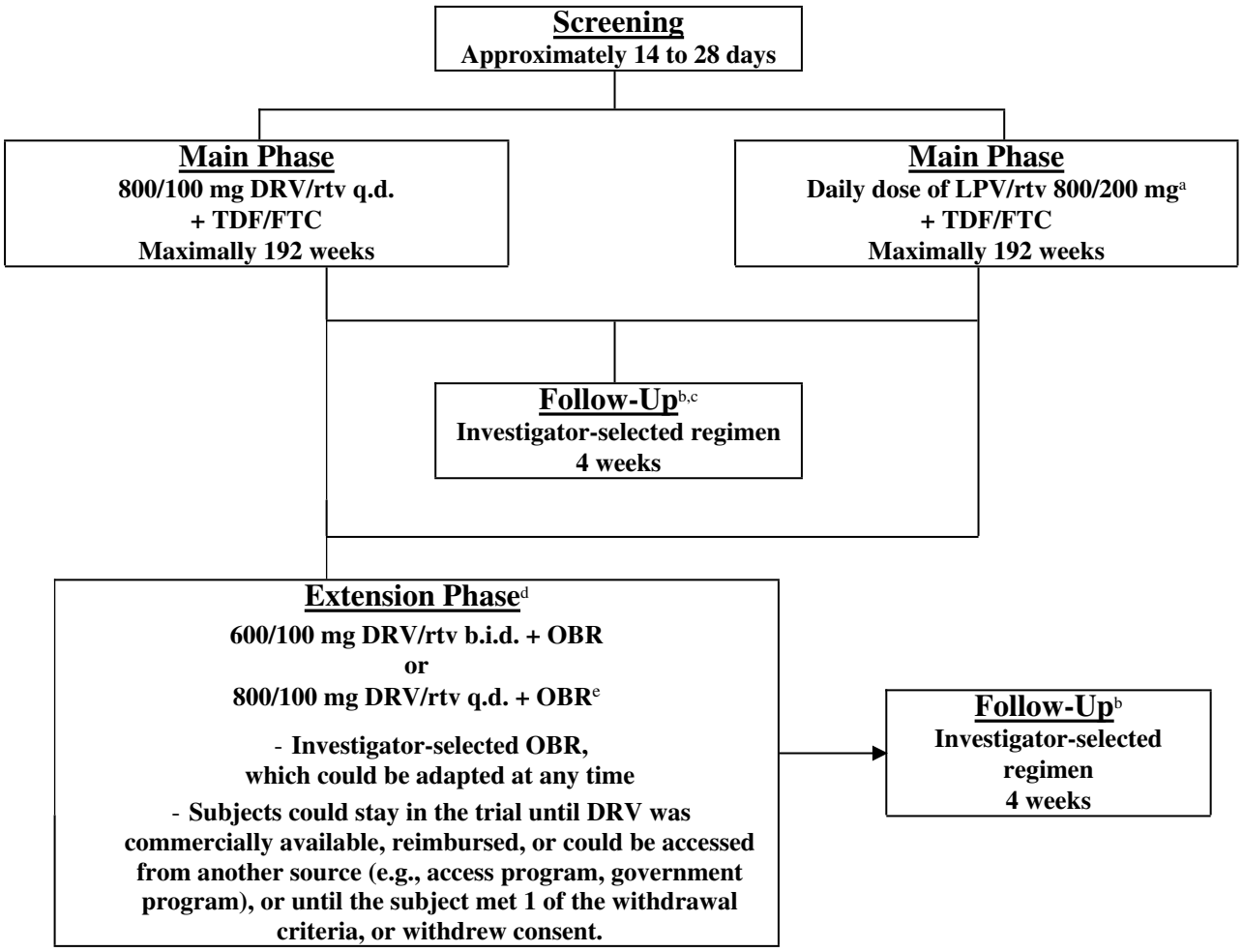
3.1.1 Overview of Study

For details on the timing of the treatments and assessments, see the flowchart in Section 3.4.1.

3.1.1.1 MAIN PHASE

Trial TMC114-C211 was a randomized controlled, open-label, Phase III trial to compare the efficacy, safety and tolerability, resistance characteristics, and pharmacokinetics of DRV/rtv versus LPV/rtv in treatment-naïve HIV-1 infected subjects. Subjects were considered treatment-naïve if they had never received treatment with an ARV drug, 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). Women who (had) used 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 chosen fixed background regimen.

A schematic overview of the trial is provided in Figure 1. The trial comprised a screening period of approximately 14 to 28 days, a 192-weeks treatment period, an optional extension period, and a 4-week follow-up period (in case a subject had an ongoing AE at withdrawal).



[a] LPV/RTV 400/100 mg b.i.d. was used in countries where the once daily use of LPV/rtv was not approved; LPV/rtv 800/200 mg q.d. could be used in countries where the once daily use of LPV/rtv was approved. Different formulations of LPV/rtv could have been used, see Section 3.3.2.

[b] The Week-4 follow-up visit was only needed for subjects with an ongoing AE at withdrawal (irrespective of the relatedness to the trial medication).

[c] Subjects who completed or were prematurely withdrawn from the main phase, were followed for survival until the last subject in the region the subject was participating in, reached Week 192, unless they withdrew consent.

[d] Only for eligible subjects, see Section 3.2.2.

[e] For selection of the dose of DRV/rtv, see Section 3.3.1.

Figure 1: Overview of the Design of Trial TMC114-C211

To determine the eligibility of the subjects, blood and urine were collected at the screening visit and were analyzed for viral load, immunology, biochemistry, hematology, and urinalysis. Subjects volunteering to participate in the trial, having signed the Informed Consent Form (ICF), and found eligible for the trial at the screening visit, were instructed to discontinue specified disallowed medications (see Section 3.3.7) to allow a washout period of ≥ 14 days prior to baseline. Once all data were available to determine the eligibility of the subject, and the subjects was found eligible, the baseline visit was scheduled (approximately 14 to 28 days after

screening, depending on medication availability), on which the subject was randomized and trial treatment was initiated.

Subjects were randomized in a 1:1 ratio to receive either 800/100 mg DRV/rtv q.d., or a daily dose of 800/200 mg LPV/rtv (400/100 mg b.i.d. was used in countries where the once daily use of LPV/rtv was not approved; 800/200 mg q.d. could be used in countries where the once-daily use of LPV/rtv was approved). Subjects on a LPV/rtv q.d. dosing schedule could switch to b.i.d. dosing if they experienced intolerance to the regimen. The reason for a change in dosing had to be well documented in the source document and captured in the electronic Case Report Form (eCRF). However, this change in dosing schedule did not apply if subjects experienced toxicity leading to withdrawal (see Section 3.2.4). A fixed background regimen consisting of TDF (300 mg q.d.) and FTC (200 mg q.d.) was initiated at baseline, in combination with the assigned PI regimen. The fixed background regimen was given as a fixed dose combination tablet (Truvada®). In exceptional cases, TDF and FTC could be administered as individual agents (see Section 3.3.2).

The ARV therapy initiated at baseline could not be changed until the end of the treatment period (except for specific reasons; see Section 3.3.3). Temporary interruption of all ARVs was allowed in the event of suspected toxicity, as long as the temporary interruption was associated with and could be linked to an AE or serious AE (SAE).

During the treatment period, subjects were seen at scheduled visits during which the investigator assessed the subjects' medical condition, any AEs, and compliance to the trial medication. Laboratory evaluations for efficacy and safety were done at these visits. To monitor potential body changes, anthropometric measurements were performed for all randomized subjects every 24 weeks from baseline onwards. Pharmacokinetic assessments (sparse sampling) were performed for all randomized subjects. The sampling occured at Weeks 4, 8, 24, 48, 72, and 96, or withdrawal.

At some sites participating in this trial, substudies such as a pharmacokinetic substudy could be performed, which required additional assessments as specified in a separate subprotocol.

Treatment could be discontinued for lack or loss of treatment response as defined in Section 3.2.4. Subjects who no longer benefitted from the DRV/rtv or LPV/rtv therapy, as judged by the investigator, or who met 1 of the withdrawal criteria could be withdrawn from the trial. Subjects with an ongoing AE (irrespective of the relatedness to trial medication) at withdrawal were followed for an additional 4 weeks to follow-up on the ongoing AEs until resolution or stabilization.

3.1.1.2 ROLLOVER PHASE

In the original Protocol (see Appendix 8.1.1, and Section 3.1.3), a rollover phase was part of the trial in which subjects randomized to DRV/rtv in the main phase of the trial could roll over to LPV/rtv-based therapy and subjects randomized to LPV/tv in the main phase could roll over to DRV/rtv-based therapy, in case they experienced virologic failure, or intolerance on their treatment in the main phase. After Protocol Amendment TMC114-C211-CTPA-GEN-III (see Appendix 8.1.1, and Section 3.1.3), this rollover phase was no longer available.

With the application of Protocol Amendment TMC114-C211-CTPA-GEN-III, subjects who received treatment with LPV/rtv in the previously existing rollover phase had to switch to commercially available LPV/rtv, and the Trial Termination page of the eCRF had to be completed. Subjects who received treatment with DRV/rtv in the previously existing rollover phase had the opportunity to continue treatment with DRV/rtv in an extension phase to the trial (see Section 3.1.1.3).

Although the rollover phase was no longer available after Protocol Amendment TMC114-C211-CTPA-GEN-III, subjects randomized to LPV/rtv in the main phase of the trial, who met the virologic failure criteria, or who experienced intolerance, could still switch to DRV/rtv-based therapy, which they could receive in the extension phase of the trial.

3.1.1.3 EXTENSION PHASE

In regions where DRV 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 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, had the opportunity to continue 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 also enter the extension phase, where they switched to a DRV/rtv-containing regimen. Subjects could remain in the extension phase of the trial until DRV was commercially available, reimbursed, or could be accessed from another source (e.g., access program, government program). Subjects with an ongoing AE at withdrawal in the extension phase were followed for an additional 4 weeks.

For subjects who used DRV/rtv in the main phase of the trial, or who used DRV/rtv in the rollover phase (see Section 3.1.1.2), the dose of DRV/rtv in the extension phase was the same as they were using before. This dose was either 800/100 mg q.d. (i.e., the dose in main phase, or the dose in the rollover phase after switching to DRV/rtv following intolerance to LPV/rtv in the main phase), or 600/100 mg b.i.d. (i.e., the dose in the rollover phase after switching to DRV/rtv following virologic failure on LPV/rtv in the main phase). Subjects who were randomized to LPV/rtv in the main phase of the trial and who switched to DRV/rtv-based therapy in the extension phase either used DRV/rtv 800/100 mg q.d. if they switched due to intolerance to LPV/rtv, or DRV/rtv 600/100 mg b.i.d. if they switched due to virologic failure on LPV/rtv.

The ARVs of the OBR in the extension phase were selected at the investigator's discretion. Only ARVs with no drug-interaction potential with DRV/rtv (see Section 3.3.7) were allowed. Subjects could continue Truvada®. The OBR could be adapted at any time. As the primary objective of the extension phase was to provide access to DRV/rtv to subjects who were not able to receive DRV in any other way (see Section 2.2), only DRV/rtv was provided during the extension phase, and not the components of the OBR.

There was not an extension phase for subjects on LPV/rtv. For subjects randomized to LPV/rtv in the main phase of the trial, the trial stopped after 192 weeks of treatment in the main phase (or until the last visit of the rollover phase for subjects on LPV/rtv in that phase, before Protocol Amendment TMC114-C211-CTPA-GEN-III, see Sections 3.1.1.2 and 3.1.3). The Trial Termination page of the eCRF had to be completed and the subjects had to switch to commercially available LPV/rtv.

3.1.1.4 FOLLOW-UP FOR SURVIVAL (MAIN PHASE ONLY)

All subjects who were prematurely withdrawn from the main phase of the trial or who completed the main phase, were followed for survival until the last subject in the trial reached Week 192 in the region the subject was participating in, unless they withdrew their consent. Investigators were asked to provide minimal information about the survival of the subjects approximately every 6 months.

3.1.2 Discussion of Trial Design and Selection of Dose in the Trial

At the time the Protocol was designed, the use of the combination of LPV/rtv (Kaletra®) and 2 NRTIs was a recommended treatment for ARV-naïve HIV-1 infected subjects[14]. The combined use of ≥ 3 active ARV drugs in treatment-naïve HIV-1 subjects was considered essential due to the inherent high mutation rate of HIV[15,16]. Therefore, all subjects in the DRV/rtv group received a fixed background regimen of 2 NRTIs (TDF/FTC) together with DRV/rtv, and all subjects in the control group received a fixed background regimen of 2 NRTIs (TDF/FTC) together with LPV/rtv (Kaletra®).

LPV/RTV was chosen as comparator as it had demonstrated efficacy and safety in treatment-naïve HIV-1 infected subjects according to the treatment guidelines and was therefore expected to provide benefit[17].

The combination of TDF (300 mg q.d.) and FTC (200 mg q.d.) was chosen as a fixed background regimen as this has low impact on lipid and mitochondrial toxicity in treatment-naïve subjects and can be administered as a once daily regimen[18,19]. When looking at the subgroup of subjects who used TDF/FTC as background regimen in the DRV/rtv dose finding trials, it was shown that there were no safety or tolerability concerns with coadministration of TDF, FTC and DRV/rtv[9]. A Phase I interaction trial between DRV/rtv and TDF showed that there is no clinically relevant interaction observed if these drugs are combined[20] (see Section 3.3.7). For safety and efficacy information on FTC or TDF in combination with other ARV agents, investigators were referred to the package insert for these products.

It was not possible to blind DRV/rtv and LPV/rtv due to operational and logistic reasons. In addition, blinding would result in a pill burden for PI components of 9 pills per day.

A trial duration of 192 weeks was chosen to evaluate the sustained efficacy, tolerability and safety of DRV/rtv in the selected population.

An independent DSMB was implemented for continued monitoring and objective assessment of AEs and laboratory abnormalities, including all SAEs, all grade 3 and 4 AEs and toxicity and of all available antiviral activity and immunology data (see Addendum 2 of the Protocol in Appendix 8.1.1).

The primary analysis was done when all subjects had been treated for 48 weeks or discontinued earlier. An updated analysis was performed after 96 weeks of treatment. The results of these analyses have been described in separte reports[12,13]. An interim analysis was performed after 24 weeks of treatment. Data of this analysis were only shared with selected sponsor representatives not directly involved in trial conduct, and the DSMB. The current analysis, performed when all subjects had been treated for 192 weeks in the main phase of the trial, or had discontinued earlier (premature withdrawal), is described in this report. This Week-192 analysis was performed on all available data, including the posttreatment visits.

3.1.2.1 SELECTION OF THE DOSE IN THE TRIAL

Phase IIb dose-finding trials TMC114-C202 and TMC114-C213 evaluated 4 dose regimens of DRV/rtv compared to control (OBR + selected PIs) in highly treatment-experienced subjects: 400/100 mg q.d., 800/100 mg q.d., 400/100 mg b.i.d., and 600/100 mg b.i.d.

The efficacy results of the Week-24 interim analysis of both trials showed that all selected dosages of DRV coadministered with 100 mg rtv exhibited a superior ARV efficacy when compared with individually optimized ARV regimens used in the control group [10]. A statistical significant difference in the $\log_{10}$ viral load change versus baseline at Week 24 (noncompleting = failure [NC = F]) of all DRV/rtv dosages compared control was obtained in this treatment-experienced population. Plasma DRV trough concentrations were above the target (550 ng/mL) defined for PI-resistant virus in the majority of the subjects in all dose groups. In addition, all dosages of DRV/rtv were generally safe and well tolerated and showed an AE profile comparable to that of control. No clear dose-related trends with respect to the incidence of AEs, laboratory abnormalities and/or abnormal investigations were apparent.

The Week-24 interim results also showed that, based on median baseline CD4+ cell count, percentage of subjects with sensitive NRTIs in the OBR, previous use of enfuvirtide, and percentage of subjects with DRV fold change in EC_{50} (FC) ≤ 4, all selected dosages of DRV/rtv exhibited a superior ARV efficacy compared to control. In addition, the DRV/rtv dose response observed in highly treatment-experienced subjects was much less pronounced in the subgroup analyses performed on subjects with ≥ 2 active NRTIs given in combination.

Based on the efficacy results after 24 weeks of treatment, the comparable safety profile among all DRV/rtv dose groups and control, and the potential to provide an effective q.d. regimen, the dose of 800/100 mg q.d. of DRV/rtv was selected for the current trial in treatment-naïve subjects. A strong antiviral response was expected at this proposed dose and in this treatment population receiving 2 active NRTIs given in combination. In addition, this dose was expected to provide a 'forgiveness' margin for any potential decreases in DRV concentrations due to extrinsic factors (e.g., drug-drug interactions). The absence of a clear dose-response for safety/tolerability also suggested that this dose of 800/100 mg q.d. would be well tolerated by treatment-naïve subjects.

The results of the Week-24 interim analysis also showed that the inhibitory quotient (IQ), reflecting the ratio between the concentration of DRV achieved in plasma and the DRV FC at baseline, was the strongest predictor of response. The IQ was primarily driven by the DRV FC at baseline, and to a lesser extent by the DRV exposure. IQs of DRV were generally very high (mean values > 200) and increased with increasing daily doses of DRV. It was expected that DRV FC would be lower in treatment-naïve subjects than in treatment-experienced subjects (approximately 1 in most subjects), related to the predominance of wild type virus, and therefore, requiring a lower DRV target C_{min} (and lower dose, 800 versus 1200 mg daily dose).

3.1.3 Changes in Conduct

At the time of reporting, the final Protocol of this trial (dated 15 July 2005), was amended 3 times (i.e., general amendments) (see Appendix 8.1.1).

General Protocol Amendment I (TMC114-C211-CTPA-GEN-I), dated 28 November 2005

Major adaptations included:

- incorporation of the new tablet formulation of Kaletra®;
- update of prior and concomitant therapy;
- update of the toxicity management to include the most recent recommendations;
- addition of follow-up for survival for all subjects who were prematurely withdrawn from the trial;
- clarification of the collection of Acquired Immune Deficiency Syndrome (AIDS)-defining illnesses;
- update of the individually optimized background regimen.
- administrative changes and changes to improve the readability of the Protocol.

General Protocol Amendment II (TMC114-C211-CTPA-GEN-II), dated 24 April 2007

Major adaptations included:

- prolongation of the main phase of the trial from 96 to 192 weeks.
- inclusion of an extension phase for subjects, who lived in regions where DRV was not yet available through the local Health System, and who had completed 192 weeks of treatment with DRV/rtv in the main phase of the trial, or 96 weeks of treatment with DRV/rtv in the rollover phase and who continued to benefit from this treatment;
- adaptation of the information on the collection of survival data.
- update of prior and concomitant therapy; inclusion of the most recent information regarding established and theoretic drug interaction data with DRV.
- administrative and textual changes.

General Protocol Amendment III (TMC114-C211-CTPA-GEN-III), dated 6 July 2007

Major adaptations included:

- update on the extension phase;
- enrolment in the rollover phase was stopped, due to the low number of subjects who qualified for entry in the rollover phase so far;
- deletion of the PRO questionnaires FAHI, EQ-5D, M-MSAS-SF;
- deletion of thyroid function tests;
- deletion of central electrocardiogram (ECG) readings; local readings could be performed if deemed necessary by the invesigator;
- administrative and textual changes.

In addition, there were 4 country-specific protocol amendments which were applicable to Switzerland, Australia, France, and South Africa.

Protocol Amendment (TMC114-C211-CTPA-Country Specific: Switzerland), dated 26 January 2006

- The wording of the trial protocol section 'Publications' was revised upon request of Swissmedic.

Protocol Amendment (TMC114-C211-CTPA-Country Specific: Australia), dated 12 October 2007

- The clinical trial protocol was amended following a request from the Ethics Committee such that subjects, who lived in regions where DRVwas not yet available through the local Health System, and who continued to benefit from treatment, had the option to enter the extension phase of the trial, either after completion of 96 weeks (as in the initial protocol) or after completion of 192 weeks of treatment with DRV/rtv in the main phase of the trial.

Protocol Amendment (TMC114-C211-CTPA-Country Specific: France), dated 7 May 2009

- Almost identical to CTPA-GEN-III. The only difference was that the Week-4 follow-up visit was needed for all subjects, whereas in CTPA-GEN-III it was only needed for subjects with an ongoing AE at withdrawal.

Protocol Amendment (TMC114-C211-CTPA-Country Specific: South Africa), dated 12 August 2009

- An update on the extension phase, specifications on the medication supply, and administrative changes.

3.1.3.1 INTERIM ANALYSES

One interim analysis was performed when all subjects had completed the 24-weeks assessment, or discontinued earlier. The purpose of this interim analysis was to assist the DSMB in their continued monitoring and assessment of the efficacy and safety in the trial. The results of the Week-24 interim analysis were confidential and available to only 3 persons, i.e., the Head Biometrics who presented the results to the DSMB, and the interim Analysis Statistician and Clinical Programmer supporting the interim analysis.

The primary analysis was done when all subjects had been treated for 48 weeks or discontinued earlier. An updated analysis was performed after 96 weeks of treatment. The results of these analyses have been described in separte reports[12,13].

3.1.3.2 CHANGES TO THE PLANNED ANALYSES

There were the following changes to the planned analyses as described in the Protocol (Appendix 8.1.1).

- The primary population for the efficacy comparison at Week 192 (defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL at Week 192) was the ITT population. In addition, efficacy analyses were performed on the OP population.
- Virologic resonse defined as the percentage of subjects with a decrease in plasma viral load of 2.0 $\log_{10}$ copies/mL compared to baseline was not calculated, as this was considered no longer clinically relevant.
- For the generalized linear mixed effects model, instead of a random statement (random intercept and slope) a repeated statement was used to account for the correlations between the time points, as this is a more versatile model without any assumption on the correlation structure.
- Viral phenotypic determinations were only performed for selected subjects (i.e., rebounders, non-responders), and therefore no descriptive statistics were calculated.
- For ECG, the determination of QTc abnormalities were based on the ICH E14 guideline[21].
- For vital signs, the Division of AIDS (DAIDS) grading table was used.

The statistical analysis plan (SAP) for the trial is provided in Appendix 8.1.8.

3.2 STUDY POPULATION

3.2.1 Main Phase

Retesting of screening values leading to exclusion was allowed only once using an unscheduled visit.

3.2.1.1 INCLUSION CRITERIA

Subjects who met all of the following criteria were eligible for the trial.

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 qualify 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.

3.2.1.2 EXCLUSION CRITERIA

Subjects meeting 1 or more of the following criteria could not be selected.

1. Presence of any currently active AIDS-defining illness (Category C conditions according to the Centers for Disease Control [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 (see Section 3.3.7).
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 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 (see Section 3.3.7).
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 (see Addendum 3 of the Protocol, Appendix 8.1.1) 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.

3.2.2 Extension Phase

The extension phase was only for subjects who were living in a region where DRV was not yet commercially available by the public and/or private health system. Subjects who completed the 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 were eligible for the extension phase. In addition, subjects randomized to LPV/rtv in the main phase of the trial, who met the virologic failure criteria or who experienced intolerance (see Section 3.2.2.1), could switch to a DRV/rtv-based therapy in the extension phase of the trial.

Only these subjects as specified above had the opportunity to continue DRV/rtv treatment in the extension phase of trial TMC114-C211, where they had access to DRV/rtv until DRV was commercially available, reimbursed, or could be accessed from another source (e.g., access program, government program).

For subjects on LPV/rtv there was no extension phase (except for subjects as specified above), and the trial stopped at Week 192 of LPV/rtv treatment in the main phase (or, if applicable, at the last visit of the rollover phase for subjects on LPV/rtv in that phase; see Section 3.1.1.2).

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

3.2.2.1 CRITERIA FOR SUBJECTS RANDOMIZED TO LPV/RTV IN THE MAIN PHASE OF THE TRIAL TO SWITCH TO DRV/RTV-BASED THERAPY IN THE EXTENSION PHASE

3.2.2.1.1 Lack or Loss of Response (Virologic Failure)

The following description applied for lack or loss of treatment response:

- 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.

Subjects with virologic failure had to have participated in the trial for ≥ 12 weeks before they could switch to DRV/rtv-based therapy in the extension phase. Subjects who discontinued treatment due to virologic failure prior to Week 12, were not be eligible to participate in the extension phase unless they also experienced treatment-limiting toxicity (see Section 3.2.2.1.2).

Subjects experiencing virologic failure (but no treatment-limiting toxicity) could remain on their current regimen or undergo a temporary treatment interruption, until they switched to DRV/rtv-based therapy in the extension phase.

In case of virologic failure, a Virco®TYPE HIV-1 report of the last available sample was forwarded to the investigator in order to assist in the selection of a new OBR.

3.2.2.1.2 Treatment-Limiting Toxicity

Treatment-limiting toxicities included at least 1 of the following specific AEs/confirmed laboratory abnormalities:

- a grade 3 or 4 cutaneous reaction/rash (according to the DAIDS grading table, see Addendum 3 of the Protocol, Appendix 8.1.1);
- 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 (see Section 3.4.6.3);
- 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, (see Section 3.4.6.3);

- 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 (see Addendum 6 of the Protocol, Appendix 8.1.1).

A temporary treatment interruption of all the components of the regimen had to be respected to allow resolution, or for the severity to decrease to ≤ grade 2, before starting intake of DRV/rtv in the extension phase. During follow-up of the abnormality, the abnormality had to be monitored according to the toxicity management referred to in Section 3.4.6.3, and unscheduled visits could be used to assess resolution of the abnormality.

The dose of DRV/rtv the subjects received in the extension phase was determined by the reason for failure (see Section 3.3.1).

3.2.3 Prohibitions and Restrictions

All HIV-1 infected subjects were advized to take the necessary precautions to reduce the risk of transmitting HIV.

Since the effects of DRV on conception and fetal development are unknown, nonvasectomized male subjects and/or female subjects of childbearing potential having heterosexual intercourse were advised to use 1 of the following birth-control methods:

- a male condom combined with either hormonal contraceptives, IUD, diaphragm, cervical cap or female condom; or
- practice abstinence.

These precautions applied from screening onwards until 1 month after the last trial drug administration, i.e., until the 30-days after the end of the treatment period or 1 month after discontinuation of the trial medication in case of premature discontinuation.

The use of above mentioned birth-control methods did not apply if the male HIV-1 infected subject had been vasectomized minimally 1 month prior to screening or if the female sexual partner had had a tubal ligation or a total hysterectomy, or if she was postmenopausal for ≥ 2 years.

For details on the existing data with regard to the reproductive toxicity of DRV, investigators were requested to refer to the current Investigator's Brochure[9].

Women were not to breastfeed when taking DRV, as the effects to their newborn child are unknown. Women who had a newborn child had to talk to their physician about the best way to feed their child. They had to be aware that there is a risk that HIV can be transmitted through breastfeeding.

For LPV/rtv and TDF/FTC, the package inserts and the ICF had to be consulted, respectively, with regard to directions concerning birth-control methods and breastfeeding.

3.2.4 Removal of Subjects From Therapy or Assessment

Subjects could be withdrawn from the trial for the following reasons.

1. An SAE occurred.
2. The subject failed to comply with the Protocol or trial staff requirements.
3. The subject started disallowed treatment (the sponsor had to be contacted for a decision).
4. The subject demonstrated lack or loss of response in the trial. The following description applied for lack or loss of treatment response:
   - 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.

Subjects had to be withdrawn from the trial if:

1. The subject withdrew consent.
2. The investigator considered it, for safety reasons, in the best interest of the subject that he/she be withdrawn.
3. The subject (in either treatment group) received additional ARV(s) during the main phase of the trial, other than DRV/rtv, LPV/tv, and TDF/FTC.
4. Pregnancy had been determined.
5. The subject experienced a grade 3 or 4 cutaneous reaction/rash (according to the DAIDS grading table, see Addendum 3 of the Protocol, Appendix 8.1.1).
6. The subject experienced 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 (see Section 3.4.6.3).
7. The subject experienced, after trial medication interruption because of a confirmed grade 3 increase in ALT or AST, a confirmed recurrence of grade 3 or 4 increase in ALT or AST. For subjects with hepatitis B or C infection present at screening, a toxicity management plan was provided (see Section 3.4.6.3).
8. The subject experienced a grade 4 AE or confirmed grade 4 laboratory abnormality considered at least possibly related to trial medication. 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 (see Addendum 6 of the Protocol, Appendix 8.1.1).
9. The subject was diagnosed with acute viral hepatitis while participating in the trial.

The date and the reason for discontinuation had to be noted on the appropriate page of the eCRF. Unless the subject withdrew consent, each subject prematurely discontinuing the trial had to be seen for a final evaluation (withdrawal visit). For subjects with an ongoing AE, a posttreatment follow-up visit was performed 4 weeks after the last dose of trial medication during the trial. After the last trial visit, the Trial Termination page and Investigator's Signature page of the eCRF had to be completed.

All subjects who were prematurely withdrawn from the main phase of the trial or who completed the main phase of the trial, were followed for survival until the last subject in trial reached Week 192 in the region the subject was participating in, unless they withdrew their consent. Investigators were asked to provide minimal information about the survival of the subjects approximately every 6 months.

3.3 TREATMENT

3.3.1 Treatments Administered

In the **main phase**, all subjects were randomized to the DRV/rtv treatment group or the LPV/rtv control group (see Figure 1).

DRV/rtv: treatment group

Screening period (approximately 14 to 28 days): no treatment administration

Main phase of the trial (maximum 192 weeks):

- fixed background regimen consisting of TDF (300 mg q.d.) and FTC (200 mg q.d.); however, in the context of prespecified AEs, the background regimen could be changed (see Section 3.3.3);
- DRV/rtv 800/100 mg q.d. given as: 2 400-mg tablets of DRV + 1 100-mg capsule of rtv per intake.

Follow-up period (4 weeks) for subjects with an ongoing AE at withdrawal: investigator-selected regimen.

LPV/rtv: control group

Screening period (approximately 14 to 28 days): no treatment administration

Main phase of the trial (maximum 192 weeks):

- fixed background regimen consisting of TDF (300 mg q.d.) and FTC (200 mg q.d.); however, in the context of prespecified AEs, the background regimen could be changed (see Section 3.3.3);
- LPV/rtv 800/200 mg total daily dose (LPV/rtv 400/100 mg b.i.d. was used in countries where the once daily use of LPV/rtv was not approved; 800/200 mg q.d. could be used in countries where the once daily use of LPV/rtv was approved).

Follow-up period (4 weeks) for subjects with an ongoing AE at withdrawal: investigator-selected regimen.

In the **extension phase**, the dose of DRV/rtv for subjects who were already on DRV/rtv remained the same, either:

- 800/100 mg q.d., i.e., the dose in main phase of trial, or the dose in rollover phase after switching from LPV/rtv to DRV/rtv due to intolerance to LPV/rtv in the main phase of the trial (see Section 3.1.1.2), or
- 600/100 mg b.i.d., i.e., the dose in rollover phase after switching from LPV/rtv to DRV/rtv due to virologic failure on LPV/rtv in the main phase of the trial.

Subjects who were randomized to LPV/rtv in the main phase and who switched to a DRV/rtv-based therapy in the extension phase used either DRV/rtv 800/100 mg q.d. if they switched to DRV/rtv due to intolerance to LPV/rtv, or DRV/rtv 600/100 mg b.i.d. if they switched due to virologic failure on LPV/rtv.

Subjects in the extension phase could continue Truvada®, but the ARVs of the OBR were selected at the investigator's discretion (only ARVs with no drug interaction potential with DRV/rtv; see Section 3.3.7). Further, the OBR could be adapted at any time in the extension phase. DRV/tv was provided during the extension phase, but not Truvada®, or other ARVs of the OBR.

3.3.2 Identity of Investigational Product(s)

The investigational medication DRV was manufactured under responsibility of Tibotec Pharmaceuticals, formerly Tibotec Pharmaceuticals Ltd.

DRV was formulated as 400-mg tablets (F021; main phase and extension phase), or 300-mg tablets (F016; extension phase) for oral administration. The tablets were composed of TMC114 ethanolate, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, magnesium stearate and Opadry®Orange.

Medication batches of DRV are listed in Appendix 8.1.5.

Ritonavir (Norvir®) was formulated as a capsule containing 100 mg rtv and the inactive ingredients butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil and titanium dioxide.

LPV/rtv (Kaletra®) was formulated as a capsule or as a tablet.

The capsule contained 133.3 mg LPV, 33.3 mg rtv and the inactive ingredients oleic acid, propylene glycol, polyoxyl 35 castor oil, purified water. The capsule shell components were: gelatine, anhydrized liquid sorbitol, glycerol, titanium dioxide, sunset yellow (E110), medium-chain triglycerides, lecithin and black ink containing: black iron oxide, propylene glycol, polyvinyl acetate phthalate, PEG400 and ammonium hydroxide.

The film-coated tablet was available for oral administration in a strength of 200 mg of LPV and 50 mg of rtv with the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The ingredients in the film coating were: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, colloidal silicon dioxide, polyethylene 3350, yellow ferric oxide E172, and polysorbate 80.

Subsequent to the availability of tablets for use in the trial and all applicable approvals from Health Authorities and local IECs/IRBs, Tibotec Pharmaceuticals provided the tablet formulation of LPV/rtv. Subjects previously randomized to LPV/rtv were required to change to the tablet formulation, while subjects randomized to LPV/rtv subsequent to the availability of the tablets,

initiated therapy with the tablet formulation. For subjects changing from the capsule formulation to the tablet formulation, the date of change had to be recorded on the eCRF. Production of the capsule formulation of LPV/rtv was ceased over the course of the trial, and once a subject had switched from the capsule to the tablet formulation, the subject had to remain on the tablet formulation for the remaining treatment period.

TDF (300 mg q.d.) and **FTC (200 mg q.d.)** were administered as the fixed dose combination (Truvada®). Truvada® was formulated as a tablet with the inactive ingredients croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch (gluten free). The tablets were coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminium lake, hypromellose, lactose monohydrate, titanium dioxide and triacetin.

In case TDF (300 mg) and FTC (200 mg) were not administered as Truvada® but as individual agents (see below), the inactive ingredients of TDF were croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch, and those of FTC were crospovidone, magnesium stearate, microcrystalline cellulose and povidone.

DRV/rtv (main phase and extension phase) and LPV/rtv (main phase) medication were delivered by Tibotec Pharmaceuticals. During the main phase of the trial, the fixed background regimen (TDF/FTC) was supplied by Tibotec Pharmaceuticals, or reimbursed until it could be provided.

Only if the fixed dose combination of TDF/FTC was not (yet) provided by the sponsor, locally purchased TDF/FTC could be used. Only if both the fixed dose combination of TDF/FTC was not (yet) provided by the sponsor and could not be purchased locally, the separate components of TDF/FTC could be used if these could be purchased locally. TDF/FTC or other ARVs of the OBR during the extension phase were not provided by Tibotec Pharmaceuticals.

3.3.3 Fixed Background Regimen

At the baseline visit, subjects initiated a fixed background regimen, consisting of TDF (300 mg q.d.) and FTC (200 mg q.d.) given as a fixed dose combination tablet (Truvada®).

TDF/FTC had to be used according to locally applicable procedures and package inserts.

The fixed background regimen could not be modified until the end of the main phase of the trial. However, a change of the background regimen was allowed in case the following AEs were reported:

- lactic acidosis;
- hepatoxicity, including severe hepatomegaly and steatosis even in the absence of marked transaminase elevations;
- renal impairment, including renal failure and Fanconi Syndrome (renal tubular injury with severe hypophosphatemia).

The changed background regimen had to include a total of 2 approved NRTIs other than TDF/FTC. In case the above-mentioned AEs were reported, the changed background medication was reimbursed by the sponsor. In this situation, subjects with a changed background regimen continued on their randomized PI regimen unless the AE was at least possibly related to the PI

component as well. The subjects were not counted as failures if they were virologically controlled.

Temporary interruption of all ARVs was allowed in the event of confirmed or suspected toxicity, as long as the temporary interruption was associated with and could be linked to an AE or an SAE. Reinitiation of therapy that included the changed background medication was only allowed once the event had resolved or decreased to a ≤ grade 2.

3.3.4 Randomization

Subjects were randomized in a 1:1 ratio to DRV/rtv or LPV/rtv.

Two stratification factors were identified for randomization and were subsequently used in the statistical analyses as a covariate in the models:

- screening plasma viral load (< 100000, ≥ 100000 copies/mL) (previous publications showed that baseline viral load can be a predictive factor for outcome[14],[22]);
- screening CD4+ cell count (< 200, ≥ 200 cells/µL).

Randomization was done at baseline, using a central randomization system. Once a subject was found to be eligible, the baseline visit was scheduled (not later than 4 weeks after screening), and at this visit, the investigator called the interactive voice response system (IVRS) following the instructions as given in the IVRS manual. Randomization was done by a predefined randomization list, constructed via random permuted blocks to ensure balance across treatments groups in each stratum of the stratification factors. Both the investigator and the subject knew to which treatment group the subject was randomized.

3.3.5 Blinding

As this was an open-label trial, blinding procedures were not applicable.

3.3.6 Dosage and Administration

At the baseline visit, subjects initiated an ART consisting of the fixed background regimen (TDF 300 mg and FTC 200 mg), and DRV/rtv or LPV/rtv. Whenever possible, TDF/FTC, and DRV/rtv or LPV/rtv had to be taken at the same time. However, the usual dosing schedule of LPV/rtv (control group) and TDF/FTC as described in the package inserts had to be respected.

Subjects on DRV/rtv treatment were instructed to take the investigational medication (DRV/rtv) orally within 30 minutes after completion of a meal, once daily. Preliminary results from a food interaction trial have demonstrated a decrease in exposure to TMC114 by 30% if taken under fasted conditions, whereas the type of meal had very little impact on exposure[23].

If a subject assigned to treatment with DRV/rtv 800/100 q.d. or 600/100 mg b.i.d. noticed that he/she had missed the combined dose, or 1 of its components (DRV and/or rtv), and it was still within 12 or 6 hours, respectively, of the time it was usually taken, the subject had to take a DRV dose with food as soon as possible together with a capsule of rtv (i.e., both compounds -DRV and rtv- had to be taken when DRV and/or rtv were not taken). The subject could then continue his/her usual dosing schedule. If a subject assigned to treatment with DRV/rtv 800/100 q.d. or 600/100 b.i.d. noticed that he/she has missed this dose more than 12 or 6 hours, respectively,

after the time it was usually taken, the subject was instructed not to take it and simply resume the usual dosing schedule.

If a subject noticed that he/she had missed a dose of LPV/rtv and/or TDF/FTC, he/she had to take the dose as soon as he/she remembered it. If it was almost time for the subject's next dose, he/she had not to take the missed dose. The subject could then continue his/her usual dosing schedule. The subject was not take a double dose to make up for a missed one, nor take more than 1 TDF/FTC tablet, or more than 6 capsules (or 4 tablets, if applicable) of LPV/rtv per day.

3.3.7 Prior and Concomitant Therapy

3.3.7.1 GENERAL

All non-ARV medications (prescriptions or over-the-counter medications, herbal and naturopathic products) continued at the start of the trial or started during the trial had to be documented on the Concomitant Therapy page of the eCRF. Reported information included a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

Female subjects of childbearing potential had to use an adequate birth-control method as outlined in Exclusion Criterion 9 (see Section 3.2.1.2), and had to be willing to continue practicing this birth-control method for the duration of the trial and until ≥ 30 days after the end of the treatment period. Oral, injectable, and implantable hormonal contraceptives were to be recorded on the Concomitant Therapy section of the eCRF.

For any concomitant therapy given as treatment for a new condition or a worsening of an existing condition occurring after signature of the ICF, the condition had to be documented on the AE/HIV-related event section of the eCRF.

Details on drug interactions with DRV were provided in a drug-interaction table (ARV and non-ARV medications) in the Protocol (Appendix 8.1.1). This table listed the medications of which coadministration with DRV under the current protocol was either allowed (sometimes with precautions) or disallowed. The proposed table was meant to give guidance for clinical intervention by providing recommendations with respect to the current protocol and by no means encouraged the use of the listed medications. It remained the decision of the investigator to coadminister 1 or more of the allowed medications with DRV in the context of this clinical trial, as part of the treatment of the trial subject, based upon his/her clinical assessment of the risk/benefit, the condition of the subject and the availability of effective alternative treatments.

3.3.7.2 ANTIRETROVIRAL AGENTS

During the main phase of the trial, no ARVs other than the trial medication and the fixed background regimen (TDF/FTC) were allowed. However, in the context of prespecified AEs, the fixed background regimen could be changed (see Section 3.3.3).

During the extension phase, subjects could continue Truvada®, but the ARVs of the OBR were selected at the investigator's discretion (only ARVs with no drug interaction potential with DRV/rtv). The OBR could be adapted at any time in the extension phase.

For the fixed background regimen, the respective package inserts had to be consulted for concomitant use with other medications and for contraindicated medications or medications not recommended for concomitant use.

3.3.7.3 OTHER CONCOMITANT (NON-ARV) MEDICATONS

3.3.7.3.1 Allowed Non-ARV Medications

Subjects on DRV/rtv could receive rifabutin, clarithromycin, atorvastatin, methadone and PDE-5 inhibitors (sildenafil, vardenafil, tadalafil) according to the recommendations provided in the drug-interaction table provided in the Protocol (see Section 3.3.7.1).The use of any of these concomitant medications had to be documented on the Concomitant Therapy section of the eCRF. In case of dose adjustments, the Concomitant Therapy section of the eCRF had to be updated accordingly.

For subjects on LPV/rtv in the control group, the package insert of LPV/rtv had to be consulted with regard to dose adjustments of concomitant medications, including methadone, and for contraindicated medications or medications that were not recommended for concomitant use.

3.3.7.3.2 Disallowed Non-ARV Medications

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* (St John's Wort);
- 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* (St John's Wort);
- 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.

3.3.8 Treatment Compliance

Compliance to trial medication (DRV/rtv or LPV/rtv) was assessed by the Modified Medication Adherence Self-Report Inventory (M-MASRI) questionnaire (see Addendum 5 of the Protocol, Appendix 8.1.1 and Section 3.4.5.1) and by pill-counts. The M-MASRI was blinded for the investigator and monitor.

The trial subjects were instructed to bring back their used and unused medication packages (DRV/rtv or LPV/rtv) with them at each visit. If a subject's medication intake was not according to the Protocol, the investigator discussed the importance of compliance with the subject and tried to identify and address factors that might negatively impact it.

3.4 STUDY EVALUATIONS

3.4.1 Flowchart

Overviews of the timing of treatment(s) and assessments in the main phase and extention phase of the trial are provided in the flowcharts in Table 1 and Table 2, respectively. Details on the assessments are provided in Sections 3.4.2 through 3.4.7.

Table 1: Flowchart of the Main Phase

	Screening	Baseline	Treatment Period																					Week-4 Follow-up Visit[c]
Time of Visit	**Week –4**	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**	**Week 36**	**Week 48**	**Week 60**	**Week 72**	**Week 84**	**Week 96**	**Week 108**	**Week 120**	**Week 132**	**Week 144**	**Week 156**	**Week 168**	**Week 180**	**Week 192**	**DRV Switch/Extension Visit[a]**	**Withdrawal Visit[b]**	
Informed consent	X													X[d]									X		
Demographic data	X																								
Pregnancy test[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion/exclusion criteria	X	X[f]																							
Criteria for extension phase																							X		
Medical/Surgical history & Concomitant diseases	X																								
Physical examination	X	X				X		X		X		X		X		X		X		X		X		X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Laboratory safety assessments[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
PBMC sample		X																				X		X	
Efficacy assessments (immunology and plasma viral load)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pharmacokinetics for DRV/rtv and LPV/rtv[h]				X[i]	X			X[i]		X		X		X										X	
Pheno-/genotype determinations	X	X		X[j]	X[j]	X[j]	X[j]	X	X[j]	X	X[j]	X	X[j]	X	X[j]	X	X[j]	X	X[j]	X	X[j]	X		X	
Vital signs (pulse, blood pressure)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
ECG	X	X		X[k]				X		X		X		X								X[l]		X[l]	
Anthropometric measurements	X[m]	X						X		X		X		X		X		X		X		X		X	
M-MASRI questionnaire				X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Dispensation of trial medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Observe/Interview for AEs and HIV-related events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Only for subjects who could enter the extension phase of the trial (see Section 3.2.2).
[b] Subjects prematurely withdrawn from the main phase of the trial, or who completed this phase, were followed for survival until the last subject in the trial reached Week 192 in the region the subject was participating in, unless they withdrew their consent.
[c] Only for subjects with an ongoing AE (irrespective of the relatedness to trial medication) at withdrawal.
[d] Confirm written informed consent before continuing the main phase of the trial after Week 96.
[e] Serum test at screening, urine test at following visits for women of childbearing potential.
[f] Recheck of the screening in- and exclusion criteria at the baseline visit.
[g] Fasting for at least 10 hours was mandatory where a blood sample was taken for biochemistry tests.
[h] In case of renal toxicity, a sample for bioanalysis of DRV/rtv had to be taken at the time of the observed toxicity (see Sections 3.3.3 and 3.4.6.3).
[i] 2 pharmacokinetic samples were drawn: the first sample immediately before intake of DRV/rtv or LPV/rtv, and the second at least 1 hour after the first 1 was drawn.
[j] At these time points samples for phenotype and genotype determinations were taken, but testing depended on the opinion of the Protocol Virologist based on HIV-1 plasma viral load.
[k] An ECG was performed following the second pharmacokinetic sample draw.
[l] ECG assessments only performed locally if deemed necessary by the investigator.
[m] Only height and weight, for the calculation of creatinine clearance.

Note: Unscheduled visits could be planned: - for a confirmatory plasma viral load determination during treatment;
- to follow-up on clinically relevant AEs or laboratory abnormalities;
- to follow-up on cutaneous reaction/rashes.

Table 2: Flowchart of the Follow-up Phase

	DRV/Switch/ Extension visit[a]	Treatment Period			Week-4 Follow-up Visit[c]
Time of Visit	**Day 1**	**Week 204 (After Main Phase or 12 Weeks After DRV Switch/ Extension visit)**	**Every 12 Weeks**	**Final / Withdrawal Visit[b]**	
Informed consent	X				
Pregnancy test[d]		X	X	X	
Criteria for participation in extension phase	X				
ARV therapy	X	X	X	X	
Collection of the following AEs[e]: - AEs considered at least possibly related to DRV/rtv; - AEs leading to discontinuations; - SAEs and pregnancies.		X	X	X	X
Treatments related to (S)AEs		X	X	X	X
Dispensation of DRV/rtv	X	X	X		
Drug accountability		X	X	X	

[a] On the same day as the Week-192 (main phase) visit (or, if applicable, same day as the last visit of the main phase for subjects on LPV/rtv in that phase, who switched to DRV/rtv in the extension phase, or same day as the last visit for subjects on DRV/rtv in the previously existing rollover phase, who continued DRV/rtv in the extension phase).

[b] When the subject no longer benefitted from DRV/rtv, as assessed by the investigator, subject met 1 of the withdrawal criteria, DRV became commercially available, was reimbursed, or could be accessed from another source (e.g., access program, government program) in the region the subject is living in (whatever comes first).

[c] Only for subjects with an ongoing AE (irrespective of the relatedness to trial medication) at withdrawal.

[d] Urine pregnancy test for the females of childbearing potential only.

[e] Other AEs only collected if required per local regulations.

3.4.1.1 TIMING OF ASSESSMENTS

3.4.1.1.1 Main Phase

Within 4 weeks after the screening visit, the site should have received all data to determine the subject's eligibility. If a subject was considered eligible, the investigator scheduled a baseline visit (not later than 4 weeks after screening).

At the time of the baseline visit, the investigator called the IVRS to randomize the subject, and the subject received DRV/rtv or LPV/rtv, together with the fixed background regimen of TDF/FTC.

The subjects were seen 2 weeks after the baseline visit, and every 4 weeks until Week 16. After Week 16 subjects were seen 8 weeks later, on Week 24. From Week 24 on, subjects were visiting the clinic every 12 weeks until Week 192 (end of treatment in the main phase). A Week-4 follow-up visit was performed for subjects with an ongoing AE at withdrawal.

Unscheduled visits could be planned:

- to perform a confirmatory plasma viral load determination during the treatment period in the event of virologic failure (see Section 3.2.4);
- to assess, confirm and follow-up on clinically relevant AEs or laboratory abnormalities (a confirmatory retest of grade 3 and 4 laboratory abnormalities had to be performed within 48 hours);
- to assess and ensure appropriate follow-up on cutaneous reaction/rashes (see Section 3.4.6.3);
- to perform a scheduled chemistry test when a subject was not fasting.

All subjects who were prematurely withdrawn from the main phase of the trial, or who completed the main phase of the trial, were followed for survival until the last subject of the trial reached Week 192 in the region the subject was participating in, unless they withdrew their consent. Investigators were asked to provide minimal information about the survival of the subjects approximately every 6 months.

3.4.1.1.2 Extension Phase

The subjects were seen at Week 204 (or 12 weeks after the DRV switch/extension visit) and preferably every 12 weeks thereafter. The investigator conducted a final/withdrawal visit (and a Week-4 follow-up visit in case the subject had an ongoing AE at withdrawal) when the subject no longer benefitted from DRV/rtv, as assessed by the investigator, when the subject met 1 of the withdrawal criteria, when DRV became commercially available, was reimbursed, or could be accessed from another source (e.g., access program, government program) in the region the subject was living in (whatever came first).

The DRV switch/extension visit took place on the same day as the Week-192 visit (main phase), or, if applicable, the same day as a last visit of the main phase for subjects on LPV/rtv in that phase, who switched to DRV/rtv in the extension phase, or same day as the last visit for subjects on DRV/rtv in the previously existing rollover phase, who continued DRV/rtv in the extension phase.

3.4.1.2 TIME WINDOWS

3.4.1.2.1 Main Phase

The following time windows were advised:

- baseline visit: ± 14 days;
- visits on Weeks 2, 4, 8, 12, and 16: ± 2 days;
- visit on Week 24: ± 4 days;
- visits on Weeks 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, and 192: ± 6 days;
- Week-4 follow-up visit (subjects with an ongoing AE at withdrawal): 4 weeks ± 4 days after withdrawal.

The visits timing from Week 2 to 192 had to be based on the date of the start of the trial medication. Some flexibility in the planning of the visits was allowed, however, the total treatment duration had to be 192 weeks. If the subject could return not within the specified time windows, extra medication could be dispensed to avoid the subject running out of medication.

3.4.1.2.2 Extension Phase

The following time windows were recommended:

- visit on Week 204 (or 12 weeks after the DRV switch/extension visit for subjects switching from LPV/rtv in main phase to DRV/rtv in extension phase, or for subjects on DRV/rtv in the previously existing rollover phase) onwards: ± 6 days;
- Week-4 follow-up visit (subjects with an ongoing AE at withdrawal): 4 weeks ± 4 days after withdrawal.

3.4.2 Initial Subject and Disease Characteristics

3.4.2.1 MAIN PHASE

At the screening visit, after signing the ICF, the overall eligibility of the subject to participate in the trial was assessed. The subject's demographics, smoking habits, alcohol use, recreational drug use, clinically relevant medical and surgical history or pre-existing conditions (active or nonactive) that could be expected to impact the subject's clinical outcome during participation in this trial (e.g., diabetes, dyslipidemia, hypertension, liver disease, neoplasms, opportunistic infections, rash and allergic reactions, etc.), concomitant diseases, and all concomitant medication were recorded. In addition, special attention had to be given to medical and surgical cardiovascular history as well as a possible history of premature (before the age of 55 years for men, 65 years for women) cardiovascular disease among the subject's genetic first degree relatives. All events occurring after signing the ICF, were recorded as AEs. Additionally, HIV-related events and the occurrence of AIDS-defining illnesses were recorded. A complete physical examination including all body parts was performed, and urine and blood samples were collected for urinalysis, biochemistry, hematology, coagulation testing, immunology, pheno-/genotype, and plasma viral load determinations. The hepatitis A, B and C infection status was determined.

Vital signs and an ECG reading were also recorded at the screening visit. In addition, height and weight were recorded for the calculation of CL_{Cr} (see Section 3.4.6.3).

For women of childbearing potential the date of last menses must be noted in the eCRF (requirement according to ICH M3 guideline[24]). A serum pregnancy test was performed at screening for all females.

3.4.2.2 EXTENSION PHASE

At the DRV switch/extension visit subjects needed to confirm their informed consent for participation in the extension phase. Subjects' eligibility for participation in the extension phase was checked.

3.4.3 Efficacy Evaluations

3.4.3.1 MAIN PHASE

At the time points specified in the flowchart (see Section 3.4.1/Table 1), samples for the determination of antiviral activity were taken. All samples for antiviral activity determinations were forwarded to the central laboratory, which, depending on the assessment that needed to be performed, could forward the samples to a referral laboratory.

3.4.3.1.1 Plasma Viral Load

Plasma viral load levels were determined using Roche Amplicor HIV-1 monitor™ test (version 1.5). Specimen preparation procedures were defined in the laboratory procedures.

3.4.3.1.2 Immunologic Change

The immunologic change was determined by changes in CD4+ and CD8+ cell counts (absolute and %).

3.4.3.2 EXTENSION PHASE

No central laboratory was used in the extension phase of the trial. All samples as required per local standard of care for this patient population were analyzed by a local laboratory.

3.4.4 Resistance Determinations

3.4.4.1 MAIN PHASE

Viral phenotypic and genotypic determinations were performed by Virco BVBA, by means of the Antivirogram® and Virco®TYPE HIV-1, respectively. A Virco®TYPE HIV-1 report was generated only if viral load was ≥ 1000 HIV-1 RNA copies/mL.

During the main phase, the samples taken at screening, baseline, Weeks 24, 48, 72, 96, 120, 144, 168, and 192, or the withdrawal visit were analyzed in real time. Samples taken at other time points were analyzed only when judged appropriate by the Protocol Virologist based on HIV-1 plasma viral load. Initially, phenotypic and genotypic determinations were only performed on plasma samples with HIV-1 RNA ≥ 1,000 copies/mL. Additional testing was performed on

samples from virologic failures with HIV-1 RNA ≥ 50 copies/mL, to better assess the relationship between virologic failure and resistance.

A Virco®TYPE HIV-1 report from the screening sample was sent to the investigator to provide information regarding the sensitivity to LPV/rtv and the background regimen. Furthermore, Virco®TYPE HIV-1 reports from samples from the Week-192 visit, or the withdrawal visit were sent to the investigator in order to assist in the selection of a new OBR, if applicable.

The results of the phenotypes and genotypes were evaluated by the Protocol Virologist. Relevant changes in the phenotype and genotype of the virus, detected by either the Antivirogram® or Virco®TYPE HIV-1 were evaluated. These changes in phenotype and genotype were not considered AEs.

A peripheral blood mononuclear cells (PBMC) sample was taken for storage at screening and at the final/withdrawal visit, to be analyzed only if deemed necessary by the Protocol Virologist to characterize archived viral resistance.

3.4.4.2 EXTENSION PHASE

No central laboratory was used in the extension phase of the trial. Any samples as required per local standard of care for this patient population were analyzed by a local laboratory.

3.4.5 Patient-Reported Outcomes (Main Phase Only)

3.4.5.1 M-MASRI QUESTIONNAIRE

Self-reported adherence to DRV and rtv, and LPV/rtv were measured by an abbreviated version of the published and validated MASRI) questionnaire[25] (see Addendum 5 of the Protocol, Appendix 8.1.1). This M-MASRI questionnaire asked subjects to report the number of doses taken, as well as the number of doses taken within the correct timing during the last month prior to the trial visit by means of a horizontal visual analogue scale (VAS) that generates a self-rated percentage of doses of DRV/rtv and LPV/RTV taken during the past month.

The M-MASRI questionnaire had to be completed by the subject at the time points specified in the flowchart (see Section 3.4.1/Table 1).

The M-MASRI questionnaire was only administered in this trial if a validated translation was available in the local language and was preferably administered prior to all other trial-related procedures planned during the visit.

Subjects completed the M-MASRI questionnaire alone without site staff supervision or assistance. Before leaving the trial site, the subject returned the completed questionnaire to the site staff in a sealed envelope, which remained unopened until collection by the trial monitor and arrival at Data Management. Trial site staff remained blinded to the content of the completed M-MASRI questionnaire and were not allowed, under any circumstance to open the sealed envelopes, containing the completed M-MASRI questionnaires.

Subjects had to be able to read to complete the M-MASRI questionnaire by themselves. Subjects were not to receive any help from anyone accompanying them (such as family members and friends), or trial staff in interpreting or responding to the questions. However, if subjects were unable to read, or had visual or other physical limitations that made it difficult to read or

complete the questionnaire, the following applied: persons independent from the trial staff (such as family members and friends) were allowed to read the questions and response options aloud, exactly as they appeared on the questionnaire, and to record the subjects'responses. Trained trial staff was not allowed to assist in any case.

3.4.6 Safety Evaluations

3.4.6.1 MAIN PHASE

3.4.6.1.1 Adverse Events/HIV-Related Events

At each visit, subjects were asked about any untoward medical occurrences and these were recorded as AEs or dermatologic events. HIV-related events and the occurrence of AIDS-defining illnesses were also recorded. Detailed definitions and reporting procedures of AEs were provided in the Protocol (Appendix 8.1.1).

3.4.6.1.2 Clinical Laboratory Tests

At the time points specified in the flowchart (see Section 3.4.1/Table 1), samples for laboratory safety tests were taken. The laboratory reports generated by the central laboratory needed to be interpreted for clinical significance, signed and dated by the investigator after which they needed to be filed in the subject's medical record. In case clinically relevant changes were observed from signing the ICF onwards, these had to be reported as AEs in the AE/HIV-related event section of the eCRF.

The central laboratory sent the investigator an alert form whenever a grade 3 or 4 laboratory abnormality (see the DAIDS AE grading table in Addendum 3 of the Protocol, Appendix 8.1.1) had been observed.

A confirmatory retest had to be performed by a local laboratory, within 48 hours in case a grade 3 or 4 laboratory abnormality occurred, with the exception of:

- subjects with pre-existing diabetes or assessments under nonfasted conditions who experienced asymptomatic glucose grade 3 or 4 elevations;
- subjects with asymptomatic or nonfasted triglyceride or cholesterol elevations of grade 3 or 4.

3.4.6.1.2.1 *Hematology*

Hematocrit, hemoglobin, mean corpuscular volume (MCV), red blood cell (RBC) count, white blood cell (WBC) count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count were assessed.

A PBMC sample was taken at the baseline visit for characterization of archived viral resistance. A final PBMC sample was taken at the end of the treatment period (Week 192, or withdrawal visit).

The analysis of additional safety blood samples in case of rash was performed by the local laboratory in order to allow immediate medical action if needed. In this event, the eosinophil count (absolute and percentage) had to be determined.

3.4.6.1.2.2 *Coagulation Tests*

Prothrombin time (PT) and activated partial thromboplastin time (PTT) were assessed at baseline, Weeks 24, 48 and 96 (or withdrawal visit). At other visits, these tests were performed in case of clinically suspected liver dysfunction. Fibrinogen and C-reactive protein were measured at the baseline visit only.

3.4.6.1.2.3 *Biochemistry*

Subjects had to have fasted for at least 10 hours prior to blood sampling for biochemistry tests.

Lipid and glucose abnormalities are commonly observed in the PI class. Therefore, fasting was mandatory when a blood sample was taken for biochemistry tests. In case the subject had not fasted, an unscheduled visit was performed to take a blood sample for biochemistry testing.

Total protein, AST, ALT, human serum albumin (HSA), alpha-1 acid glycoprotein (AAG), total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase (ALP), urea, uric acid, creatinine, sodium, potassium, chloride, bicarbonate, calcium, calcium corrected for albumin, phosphate, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, pancreatic amylase, lipase, total insulin and glucose were assessed.

The analysis of the samples for biochemistry taken at screening included a serum pregnancy test (ß-subunit of human chorionic gonadotropin [HCG]) for all female subjects.

Apolipoprotein A1 (Apo A1), Apolipoprotein B (Apo B), HAS, and AAG were assessed as specified in the laboratory manual.

Lactate was assessed in case of suspicion of lactic acidosis syndrome.

The analysis of additional safety blood samples in case of rash was performed by the local laboratory in order to allow immediate medical action, if needed. The following parameters ahd to be tested: ALT,AST, ALP and bilirubin (total and fractionated, if possible). These additional results were captured in the eCRF.

3.4.6.1.2.4 *Hepatitis Serology/Viremia*

Hepatitis A, B and C test were performed at screening. At other visits an extra test was performed only if the diagnosis was suspected. Hepatitis A infection status had to be confirmed by hepatitis A antibody immunoglobulin M (IgM). Hepatitis B infection status had to be confirmed by hepatitis B surface antigen. Hepatitis C infection status had to confirmed by hepatitis C virus (HCV) antibody, and HCV RNA if antibody was present.

In case of confirmed hepatitis B infection, serology of hepatitis D virus had to be checked by reflex testing.

3.4.6.1.2.5 *Urinalysis*

Urinalysis by dipstick for color, appearance, specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin and urobilinogen wasperformed. If abnormal, microscopic examination for WBC, RBC, and casts were performed.

At baseline and at each following visit until the Week 192 visit (or withdrawal visit), a local urine pregnancy test was performed for female subjects of childbearing potential only.

3.4.6.1.3 Cardiovascular Safety

At the time points specified in the flowchart (see Section 3.4.1/Table 1), vital signs and an ECG were recorded. Any clinically relevant changes occurring during the treatment period (from signing the ICF onwards until the last trial-related visit) had to be recorded on the AE/HIV-related event pages of the eCRF.

3.4.6.1.3.1 *Vital Signs*

Systolic and diastolic blood pressure (SBP and DBP) were measured supine (after 5 minutes of rest) and standing (after 1 minute standing). Pulse (supine and standing) was recorded at the same time points.

3.4.6.1.3.2 *ECG*

Central ECG readings were performed by a central ECG laboratory.

At Week 4, an ECG was performed following the second pharmacokinetic sample draw. The time was recorded on the eCRF. ECG readings at the Week-192 (or withdrawal) visit were only performed locally if deemed necessary by the investigator.

Instructions for ECG acquisition and ECG transmission were described in the manual provided by the ECG laboratory. The opinion of the investigator ruled over the interpretation of the ECG laboratory.

3.4.6.1.4 Other Safety Evaluations

3.4.6.1.4.1 *Physical Examination*

A full physical examination, in which all body parts were reviewed, with special attention to skin and mucosal areas, was performed at the time points specified in the flowchart (see Section 3.4.1/Table 1). Subjects had to be undressed during these full physical examinations.

Any clinically relevant changes from the condition at screening were recorded as AEs/HIV-related events. The occurrence of AIDS-defining illnesses had to be recorded also.

3.4.6.1.4.2 *Anthropometric Measurements*

Height had to be measured barefoot and only at the screening visit. Weight was measured at all time points specified in the flow chart (see Section 3.4.1/Table 1). To obtain the actual body weight, subjects had to be weighed lightly clothed.

Waist, hip, breast and neck circumferences were measured at baseline and every 24 weeks thereafter, until Week 192 (or withdrawal visit). For the measurement of the waist, hip, breast and neck circumferences, only the provided insertion tape was to be used. A detailed description of these measurements was provided in Addendum 4 of the Protocol (Appendix 8.1.1). Whenever possible, the measurements had to be done by the same person throughout the trial.

3.4.6.2 EXTENSION PHASE

3.4.6.2.1 Adverse Events/HIV-Related Events

Information on the following AEs was collected:

- AEs considered (by the investigator) to be at least possibly related to DRVrtv;
- AEs leading to discontinuation;
- SAEs and pregnancies.

Antiretroviral therapy and treatments related to (S)AEs for which information was collected (see above) were also recorded.

3.4.6.2.2 Clinical Laboratory Tests

Any tests were performed by local laboratories.

A local urine pregnancy test had to be performed at every visit throughout the trial for female subjects of childbearing potential. No other laboratory tests were required. However, the sponsor recommended to perform routine safety assessments, which is consistent with the local standard of care. These results were not recorded on the eCRF.

The laboratory reports generated by the local laboratory had to be reviewed, interpreted, signed and dated by the investigator, after which they were filed in the subject's medical record.

3.4.6.3 MONITORING AND SAFETY FOR SPECIFIC TOXICITIES

Monitoring and safety guidelines for specific toxicities, as described in the Sections 5.7 and 5.8 of the Protocol (see Appendix 8.1.1) were applicable for the entire trial period, including the screening period, baseline period, and the treatment period (main phase) of the trial. In addition, investigators were requested to follow these guidelines and apply the same safety measures for the subjects in the extension phase (and the previously existing rollover phase).

In case a treatment interruption was needed during the screening period because of the guidelines for toxicity management, subjects were not excluded from the trial. The baseline visit could take place as soon as the toxicity had resolved.

Guidelines for the the following specific toxicities were provided:

- cutaneous events/rash;
- acute sytemic allergic reaction;
- AST and ALT elevation;
- clinical hepatis;
- renal complications;
- skin dicoloration;
- nausea;
- diarrhea;
- spedific AEs with concomitant ARVs:
  - hyperglycemia;
  - hypertriglyceridemia and hypercholesterolemia;

- lactic acidosis;
- lipodystrophy/fat redistribution/body changes;
- pancreatitis;

- other toxicities.

3.4.7 Pharmacokinetic Evaluations (Main Phase Only)

At the time points specified in the flowchart (see Section 3.4.1/Table 1), blood samples were taken to determine the DRV or LPV, and rtv plasma concentrations. At Weeks 4 and 24, 2 samples were drawn; the first sample immediately before DRV/rtv or LPV/rtv intake, and the second at least 1 hour after the first one was drawn. At Week 4, an ECG was performed following the second sample draw (time was recorded in the eCRF). No time restrictions towards DRV/rtv or LPV/rtv intake were needed for the other pharmacokinetic samples taken during the trial (Weeks 8, 48, 72 and 96, or withdrawal). Exact times of blood sampling and last intake of DRV/rtv or LPV/rtv were recorded on the eCRF.

In case a subject on DRV/rtv had a hepatic AE (grade 3 or 4 elevations in liver function tests (LFTs), or bilirubin), an extra sample for bioanalysis of DRV/rtv had to be taken at the time of the observed toxicity or at the unscheduled visit within 48 hours for confirmation of toxicity (see Section 3.4.6.3).

3.4.8 Appropriateness of Measurements

All described efficacy and safety assessments were performed according to accepted standard methods.

3.5 DATA QUALITY ASSURANCE

The trial was monitored by the sponsor or representatives according to the current standard operating procedure for the monitoring of clinical trials.

Shortly before the trial started, the monitor met with the investigator and all staff involved to review the procedures regarding trial conduct and recording the data into the eCRF system. During the trial, the investigator permitted the monitor to verify the progress of the trial at the center as frequently as necessary. The investigator made the electronic data screens available, provided missing or corrected data and corrected the data in the eCRF system. Personal information was treated as strictly confidential and was not made publicly available.

The sponsor ensured that appropriate Quality Control steps were included into the different clinical processes to guarantee adequate protection of the subjects and quality of the data.

An independent Quality Assurance department, regulatory authorities and/or IECs/IRBs could review this trial. This implied that auditors/inspectors had the right to inspect the trial center(s) at any time during and/or after completion of the trial and had access to source documents, including the subject's file. By participating in this trial, investigators agreed to this requirement.

For any data transfer, measures were undertaken to protect subject data handed over against disclosure to unauthorized third parties and subject confidentiality was maintained at all times.

3.6 STATISTICAL METHODS

In this Week-192 analysis, the primary objective was the efficacy comparison with respect to noninferiority of confirmed virologic response at Week 192 (defined as plasma viral load < 50 copies/mL, TLOVR) with DRV/rtv versus LPV/rtv treatment, both administered with a fixed background regimen.

In addition, the following secondary objectives were evaluated:

- the superiority for virologic response in case DRV was noninferior at Week 192;
- the durability of virologic response over 192 weeks;
- the immunologic response;
- the resistance characteristics;
- the subject-reported adherence to the ARV medication in subjects treated with DRV/rtv and LPV/rtv, in combination with TDF/FTC;
- safety and tolerability over 192 weeks;
- potential body changes through anthropometric measurements.

All statistical tests were interpreted at the 1-sided 2.5% significance level, unless specified differently.

The analyses were performed per treatment phase, and the focus was on the comparison between LPV/rtv and DRV/rtv in the main phase of the trial. The methodology described in this section concerns the main phase only (Sections 4.1 through 4.8). The data collected in the rollover phase, which was part of the trial before Protocol Amendment TMC114-211-CTPA-GEN-III (see Section 3.1.3), have been summarized descriptively in a separate section (Section 4.9). The DRV/rtv safety and tolerability data from the extension phase will be described in a supplemental report.

The randomization was stratified for the baseline plasma viral load. The statistical analysis was also stratified for this parameter.

The primary analysis was performed when all subjects completed the Week-48 assessment or discontinued earlier in the main phase of the trial. An interim analysis was performed when all subjects completed the Week-24 assessment or discontinued earlier (data of this analysis were shared with selected sponsor representatives not directly involved in trial conduct and the DSMB only). An updated analysis was performed when all subjects had been treated for 96 weeks or discontinued earlier. The Week-192 analysis, described in this report, was performed when all subjects had been treated for 192 weeks or discontinued earlier. This analysis was performed on all available data, including the posttreatment visits. See also Section 3.1.3.1.

3.6.1 Determination of Sample Size

The primary efficacy parameter of the trial was virologic response, defined as a confirmed plasma viral load < 50 copies/mL at Week 48 (as defined by the TLOVR algorithm). Assuming a response rate of 70% at 48 weeks for both treatment arms, 306 subjects were required per treatment arm to establish noninferiority of DRV/rtv versus LPV/rtv with a maximum allowable difference of 12%, with a 1-sided significance level of $\alpha = 0.025$ and 90% power. To account for an approximate 10% subjects to be excluded for the on-protocol analysis, a total of 660 HIV-1 infected subjects were to be randomized in the trial, 330 per treatment group.

The delta of 12% was considered appropriate, as it is small relative to observed differences between LPV/rtv and other active regimens or between other ARTs in a similar subject population. For instance, in the Abbott trial 888, the difference between LPV/rtv and control PI was 24% in virologic response (viral load < 400 copies/mL) at Week 48[26]. In the BMS trial AI424045, a difference of 20% was observed at Week 48 between LPV/rtv versus atazanavir + saquinavir[27].

As recommended by FDA guidance, the proposed delta was accepted by FDA during the protocol development stage.

3.6.2 Populations in Analysis

An intent-to-treat (ITT) and an on-protocol (OP) population were defined:

- ITT population: all subjects who where randomized and who had taken trial medication, regardless of their compliance with the Protocol;
- OP population: all subjects who where randomized, who had taken trial medication, and who did not take any disallowed ART medication as described in the protocol for > 1 week.

The ITT population was the primary population. The OP population was also analyzed to investigate the impact of protocol deviations with respect to disallowed ART medication.
As additional sensitivity analysis, some efficacy analyses were also performed on the population excluding all major protocol deviations (see also Section 3.6.4.1.3).

3.6.3 Initial Subject and Disease Characteristics

Demographic data and baseline characteristics were descriptively presented and tabulated per treatment group as well as overall, for both the ITT and the OP population.

3.6.4 Efficacy

In the analyses, the change in plasma viral load from baseline was $\log_{10}$ transformed. Plasma viral load values < 50 copies/mL (assay detection limit) were scored as 49 copies/mL, unless otherwise specified. The efficacy analysis included the ITT population as primary population. The OP population was also analyzed where specified.

3.6.4.1 PLASMA VIRAL LOAD

3.6.4.1.1 Primary Efficacy Variable

Virologic response defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL at Week 192. The FDA TLOVR algorithm was used to derive response, i.e., response and loss of response needed to be confirmed at 2 consecutive visits and subjects who discontinued the trial were considered as nonresponders after discontinuation. Subjects who changed their fixed background regimen for other reasons than prespecified toxicity (see Section 3.3.3) were considered as failures from the time point on which the fixed background regimen was changed onwards. Additionally, intermittent missing values were imputed as responders only if the subject was responding at the preceding and following visit. Subjects were considered failures at all visits following confirmed rebound, even if confirmed resuppression (plasma viral load < 50 copies/mL) was observed.

3.6.4.1.2 Secondary Efficacy Variables

- Virologic response defined as the percentage of subjects with plasma viral load < 50 copies/mL at other time points, and time to reach first virologic response by this definition (TLOVR imputation);
- percentage of subjects with plasma viral load < 400 copies/mL at all time points;
- change in $\log_{10}$ viral load at all time points (NC = F imputation: for subjects who discontinued, the missing plasma viral load value was imputed with the subject's baseline plasma viral load value);
- time to first virologic response and time to loss of virologic response for all definitions of virologic response (TLOVR imputation).

3.6.4.1.3 Analyses

A logistic regression model including baseline plasma viral load and baseline CD4+ cell count as covariates was applied to estimate the difference in **virologic response** rate (defined as a confirmed plasma viral load < 50 copies/mL) between DRV/rtv and LPV/rtv. For this purpose, 95% 2-sided confidence intervals (CIs) were derived to compare treatment groups at all time points. The main comparison was at Week 192, using the TLOVR algorithm: if at Week 192, the lower limit of the 95% 2-sided CI of the difference between DRV/rtv and LPV/rtv exceeded -12%, noninferiority of DRV/rtv versus LPV/rtv was concluded. Additionally, a 95% CI of the difference in proportion of response between the 2 treatments was derived by means of a normal approximation of the binomial distribution.

The following sensitivity analysis were performed.

- Observed response analysis on the ITT population.
- TLOVR analysis on the population excluding all major protocol deviations.

- A TLOVR non-virologic failure (non-VF) censored analysis on the ITT population: for subject who discontinued for reasons other than virologic failure, the viral load changes or responses at time points after the discontinuation were not imputed, except for subjects whose viral load rebounded before discontinuation. Moreover, subjects who discontinued before Week 12 (i.e., who did not have the full opportunity to show virologic response) were not taken into account to determine virologic failures.
- Impact of discontinuation due to patient wish (DCPW: withdrawal of consent or loss to follow-up) in the control group was assessed by a last observation carried forward (LOCF) analysis: only for subjects in the control group, the last observed plasma viral load was carried forward to Week 48 (LOCF-DCPW - ITT).
- NC = F analysis (ITT).
- Missing = Failure analysis (M = F - ITT): in case of discontinuation, a value of 0 was imputed for the change from baseline in $\log_{10}$ viral load and intermittent missings were also imputed with 0 (without requiring confirmation of response or loss of response)[28].

Additionally, a longitudinal analysis was performed, which included all observations, without imputing missing values. This longitudinal model was applied to estimate and compare treatments over time with respect to virologic response rate. This model accounted for time, treatment and their interaction, and also included baseline plasma viral load and baseline CD4+ cell count as a covariates. Using this model, a 95% 2-sided CI was derived for the difference in virologic response rate at each time point.

The same models and sensitivity analyses were applied for the other virologic response definitions (viral load < 400 copies/mL, decrease of 2.0 $\log_{10}$ in plasma viral load).

For the **change of $\log_{10}$ plasma viral load** at 192 weeks and other time points, the least square mean (LSmean) of the difference between the 2 treatment groups and its 2-sided 95% CI was estimated by means of an analysis of covariance (ANCOVA) including the factor treatment and time, and the covariates baseline $\log_{10}$ plasma viral load and baseline CD4+ cell count. In this analysis, a change of 0 was imputed for all subjects who discontinued prematurely (NC = F).

Sensitivity analayses were also performed for the change of $\log_{10}$ plasma viral load at Week 192.

In addition, a generalized linear mixed effects model was used to further describe the plasma viral load changes over time. This model allowed testing for time effects, treatment effects and their interaction. This model was used to derive 2-sided 95% CI of the difference between the treatment groups at Week 48 and other time points.

Time to first virologic response and **time to loss of virologic response** (both definitions, ITT - TLOVR) were graphically presented by means of Kaplan-Meier curves and treatment groups were compared by means of the Cox proportional hazards model, including the same covariate and factors as the logistic regression model above. With this model, the hazard ratio and its 95% 2-sided CI was calculated.

For the **DAVG in $\log_{10}$ plasma viral load** at all time points, the 95% CI was derived using the same ANCOVA model as for the change in $\log_{10}$ viral load.

3.6.4.2 IMMUNOLOGIC CHANGE

- change in CD4+ cell count (absolute and percentage);
- change in CD8+ cell count (absolute and percentage);
- change in CD4/CD8 ratio.

Raw data and changes versus baseline were descriptively and graphically presented.

The CD4+ cell count was analyzed using the observed response, the NC = F imputation.

For the change in CD4+ cell count at each time point the LSmean difference between the 2 treatment groups and its 95% CI were estimated by means of an ANCOVA including the covariates baseline CD4+ cell count and baseline plasma viral load.

As additional sensitivity analyses, observed case analysis on the ITT population and NC = F analysis on the OP population were also performed.

In addition, a generalized linear mixed effects model was used to further describe the CD4+ cell count changes over time. This model allowed testing for time effects, treatment effects and their interaction.

3.6.5 Resistance Determinations

The number of all protease (PR) mutations (primary PI mutations, PI resistance-associated mutations [RAMs], DRV RAMs and LPV RAMs as defined by the International AIDS Society (IAS)-USA 2009 guidelines[29], and LPV RAMs by King's list[30]), and number of all reverse transcriptase (RT) mutations (NRTI RAMs and NNRTI RAMs as defined by the IAS-USA 2009 guidelines[29], and extended NNRTI RAMs[31]) were tabulated per treatment group. The incidence of all individual PR and RT mutations was also tabulated. Data at baseline and prebaseline were concatenated to calculate the baseline mutations.

The FC measured by Antivirogram® was analyzed, and categorized into 'susceptible' or 'resistant' based on cut-off values. Isolated patient viruses were considered susceptible to an ARV drug when the FC was below or equal to the low clinical cut-off when this was available (i.e., LPV, TDF, abacavir, tipranavir, and DRV), or below or equal to the biological cut-off otherwise. Furthermore, descriptive statistics were calculated for the FC.

3.6.6 Patient-Reported Outcomes

3.6.6.1 M-MASRI

Subject-reported adherence rates to DRV/rtv and LPV/rtv respectively at the different trial visits were tabulated per treatment group and descriptively presented. No imputation of missing data were performed in the initial analysis. Between-group comparisons of the adherence rates were done using the Mann-Withney-U test.

The subject-reported adherence rates were also transformed to binary variables by using a 95% cut-off to define 'adherent subjects' (i.e., subjects reporting > 95% adherence) and 'nonadherent subjects' (i.e., subjects reporting ≤ 95% adherence), as this level of adherence has been shown to be needed to achieve optimal ARV efficacy[32]. Between-group comparisons and within-group comparisons versus baseline were assessed via Pearson's chi square test, or the Fisher's exact test if 1 or more of the cells had an expected frequency of ≤ 5.

Further exploratory univariate and multivariate analyses were performed to identify predictors of adherence. These analyses are detailed in a separate PRO-analysis plan (see Appendix 8.1.8).

3.6.7 Safety

The safety analysis included all subjects who had been treated.

3.6.7.1 ADVERSE EVENTS

The type and incidence of all AEs, HIV-related events and AIDS-defining illnesses, from signing of the ICF onwards, were tabulated per treatment group. Separate tabulations were made by severity, drug relationship and outcome of the AEs. SAEs and AIDS-defining illnesses were tabulated separately. Special attention was also given to those subjects who had discontinued the trial for an AE/HIV-related event, or who experienced a grade 3 or 4 AE, or an SAE.

Descriptive statistics of the duration and onset of all AEs were presented by treatment group.

All events of rash or other systemic AEs were evaluated in conjunction with other systemic symptoms and laboratory abnormalities: information on time to onset, duration of events, time to resolution, concomitant therapy and DRV were summarized.

3.6.7.2 CLINICAL LABORATORY TESTS

For the clinical laboratory data, descriptive statistics were generated for all tests performed (actual values and changes from baseline). Additionally, for the tests available, laboratory abnormalities were calculated according to the adapted DAIDS grading table (see Addendum 3 of the Protocol, Appendix 8.1.1). The worst toxicity grade after baseline was tabulated per treatment group.

The method of Friedewald et al. was used to calculate LDL[33]:

LDLc = total cholesterol – HDL – triglycerides/5).

This method applies only when triglyceride levels are < 400 mg/dL. For subjects with triglyceride levels > 400 mg/dL, LDL was not calculated.

Special attention was given to the subjects who developed grade 3 and 4 toxicities.

3.6.7.3 CARDIOVASCULAR SAFETY

The effects on cardiovascular parameters were evaluated by means of descriptive statistics and frequency tabulations. These tables included shifts from baseline values to allow detection of relevant changes in individuals.

The ECG parameters analyzed are heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB (QT corrected for heart rate according to Bazett[1]) and QTcF (QT corrected for heart rate according to Fridericia[2]). Vital signs included pulse, SBP, and DBP.

Within-group comparisons of the change from baseline in ECG and vital sign parameters were done using Wilcoxon's matched pairs signed ranks test. Between-group comparisons were done using the Mann-Withney-U test. The percentage of subjects with abnormalities as defined below were tabulated.

Vital Signs (Based on the DAIDS AE Grading Table)

Pulse (beats per minute, bpm):

- abnormally high: ≥ 120 bpm
- abnormally low: ≤ 50 bpm

DBP (mmHg):

- abnormally high: grade 1 or mild: > 90 to < 100 mmHg
  grade 2 or moderate: ≥ 100 to < 110 mmHg
  grade 3 or severe: ≥ 110 mmHg
- abnormally low: ≤ 50 mmHg

SBP (mmHg):

- abnormally high: grade 1 or mild: > 140 to < 160 mmHg
  grade 2 or moderate: ≥ 160 to < 180 mmHg
  grade 3 or severe: ≥ 180 mmHg
- abnormally low: ≤ 90 mmHg

ECG

Heart rate (beats per minute):

- abnormally high: ≥ 120 bpm
- abnormally low: ≤ 50 bpm

PR (ms):

- abnormally high: ≥ 210 ms

QRS (ms):

- abnormally high: ≥ 120 ms
- abnormally low: ≤ 50 ms

QTc (ms) (based on ICH E14[21]):

- borderline: > 450 ms to ≤ 480 ms
- prolonged: > 480 ms to ≤ 500 ms
- pathologically prolonged: > 500 ms

QTc increase (ms) (ICH E14[21]):

- borderline: ≥ 30 to ≤ 60 ms
- abnormally high: > 60 ms

3.6.7.4 OTHER SAFETY EVALUATIONS

Weight, body mass index (BMI), anthropometric measurements (neck, breast, hip, and waist circumferences), and physical examination findings were tabulated per treatment group and descriptively presented. Between-group comparisons were done using Mann-Withney-U test, and within-group comparisons versus baseline were done using Wilcoxon's matched pairs signed ranks test.

3.6.8 Pharmacokinetics

No updated pharmacokinetic analysis was performed. The results of the pharmacokinetic analyses of samples taken up to Week 48 have been presented in the report on the Week-48 primary analyses[12].

3.6.9 Pharmacokinetic/Pharmacodynamic Relationships

No updated pharmacokinetic/pharmacodynamic analysis was performed. The results of the Week-48 pharmacokinetic/pharmacodynamic analyses have been presented in the report on the Week-48 primary analyses[12].

4 RESULTS

This section describes the results of the planned Week-192 efficacy and safety analyses of ongoing trial TMC114-C211. Data from the trial start date of 15 July 2005 up to the cut-off date of 29 March 2010 are included.

The analysis was performed by trial phase: screening, treatment period (main phase), and rollover phase. The main focus was the comparison between the DRV/rtv and LPV/rtv treatment groups during the treatment period; the results of this comparison are described in Sections 4.1 through 4.8.

The presentation of the data is structured as follows:

- **DRV/rtv**: all subjects who were randomized to and received DRV/rtv 800/100 mg q.d.;
- **LPV/rtv**: all subjects who were randomized to and received LPV/rtv 800/200 mg total daily dose (either as LPV/rtv 800/200 mg q.d. or LPV/rtv 400/100 mg b.i.d.);
- **All Subjects**: all subjects who received trial medication (DRV/rtv or LPV/rtv).

The analyses of the rollover phase were descriptive and reported as such in Section 4.9.

The data of the extension phase are planned to be described in a supplemental report.

4.1 SUBJECTS AND TREATMENT INFORMATION

Information pertaining to pretrial and screening data was not reanalyzed at Week 192. For completeness, these data are included in this report using listings and displays from the Week-48 analysis as source.

The analyses for subjects and treatment information were conducted on the ITT population, unless otherwise specified.

4.1.1 Completion/Withdrawal Information

One hundred and seventeen investigators in twenty-six countries participated in this trial. An overview of the number of subjects enrolled by main investigator and by country is provided in Display GEN.1 (Week 48).

The subject disposition and trial termination reasons for the ITT and OP populations are summarized in Table 3.

In total, 843 subjects were screened, of which 689 subjects were randomized and treated, and 152 were not randomized and not treated. An additional 2 subjects were randomized but received no treatment. The majority of subjects who were not randomized were considered screening failures, mostly because they did not fulfill all inclusion/exclusion criteria (128 subjects, 84.2%). Of the 2 subjects randomized, but not treated, 1 subject did not fulfill all inclusion/exclusion criteria and the other withdrew consent. These subjects were not included in the ITT population or the OP population (Display GEN.5 [Week 48]).

Three subjects randomized to the DRV/rtv group received LPV instead of rtv for a short period, in violation of the Protocol (CRF ID 211-0451, 34 days; CRF ID 211-0504, 14 days; CRF ID 211-0701, 9 days). On identification of these protocol violations, corrective measures were put

in place immediately to prevent further such occurrences. All 3 subjects stopped LPV intake and continued in the trial with DRV/rtv as per protocol. In addition, 1 subject in the LPV/rtv group (CRF ID 211-0040) had a disallowed change of the underlying OBR (from TDF/FTC to abacavir/lamivudine). These 4 subjects were included in the ITT analysis population but were excluded from the OP population.

Table 3: Subject Disposition - ITT and OP Populations

	DRV/rtv	LPV/rtv	All Subjects
Intent-to-Treat Population			
N screened	-	-	843
N not randomized - not treated	0	0	152
N randomized - not treated	2	0	2
N randomized – treated	343	346	689
Discontinuations – Reason[a], n (%)			
Any reason	***85 (24.8)***	***114 (32.9)***	***199 (28.9)***
Adverse event/HIV related event[a]	16 (4.7)[b,c]	44 (12.7)[b]	60 (8.7)[b]
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[a]	5 (1.5)[d]	9 (2.6)[d]	14 (2.0)[d]
Sponsor's decision	1 (0.3)	1 (0.3)	2 (0.3)
On-Protocol Population			
N randomized – treated	340	345	685
Discontinuations – Reason[a], n (%)			
Any reason	***84 (24.7)***	***114 (33.0)***	***198 (28.9)***
Adverse event/HIV related event[a]	15 (4.4)[b,c]	44 (12.7)[b]	59 (8.6)[b]
Subject lost to follow-up	21 (6.2)	17 (4.9)	38 (5.5)
Subject withdrew consent	19 (5.6)	18 (5.2)	37 (5.4)
Subject noncompliant	7 (2.1)	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[a]	5 (1.5)[d]	9 (2.6)[d]	14 (2.0)[d]
Sponsor's decision	1 (0.3)	1 (0.3)	2 (0.3)

N = number of subjects; n = number of observations

[a] As assessed by the investigator.

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

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

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

Source: Display GEN.1, Display GEN.2, Display GEN.3

Twenty-nine additional subjects were recruited compared to the 660 subjects planned per protocol (see Section 3.6.1). This was due to the number of subjects already in screening when the target sample size was reached. For ethical and practical reasons subjects already in screening who met the inclusion/exclusion criteria and were eligible for the trial were randomized and treated.

At the Week-192 analysis, of the 689 subjects receiving treatment in trial TMC114-C211, 199 (28.9%) had prematurely discontinued; the overall discontinuation rate (for any reason) was lower in the DRV/rtv group (24.8%) than in the LPV/rtv group (32.9%). The difference between the treatment groups was mostly due to the different rate in discontinuations due to AE/HIV-related events, which were the most frequent reason for discontinuation (overall 8.7%), and which were less frequent with DRV/rtv (4.7%) than with LPV/rtv (12.7%). Loss to follow-up and withdrawal of consent were reason for discontinuation in 5.5% and 5.4% of subjects, respectively, and their incidence was comparable between the treatment groups. All other reasons for discontinuation occurred in at most 2.2% of subjects, and were also observed with comparable frequency in both treatment groups.

The difference between the ITT and OP analysis populations was only 4 subjects. Consequently, similar results were observed for the OP and ITT populations.

Figure 2 provides a graphical presentation (Kaplan-Meier curve) of the estimated time to discontinuation. The rate of discontinuations in both treatment groups remained relatively constant throughout the trial period with discontinuations occurring less frequently in the DRV/rtv group than in the LPV/rtv group.

Note that discontinuations due to virologic failure applied only at or beyond Week 12 (see Section 3.2.3). If lack or loss of virologic response was observed at Week 12, subjects could discontinue if this was confirmed at 2 consecutive assessments (unscheduled visits). All subjects who withdrew due to virologic failure did so in adherence with these withdrawal criteria.

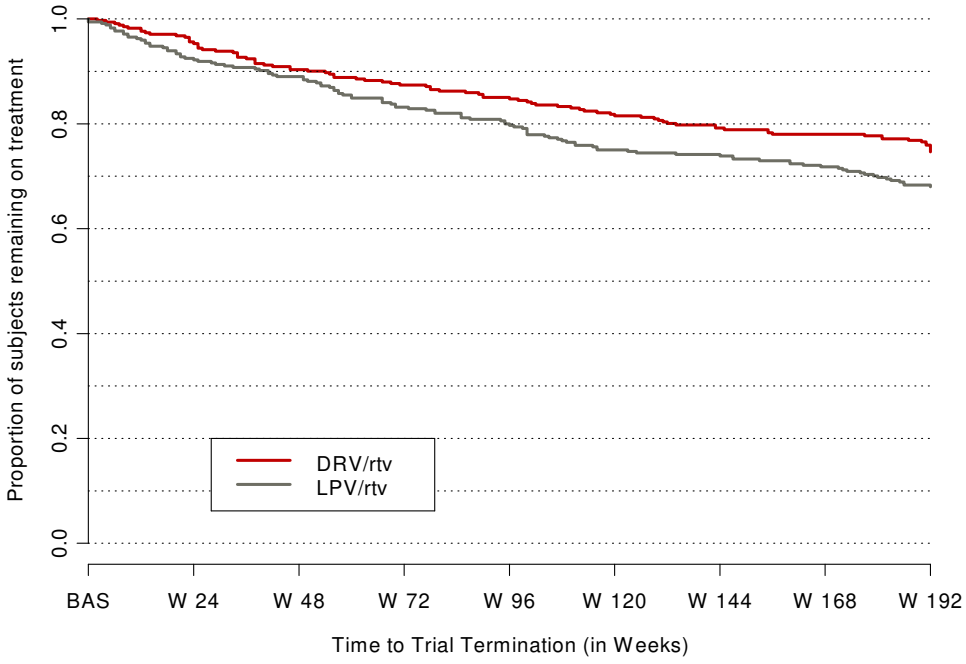


Figure 2: Time to Discontinuation for any Reason - ITT Population (Kaplan-Meier Curve)

Source: Display GEN.5

4.1.2 Extent of Exposure

Treatment duration is summarized in Table 4. Comprehensive information on treatment duration is provided in Display GEN.8.

The mean duration of medication intake was somewhat longer in the DRV/rtv and LPV/rtv groups (162.5 versus 153.5 weeks). Total patient years of exposure was 1072.0 years in the DRV/rtv group versus 1021.4 years in the LPV/rtv group.

Table 4: Duration of Medication Intake During the Treatment Period

Total Duration (Weeks)	DRV/rtv N = 343	LPV/rtv N = 346	All Subjects N = 689
Mean (SE)	162.5 (3.18)	153.5 (3.45)	158.0 (2.35)
Median (range)	192.1 (1.9; 201.3)	191.9 (0.1; 203.1)	192.0 (0.1; 203.1)
Patient years of exposure[a]	1072.0	1021.4	2093.4

N = number of subjects

[a] Patient years exposure = mean number of weeks treated x N / 52 weeks

Source: Display GEN.8

The extent of exposure based on visit data is presented in Table 5. There was a higher discontinuation rate in the LPV/rtv group compared to the DRV/rtv group through to Week 192. At Week 192, 74.6% of DRV/rtv subjects remained in the trial versus 66.2% of LPV/rtv subjects.

Table 5: Exposure Based on Visit Data: Number of Subjects at Different Visits

Visit, n (%)	DRV/rtv N = 343	LPV/rtv N = 346	All Subjects N = 689
Baseline	343 (100.0)	346 (100.0)	689 (100.0)
Week 2	340 (99.1)	334 (96.5)	674 (97.8)
Week 4	337 (98.3)	335 (96.8)	672 (97.5)
Week 8	335 (97.7)	329 (95.1)	664 (96.4)
Week 12	330 (96.2)	328 (94.8)	658 (95.5)
Week 16	328 (95.6)	321 (92.8)	649 (94.2)
Week 24	320 (93.3)	314 (90.8)	634 (92.0)
Week 36	311 (90.7)	309 (89.3)	620 (90.0)
Week 48	306 (89.2)	304 (87.9)	610 (88.5)
Week 60	300 (87.5)	292 (84.4)	592 (85.9)
Week 72	295 (86.0)	286 (82.7)	581 (84.3)
Week 84	293 (85.4)	279 (80.6)	572 (83.0)
Week 96	289 (84.3)	275 (79.5)	564 (81.9)
Week 108	283 (82.5)	260 (75.1)	543 (78.8)
Week 120	275 (80.2)	258 (74.6)	533 (77.4)
Week 132	273 (79.6)	253 (73.1)	526 (76.3)
Week 144	269 (78.4)	251 (72.5)	520 (75.5)
Week 156	264 (77.0)	249 (72.0)	513 (74.5)
Week 168	263 (76.7)	246 (71.1)	509 (73.9)
Week 180	262 (76.4)	236 (68.2)	498 (72.3)
Week 192	256 (74.6)	229 (66.2)	485 (70.4)

N = number of subjects; n = number of observations

Source: Display GEN.1

4.1.3 Protocol Deviations

Major protocol deviations are summarized in Display GEN.6. Individual subject data on protocol deviations are provided in Listing GEN.5.

Major protocol deviations were defined as use of disallowed concomitant medication, disallowed ARV use, relevant noncompliance with the trial medication, or violations with respect to inclusion and exclusion criteria and/or procedures that might impact the primary efficacy endpoint at Week 48.

Major protocol deviations were noted in 7.9% of subjects in the DRV/rtv group and 5.5% of subjects in the LPV/rtv group. Major deviations occurring in > 2 subjects overall were:

- procedure deviation: 9 (2.6%) DRV/rtv subjects, 5 (1.4%) LPV/rtv subjects;
- noncompliance with the trial medication: 7 (2.0%) DRV/rtv subjects, 6 (1.7%) LPV/rtv subjects;
- deviation of underlying ARV intake: 2 (0.6%) DRV/rtv subjects, 7 (2.0%) LPV/rtv subjects;
- informed consent not signed: 6 (1.7%) DRV/rtv subjects, 1 (0.3%) LPV/rtv subjects;
- disallowed underlying ARV intake: 3 (0.9%) DRV/rtv subjects, 0 LPV/rtv subjects:
  - 3 subjects received DRV/LPV instead of DRV/rtv (CRF ID 211-0451, 34 days; CRF ID 211-0504, 14 days; CRF ID 211-0701, 9 days). On identification of these protocol violations, corrective measures were put in place to prevent further such occurrences. All 3 subjects stopped LPV intake and continued in the trial with DRV/rtv as per protocol.

In addition, 1 subject (CRF ID 211-0083) took *Hypericum perforatum* during the treatment period for 28 days, but this was not coded as a protocol deviation.

To account for potential effects of major protocol deviations with respect to disallowed ARV intake on the outcome of the primary efficacy analysis, OP analysis in which subjects with these deviations were excluded was performed, as well as an analysis on the ITT population (for details, see Section 3.6.2). Comparison of the results obtained from these multiple analyses demonstrated that these major protocol deviations did not have a relevant impact on the outcome of the efficacy analyses (for details, see Sections 4.2.4 and 4.2.5).

4.1.4 Demographic and Baseline Characteristics

4.1.4.1 Demographic and Baseline Disease Characteristics

The main demographic and disease baseline characteristics are summarized in Table 6 and Table 7, respectively; comprehensive information is provided in Display GEN.8 (Week 96) and Display GEN.10 (Week 96) respectively. Information on the demographics and baseline characteristics for subjects in the OP population is provided in Display GEN.9 (Week 96) and Display GEN.11 (Week 96), respectively. An overview of the hepatitis coinfection status at baseline is provided in Display GEN.12 (Week 96). Individual subject data are provided in Listing GEN.6 (Week 96) and Listing GEN.7 (Week 96).

Thirty percent of the subjects enrolled in the trial were female (209 subjects). The median age was 34 years (range, 18 - 70 years). Forty-two percent were Caucasian (290 subjects), 22% (151 subjects) were Black and 22% (154 subjects) were Hispanic.

The mean (SD) baseline $\log_{10}$ viral load for all subjects was 4.85 (0.621) $\log_{10}$ copies/mL; 18.7% of subjects had a baseline viral load < 20,000 copies/mL, while 34.4% of subjects had a baseline viral load ≥ 100,000 copies/mL. The median baseline CD4+ cell count for all subjects was 225 x 10^6/L (range: 2 - 750 x 10^6/L); 58.1% of subjects had a baseline CD4+ cell count ≥ 200 x 10^6/L, while 16.2% of subjects had a baseline CD4+ cell count < 100 x 10^6/L. Consistent with the naïve ARV treatment status of subjects, the majority (64.3%) had CDC category A HIV infection at time of entry into the trial; only 8.7% had CDC category C disease. The mean known time since HIV-1 infection diagnosis was 2.5 years.

Ninety-one (13.2%) subjects were coinfected with hepatitis B or C virus; the number of coinfected subjects was similar in the DRV/rtv (12.5%) and LPV/rtv (13.9%) treatment groups.

Table 6: Demographic Data

Demographic Parameter	DRV/rtv	LPV/rtv	All Subjects
Sex, n (%), N	343	346	689
Female	104 (30.3)	105 (30.3)	209 (30.3)
Male	239 (69.7)	241 (69.7)	480 (69.7)
Age (years), N	343	346	689
Mean (SD)	35.5 (9.23)	35.3 (9.22)	35.4 (9.22)
Median (range)	34.0 (18; 70)	33.0 (19; 68)	34.0 (18; 70)
Age, n (%), N	343	346	689
≤ 30	115 (33.5)	124 (35.8)	239 (34.7)
31 - ≤ 45	175 (51.0)	172 (49.7)	347 (50.4)
46 - ≤ 55	44 (12.8)	40 (11.6)	84 (12.2)
56 - ≤ 65	8 (2.3)	9 (2.6)	17 (2.5)
> 65	1 (0.3)	1 (0.3)	2 (0.3)
Height (cm), N	341	344	685
Mean (SD)	169.8 (9.90)	170.6 (10.59)	170.2 (10.25)
Median (range)	170.2 (143; 194)	171.5 (138; 196)	171.0 (130; 196)
Weight (kg), N	343	346	689
Mean (SD)	69.6 (13.43)	71.2 (16.31)	70.4 (14.96)
Median (range)	68.0 (39; 119)	69.4 (34; 141)	68.6 (34; 141)
Body mass index (kg/m²), N	341	344	685
Mean (SD)	24.1 (4.12)	24.3 (4.82)	24.2 (4.48)
Median (range)	23.5 (16; 39)	23.4 (16; 44)	23.4 (16; 44)
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)
Missing	1	2	3
Region, n (%), N	343	346	689
Africa	35 (10.2)	50 (14.5)	85 (12.3)
Asia	37 (10.8)	34 (9.8)	71 (10.3)
Europe	100 (29.2)	90 (26.0)	190 (27.6)
Australia	18 (5.2)	20 (5.8)	38 (5.5)
Latin America	60 (17.5)	64 (18.5)	124 (18.0)
North America	93 (27.1)	88 (25.4)	181 (26.3)
Hepatitis B or C coinfection status, n (%), N	343	346	689
Coinfected	43 (12.5)	48 (13.9)	91 (13.2)
Not Coinfected	300 (87.5)	298 (86.1)	598 (86.8)

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

Source: Display GEN.8 (Week 96), Display GEN.12 (Week 96)

Table 7: Baseline Disease Characteristics

Baseline Characteristic	DRV/rtv	LPV/rtv	All Subjects
Log_{10} viral load (copies/mL), N	343	346	689
Mean (SD)	4.86 (0.638)	4.84 (0.604)	4.85 (0.621)
Median (range)	4.85 (2.92; 6.75)	4.79 (2.82; 6.66)	4.83 (2.82; 6.75)
Viral load baseline (copies/mL), n (%), N	343	346	689
< 20,000	64 (18.7)	65 (18.8)	129 (18.7)
20,000 - < 50,000	73 (21.3)	84 (24.3)	157 (22.8)
50,000 - < 100,000	89 (25.9)	77 (22.3)	166 (24.1)
≥ 100,000	117 (34.1)	120 (34.7)	237 (34.4)
CD4+ cell count (x 10^6/L), N	343	346	689
Mean (SD)	245 (148.8)	231 (132.6)	238 (141.0)
Median (range)	228 (4; 750)	218 (2; 714)	225 (2; 750)
CD4+ cell count (x 10^6/L), n (%), N	343	346	689
< 50	30 (8.7)	30 (8.7)	60 (8.7)
50 - < 100	23 (6.7)	29 (8.4)	52 (7.5)
100 - < 200	88 (25.7)	89 (25.7)	177 (25.7)
200 - < 350	130 (37.9)	137 (39.6)	267 (38.8)
≥ 350	72 (21.0)	61 (17.6)	133 (19.3)
Known duration of HIV infection (years), N	343	346	689
Mean (SD)	2.4 (3.63)	2.5 (3.56)	2.5 (3.59)
Median (range)	1.1 (0; 22)	1.2 (0; 21)	1.1 (0; 22)
CDC Clinical stage of HIV infection, n (%), N	343	346	689
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)
HIV Clade, n (%), N	342	346	688
B	210 (61.4)	208 (60.1)	418 (60.8)
C	39 (11.4)	51 (14.7)	90 (13.1)
CRF01_AE	62 (18.1)	55 (15.9)	117 (17.0)
Other	31 (9.1)	32 (9.2)	63 (9.2)

N = number of subjects; n = number of observations

Source: Display GEN.10 (Week 96)

4.1.4.2 BASELINE GENOTYPE

The PR and RT mutations at baseline (see Section 3.6.5) are summarized in Table 8. A comprehensive overview of all PR and RT mutations at baseline is provided in Display VIR.5 and Display VIR.6 (descriptive statistics). A list of the individual mutations is provided in Display VIR.7. Individual data on baseline mutations of subjects containing ≥ 1 DRV RAM are provided in Listing VIR.3.

There were some differences in the baseline genotype data of the Week-192 analysis compared to the Week-96 analysis, because in the present analysis, the updated 2009 IAS USA list of mutations[29] was used, and baseline and prebaseline genotype data were concatenated when counting baseline mutations, whereas in the Week-96 analysis the 2007 IAS USA list of mutations[15] was used, and only the baseline genotype data were taken into account.

As expected, in this treatment-naïve population, most subjects did not have evidence of resistance at screening (96.9% had no primary PI mutations, 98.8% had no DRV RAMs and 83.4% had ≤ 1 LPV RAM.

Overall, the median number of primary PI mutations was 0 (range: 0 - 3); the median number of PI RAMs was 4 (range: 0 - 11). The median number of DRV RAMs and LPV RAMs (IAS USA) was 0 (range: 0 - 2) and 1 (range: 0 - 6), respectively.

The number of PI RAMs at baseline in this treatment-naïve population is a reflection of the occurrence of natural polymorphisms in the different clades encountered in the subjects included in this trial. The majority (60.8%) of subjects harbored HIV-1 clade B; 13.1% harbored HIV-1 clade C; 17.0% harbored HIV-1 clade CRF01_AE, and 9.2% harbored another HIV-1 clade (see Table 7). The prevalence of PI RAMs in the different clades is shown in Display GEN.22 (Week 96).

Graphical presentations of the prevalence of DRV and LPV RAMs at baseline are provided in Figure 3. LPV RAMs were most frequently observed at positions L63, L10, A71, and K20. PR mutation L63P is frequently observed in viruses that have never been exposed to PIs. By itself L63P does not cause resistance to any PI, but it has been shown that L63P, when present with multiple other mutations, is associated with clinical failure to LPV/rtv treatment[15].

The prevalence of PI RAMs in this trial is in agreement with the reported prevalence in PI-naïve infected subjects[34].

There were no relevant differences between the treatment groups with respect to any baseline mutations.

Table 8: Number of PR and RT Mutations at Baseline[a]

	DRV/rtv N = 342	LPV/rtv N = 346	All Subjects N = 688
All PR mutations[b]			
Median (range)	9.0 (2; 20)	9.0 (3; 17)	9.0 (2; 20)
All PR mutations, n (%)			
≤ 5	34 (9.9)	34 (9.8)	68 (9.9)
6 - 10	198 (57.9)	198 (57.2)	396 (57.6)
11 - 15	104 (30.4)	111 (32.1)	215 (31.3)
≥ 16	6 (1.8)	3 (0.9)	9 (1.3)
Primary PI mutation[b]			
Median (range)	0.0 (0; 3)	0.0 (0; 2)	0.0 (0; 3)
Primary PI mutations, n (%)			
0	326 (95.3)	341 (98.6)	667 (96.9)
1	11 (3.2)	4 (1.2)	15 (2.2)
2	4 (1.2)	1 (0.3)	5 (0.7)
3	1 (0.3)	0	1 (0.1)
PI RAMs[b]			
Median (range)	4.0 (0; 11)	3.5 (0; 8)	4.0 (0; 11)
PI RAMs, n (%)			
≤ 2	83 (24.3)	80 (23.1)	163 (23.7)
3 - 4	161 (47.1)	172 (49.7)	333 (48.4)
5 - 9	96 (28.1)	94 (27.2)	190 (27.6)
≥ 10	2 (0.6)	0	2 (0.3)

Table 8: Number of PR and RT Mutations at Baseline (Cont'd)

	DRV/rtv N = 342	LPV/rtv N = 346	All Subjects N = 688
DRV RAMs[b]			
Median (range)	0.0 (0; 2)	0.0 (0; 1)	0.0 (0; 2)
DRV RAMs, n (%)			
0	337 (98.5)	343 (99.1)	680 (98.8)
1	4 (1.2)	3 (0.9)	7 (1.0)
2	1 (0.3)	0	1 (0.1)
LPV RAMs[b]			
Median (range)	1.0 (0; 6)	1.0 (0; 3)	1.0 (0; 6)
LPV RAMs, n (%)			
0	131 (38.3)	135 (39.0)	266 (38.7)
1	157 (45.9)	151 (43.6)	308 (44.8)
2	45 (13.2)	59 (17.1)	104 (15.1)
≥ 3	9 (2.6)	1 (0.3)	10 (1.5)
LPV RAMs (King's List[c]**)**			
Median (range)	1.0 (0; 5)	1.0 (0; 3)	1.0 (0; 5)
LPV RAMs (King's List), n (%)			
0	140 (40.9)	141 (40.8)	281 (40.8)
1	136 (39.8)	146 (42.2)	282 (41.0)
2	57 (16.7)	51 (14.7)	108 (15.7)
≥ 3	9 (2.6)	8 (2.3)	17 (2.5)
NRTI RAMs[b]			
Median (range)	0.0 (0; 5)	0.0 (0; 2)	0.0 (0; 5)
NRTI RAMs, n (%)			
0	313 (91.5)	322 (93.1)	635 (92.3)
1	22 (6.4)	21 (6.1)	43 (6.3)
≥ 2	7 (2.0)	3 (0.9)	10 (1.5)

N = number of subjects; n = number of observations

[a] Data at baseline and prebaseline were concatenated to calculate resistance baseline values.

[b] IAS-USA 2009 list[29]

[c] King's list[30]

Source: Display VIR.5, Display VIR.6

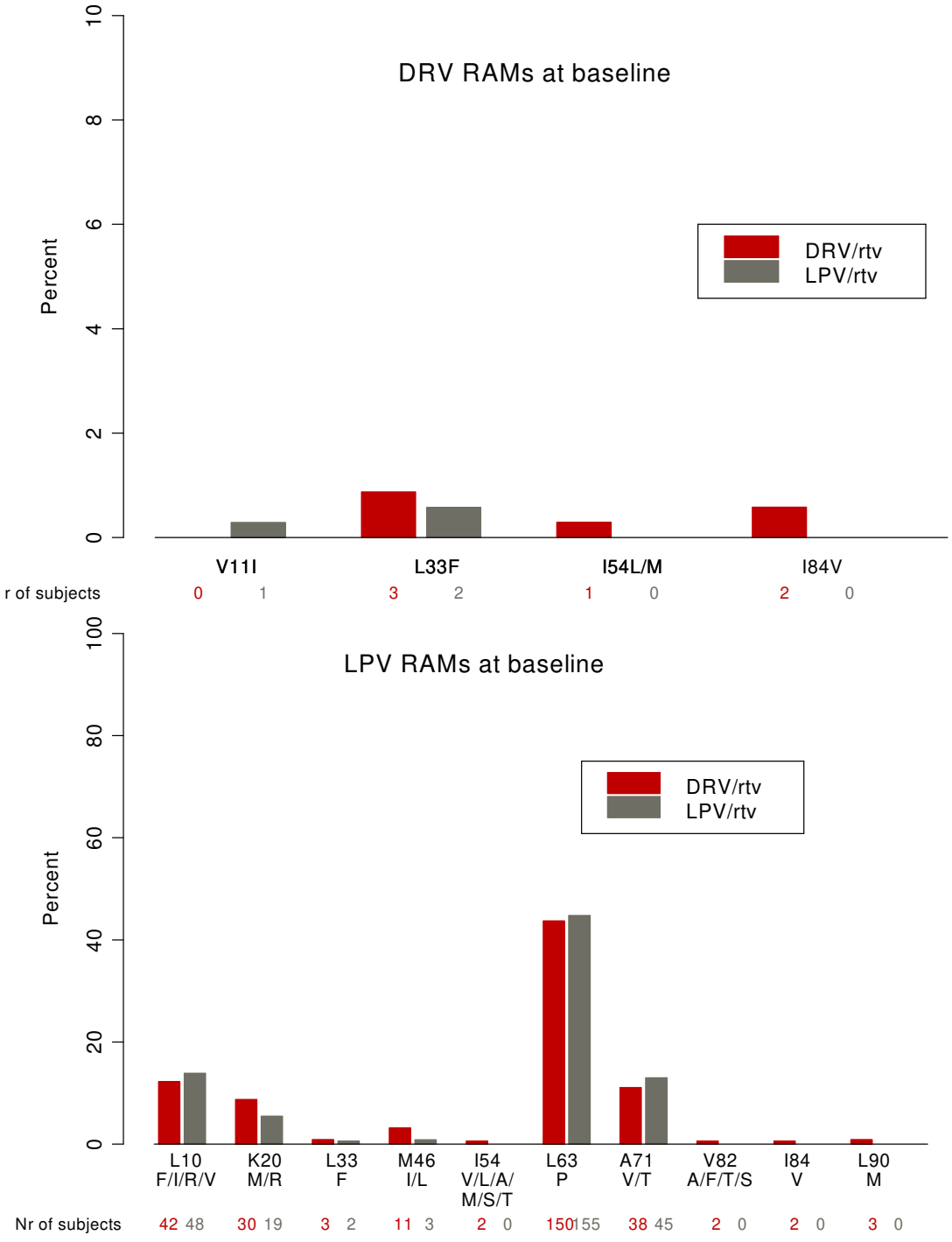


Figure 3: Prevalence of DRV RAMs (Upper Graph) and LPV RAMs (Lower Graph) at Baseline

Source: Display VIR.7

4.1.4.3 MEDICAL HISTORY AND CONCOMITANT DISEASE

An overview of the active concomitant diseases (by organ system) at screening is provided in Table 9. A more comprehensive overview of the medical history and currently active concomitant diseases at screening (by organ system) is provided in Display GEN.15 (Week 96). Individual subject data on medical history are provided in Listing GEN.8 (Week 96).

The incidence of concomitant diseases at screening was high. A wide range of concomitant diseases were reported in both treatment groups; the most frequent were dermatologic conditions (28.2%) and conditions related to the GI system (22.6%). There were no relevant differences between the DRV/rtv and LPV/rtv treatment groups with respect to the concomitant diseases reported at screening.

Table 9: Active Concomitant Disease at Screening

Currently Active Concomitant Disease, n (%)	DRV/rtv N = 343	LPV/rtv N = 346	All Subjects N = 689
Allergic/Immunologic	58 (16.9)	57 (16.5)	115 (16.7)
Allergic/Immunologic - other	25 (7.3)	21 (6.1)	46 (6.7)
Cardiovascular	42 (12.2)	33 (9.5)	75 (10.9)
Dermatologic	91 (26.5)	103 (29.8)	194 (28.2)
Ears, nose, throat	50 (14.6)	64 (18.5)	114 (16.5)
Endocrine	19 (5.5)	33 (9.5)	52 (7.5)
Eyes	36 (10.5)	47 (13.6)	83 (12.0)
Gastrointestinal	71 (20.7)	85 (24.6)	156 (22.6)
Genito-urinary	68 (19.8)	60 (17.3)	128 (18.6)
Hematologic	29 (8.5)	25 (7.2)	54 (7.8)
Musculoskeletal	46 (13.4)	45 (13.0)	91 (13.2)
Neurologic	42 (12.2)	41 (11.8)	83 (12.0)
Psychiatric	52 (15.2)	44 (12.7)	96 (13.9)
Respiratory	24 (7.0)	26 (7.5)	50 (7.3)
Other medical/surgical history/concomitant disease	68 (19.8)	78 (22.5)	146 (21.2)

N = number of subjects; n = number of observations

Source: Display GEN.15 (Week 96)

4.1.5 Prior and Concomitant Therapies

4.1.5.1 ARV THERAPIES IN THE INITIAL FIXED BACKGROUND REGIMEN

An overview of the number and classes of the ARVs used in the initial fixed background ART are provided in Display GEN.14 (Week 96). Initial fixed background ART was defined as the ART taken on Day 7 (relative to the start of the treatment period), or the last day of treatment in case of discontinuation during the first 7 days of treatment. As defined in the Protocol, the only allowed ARVs were the NRTIs TDF and FTC.

Four subjects (1.2%) in the DRV/rtv group did not receive an NRTI in their background regimen as determined on Day 7. Three of these four subjects started TDF/FTC later than Day 7 (Days 12, 13 and 14, respectively). The fourth subject had stopped using TDF/FTC prior to Day 7 because of AEs that were considered possibly related to these NRTIs, and started with zidovudine and lamivudine on Day 14. One subject in the LPV/rtv treatment group received

only FTC as determined on Day 7, TDF was added a few days later (Day 11). These 4 cases were coded as major protocol deviations. All other subjects received TDF and FTC as per protocol.

4.1.5.2 NON-ARV THERAPIES

An overview of all non-ARV concomitant therapies used during the course of the trial is provided in Display GEN.7.

The majority of non-ARV concomitant therapies used during this trial were for the treatment of underlying disease. There were no relevant (> 10%) differences between the DRV/rtv and LPV/rtv groups with respect to non-ARV concomitant therapies at trial start, or during the trial with the exception of antidiarrheals, which were taken by a lower percentage of subjects in the DRV/rtv group than in the LPV/rtv group (27.7% versus 38.7%). An overview of the most frequently used (by ≥ 10% of subjects in any treatment group) concomitant medication classes during the treatment period is provided in Table 10.

Table 10: Concomitant Non-ARV Therapy Classes Used by ≥ 10% of Subjects in Any Group During the Treatment Period

Class, n (%)	DRV/rtv N = 343	LPV/rtv N = 346	All Subjects N = 689
All other therapeutic products	45 (13.1)	40 (11.6)	85 (12.3)
Analgesics	186 (54.2)	201 (58.1)	387 (56.2)
Antibacterials for systemic use	223 (65.0)	230 (66.5)	453 (65.7)
Antibiotics and chemotherapy for dermatological use	104 (30.3)	131 (37.9)	235 (34.1)
Antidiarr., intest. antiinfl./antiinfect. agents	95 (27.7)	134 (38.7)	229 (33.2)
Antifungals for dermatological use	85 (24.8)	83 (24.0)	168 (24.4)
Antihistamines for systemic use	88 (25.7)	78 (22.5)	166 (24.1)
Antiinflammatory and antirheumatic products	47 (13.7)	44 (12.7)	91 (13.2)
Antipruritics, incl. antihist., anesthet., etc.	48 (14.0)	44 (12.7)	92 (13.4)
Antivirals for systemic use	42 (12.2)	23 (6.6)	65 (9.4)
Cardiac therapy	96 (28.0)	99 (28.6)	195 (28.3)
Corticosteroids, dermatological preparations	73 (21.3)	51 (14.7)	124 (18.0)
Cough and cold preparations	73 (21.3)	76 (22.0)	149 (21.6)
Drug for acid related disorders	76 (22.2)	72 (20.8)	148 (21.5)
Drugs for functional gastrointestinal disorders	47 (13.7)	63 (18.2)	110 (16.0)
Drugs for obstructive airway diseases	29 (8.5)	41 (11.8)	70 (10.2)
Lipid modifying agents	40 (11.7)	49 (14.2)	89 (12.9)
Nasal preparations	62 (18.1)	53 (15.3)	115 (16.7)
Psychoanaleptics	57 (16.6)	55 (15.9)	112 (16.3)
Psycholeptics	79 (23.0)	91 (26.3)	170 (24.7)
Sex hormones and modulators of the genital system	44 (12.8)	47 (13.6)	91 (13.2)
Stomatological preparations	162 (47.2)	168 (48.6)	330 (47.9)
Vaccines	95 (27.7)	91 (26.3)	186 (27.0)
Vitamins	102 (29.7)	103 (29.8)	205 (29.8)

N = number of subjects; n = number of observations

Source: Display GEN.7

4.1.6 Treatment Compliance

Compliance with trial treatment (DRV/rtv or LPV/rtv) was assessed by the M-MASRI questionnaire (for details, see Section 3.6.6.1). A summary of the results on compliance with trial treatment as determined by this M-MASRI questionnaire is provided in Section 4.4.1.

Compliance with the trial treatment (DRV/rtv and LPV/rtv) was also assessed by pill count, based on the start and stop dates of the trial medication intake at each visit. A summary listing of the trial medication intake is provided in Listing GEN.6.

Compliance data based on pharmacokinetic sampling up to Week 48 are provided in Display PK/PD.9 (Week 48). Compliance up to Week 48 was generally high in both treatment groups: the proportion of subjects with DRV plasma concentrations below the detection limit was ≤ 3% at all time points, and the proportion of subjects with LPV plasma concentrations below the detection limit was ≤ 6% at all time points.

4.1.7 Conclusions on Subject and Treatment Information

The baseline characteristics of the subjects in this trial show a homogeneous population of ARV naïve subjects that included a majority of subjects with early stage of HIV disease. The trial included a diverse population representative of different ethnic background, gender, and geographic regions.

In total 689 subjects were randomized, of which 343 subjects were treated with DRV/rtv and 346 subjects with LPV/rtv. Twenty-nine supplementary subjects were recruited compared to the 660 subjects planned per protocol. This was due to the number of subjects already in screening at the time the target enrolment was reached. Due to ethical and practical reasons, all subjects in screening at this point who were eligible for the trial were randomized, resulting in a slight over-recruitment.

Discontinuations to Week 192 (overall rate, 28.9%) occurred at a relatively constant rate and less frequently with DRV/rtv than with LPV/rtv. Discontinuation due to AE/HIV-related events (as reported by the investigator) occurred less frequently with DRV/rtv than with LPV/rtv (4.7% versus 12.7%). The overall rate of discontinuations due to virologic failure was very low, with comparable frequency with DRV/and LPV/rtv (1.5% versus 2.6%). The mean duration of treatment was 162.5 weeks for the DRV/rtv group and 153.5 weeks for the LPV/rtv group.

There was a high percentage of female subjects (approximately 30%; 209 subjects) and different ethnic backgrounds; 42% of subjects were Caucasian, 22% were Black, 22% were Hispanic and 12% were Asian. A similar percentage of subjects in the DRV/rtv and LPV/rtv treatment groups were coinfected with hepatitis B or C virus (12.5% versus 13.9%, respectively).

At baseline, the mean $\log_{10}$ viral load for all subjects was 4.85 $\log_{10}$ copies/mL; less than 20% (18.7%) of subjects had a baseline viral load < 20,000 copies/mL and 34.4% had a baseline viral load ≥ 100,000 copies/mL. The median baseline CD4+ cell count for all subjects was 225 x 10^6/L; 58.1% of subjects had a baseline CD4+ cell count ≥ 200 x 10^6/L and 16.2% had a baseline CD4+ cell count < 100 x 10^6/L. The majority (64.3%) had CDC category A HIV infection at time of entry into the trial; only 8.7% had CDC category C disease. The mean time since HIV-1 infection diagnosis was 2.5 years.

As expected in this treatment-naïve patient population, most subjects did not have evidence of resistance at screening. The median number of primary PI mutations was 0 (range: 0 - 3); the median number of PI RAMs was 4 (range: 0 - 11). The median number of DRV RAMs and LPV RAMs was 0 (range: 0 - 2) and 1 (range: 0 - 6), respectively. The number of PI RAMs at baseline in this population is a reflection of the occurrence of natural polymorphisms in the different clades encountered in the subjects included in this trial.

Comparison of the demographic and disease characteristics of the DRV/rtv and LPV/rtv treatment groups revealed no relevant between-group differences.

4.2 EFFICACY RESULTS

4.2.1 Data Sets Analyzed

The primary population for testing the primary efficacy parameter of the Week-192 analysis (defined as the percentage of subjects with confirmed plasma vial load < 50 copies/mL at Week 192) was the ITT population. In addition, analyses were performed on the OP population.

For the virologic response parameters, change in $\log_{10}$ viral load from baseline, and immunologic change, subgroup analyses by the following parameters (categories provided in parentheses) were performed:

- baseline plasma viral load (< 100,000, ≥ 100,000 copies/mL);
- baseline CD4+ cell count (< 50, 50 - < 100, 100 - < 200, 200 - < 350, ≥ 350 x 10^6/L);
- baseline CD4+ cell count (< 200, ≥ 200 x 10^6/L);
- gender (male, female);
- age (≤ 30, 30 - ≤ 45, 45 - ≤ 55, 55 - ≤ 65, > 65);
- race (Black, Caucasian/White, Hispanic, Oriental/Asian, Other);
- region (Africa, Asia, Europe, Australia, Latin America, North-America);
- clade (for clades with n ≥ 10%, the remainder grouped under 'Other');
- number of IAS-USA primary PI mutations[29] at baseline (0, ≥ 1);
- number of PI RAMs[29] at baseline (0-1, 2, 3, 4, 5, ≥ 6);
- number of IAS USA LPV RAMs[29] at baseline (0, 1, 2, ≥ 3);
- number of LPV RAMs King's list[30] at baseline (0, 1, 2, ≥ 3);
- adherence (yes, no).

4.2.2 Interim Analyses

See Section 3.1.3.1.

4.2.3 Significance Level Correction

In the present Week-192 analysis, the primary objective was to demonstrate noninferiority in virologic response (defined as a confirmed plasma viral load of < 50 copies/mL) with DRV/rtv 800/100 mg q.d. compared to LPV/rtv 800/200 mg (total daily dose), both combined with a fixed background regimen of TDF/FTC, at Week 192. This objective was tested at the 5% 2-sided (or 2.5% 1-sided) significance level.

As no formal interim analyses were performed (only 1 DSMB interim analysis at Week 24 for human subject protection, see Section 3.1.3.1), no multiplicity correction was implemented.

A secondary objective was to test for superiority, in case the noninferiority criteria were met. According to FDA and European guidance[35,36] there is no multiplicity argument when the same 95% 2-sided CI of the difference in response between treatment groups (DRV/rtv and LPV/rtv)

is used to evaluate 1) noninferiority, through evaluation whether the lower limit exceeds -12%, as well as 2) statistical superiority, through evaluation whether the lower limit exceeds 0.

4.2.4 Primary Efficacy Variable

In the present Week-192 analysis, the primary antiviral activity parameter was virologic response defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL at Week 192, calculated according to the FDA TLOVR algorithm (see Section 3.6.4.1). The analyses were performed on both the ITT population as primary population, and the OP population. The difference between the ITT and OP populations was 4 subjects, all of whom were excluded from the DRV/rtv group.

Descriptive statistics for virologic response defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL are provided in Display EFF.18 for the ITT population and Display EFF.19 for the OP population. Statistical comparisons between the treatment groups for this virologic response parameter using a logistic regression model (including baseline CD4+ cell count and baseline $\log_{10}$ viral load as covariates and treatment as factor, see Section 3.6.4.1.3) are provided in Display EFF.25 (ITT population) and Display EFF.26 (OP population). Individual subject data for virologic response are provided in Listing EFF.1.

Virologic response defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL per time point is summarized in Table 11 (ITT - TLOVR) and Table 12 (OP - TLOVR). A graphical presentation of this virologic response parameter over time, and of the difference between the DRV/rtv and LPV/rtv treatment groups over time for the ITT population are provided in Figure 4 and Figure 5, respectively. Statistical comparisons between the treatment groups at Week 192 (logistic regression model, ITT & OP - TLOVR) are summarized in Table 13.

Virologic response defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL was similar up to Week 12 in the DRV/rtv and LPV/rtv treatment groups, after which a greater percentage of subjects in the DRV/rtv group had this level of viral suppression at all further time points, with the difference between the treatment groups becoming more pronounced over time. The lower 95% confidence interval limit for the difference between treatments was greater than zero at all time points after Week 60.

At Week 192, virologic response in the ITT population was 68.8% for the DRV/rtv group and 57.2% for the LPV/rtv group. The difference in virologic response [95% CI] between the treatment groups was 11.6 [4.4; 18.8]. The lower limit of the 95% CI of the difference between the treatment groups was > -12%, therefore, noninferiority of DRV/rtv versus LPV/rtv was concluded. Statistical comparison using the logistic regression model showed an estimated difference [95% CI] in virologic response at Week 192 between the DRV/rtv and LPV/rtv treatment groups of 11.7 [4.5; 18.9], with a p-value of < 0.001 confirming noninferiority.

A secondary objective was to test for superiority of DRV/rtv over LPV/rtv in the event of noninferiority being confirmed. The p-value for the estimated difference in response between DRV/rtv and LPV/rtv at Week 192 was 0.002, thus superiority of DRV/rtv over LPV/rtv in this patient population was concluded.

Similar results were obtained for the OP population: virologic response at Week 192 was 69.1% and 57.1% for the DRV/rtv and LPV/rtv groups, respectively. The difference [95% CI] between

the treatment groups was 12.0 [4.8; 19.2], confirming noninferiority of DRV/rtv versus LPV/rtv (lower limit of the 95% CI > -12%). Statistical comparison (logistic regression) showed an estimated difference in virologic response at Week 192 between the DRV/rtv and LPV/rtv treatment groups of 12.1 [4.9; 19.3]. The p-value for noninferiority was < 0.001. In addition, superiority of DRV/rtv over LPV/rtv was also concluded with a p-value of 0.002 for the estimated difference in response between DRV/rtv and LPV/rtv.

Table 11: Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL per Time Point (ITT – TLOVR)

	DRV/rtv		LPV/rtv		DRV/rtv - LPV/rtv	
Time Point	N	n (%)	N	n (%)	Difference in % Response	95 % CI of Difference in % Response[a]
Week 2	343	2 (0.6)	346	3 (0.9)	-0.3	-1.6; 1.0
Week 4	343	26 (7.6)	346	21 (6.1)	1.5	-2.3; 5.3
Week 8	343	84 (24.5)	346	97 (28.0)	-3.5	-10.1; 3.0
Week 12	343	159 (46.4)	346	162 (46.8)	-0.5	-7.9; 7.0
Week 16	343	228 (66.5)	346	219 (63.3)	3.2	-4.0; 10.3
Week 24	343	273 (79.6)	346	266 (76.9)	2.7	-3.5; 8.9
Week 36	343	288 (84.0)	346	275 (79.5)	4.5	-1.3; 10.3
Week 48	343	288 (84.0)	346	276 (79.8)	4.2	-1.6; 10.0
Week 60	343	281 (81.9)	346	271 (78.3)	3.6	-2.4; 9.6
Week 72	343	280 (81.6)	346	261 (75.4)	6.2	0.1; 12.3
Week 84	343	275 (80.2)	346	250 (72.3)	7.9	1.6; 14.3
Week 96	343	269 (78.4)	346	245 (70.8)	7.6	1.1; 14.1
Week 108	343	265 (77.3)	346	236 (68.2)	9.1	2.4; 15.7
Week 120	343	256 (74.6)	346	233 (67.3)	7.3	0.5; 14.1
Week 132	343	253 (73.8)	346	229 (66.2)	7.6	0.7; 14.4
Week 144	343	249 (72.6)	346	223 (64.5)	8.1	1.2; 15.1
Week 156	343	246 (71.7)	346	220 (63.6)	8.1	1.2; 15.1
Week 168	343	242 (70.6)	346	216 (62.4)	8.1	1.1; 15.2
Week 180	343	238 (69.4)	346	201 (58.1)	11.3	4.2; 18.4
Week 192	343	236 (68.8)	346	198 (57.2)	11.6	4.4; 18.8

N = number of subjects; n = number of observations

[a] Based on a normal approximation of the difference in % response

Source: Display EFF.18

Table 12: Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL per Time Point (OP – TLOVR)

	DRV/rtv		LPV/rtv		DRV/rtv - LPV/rtv	
Time Point	N	n (%)	N	n (%)	Difference in % Response	95 % CI of Difference in % Response[a]
Week 2	340	2 (0.6)	345	3 (0.9)	-0.3	-1.6; 1.0
Week 4	340	26 (7.6)	345	21 (6.1)	1.6	-2.2; 5.4
Week 8	340	84 (24.7)	345	97 (28.1)	-3.4	-10.0; 3.2
Week 12	340	159 (46.8)	345	162 (47.0)	-0.2	-7.7; 7.3
Week 16	340	227 (66.8)	345	218 (63.2)	3.6	-3.6; 10.7
Week 24	340	272 (80.0)	345	265 (76.8)	3.2	-3.0; 9.4
Week 36	340	286 (84.1)	345	274 (79.4)	4.7	-1.1; 10.5
Week 48	340	286 (84.1)	345	275 (79.7)	4.4	-1.4; 10.2
Week 60	340	279 (82.1)	345	270 (78.3)	3.8	-2.2; 9.8
Week 72	340	278 (81.8)	345	260 (75.4)	6.4	0.3; 12.5
Week 84	340	273 (80.3)	345	249 (72.2)	8.1	1.8; 14.5
Week 96	340	267 (78.5)	345	244 (70.7)	7.8	1.3; 14.3
Week 108	340	263 (77.4)	345	235 (68.1)	9.2	2.6; 15.9
Week 120	340	254 (74.7)	345	232 (67.2)	7.5	0.7; 14.2
Week 132	340	251 (73.8)	345	228 (66.1)	7.7	0.9; 14.6
Week 144	340	247 (72.6)	345	222 (64.3)	8.3	1.4; 15.2
Week 156	340	244 (71.8)	345	219 (63.5)	8.3	1.3; 15.3
Week 168	340	241 (70.9)	345	215 (62.3)	8.6	1.5; 15.6
Week 180	340	237 (69.7)	345	200 (58.0)	11.7	4.6; 18.9
Week 192	340	235 (69.1)	345	197 (57.1)	12.0	4.8; 19.2

N = number of subjects; n = number of observations

[a] Based on a normal approximation of the difference in % response

Source: Display EFF.19

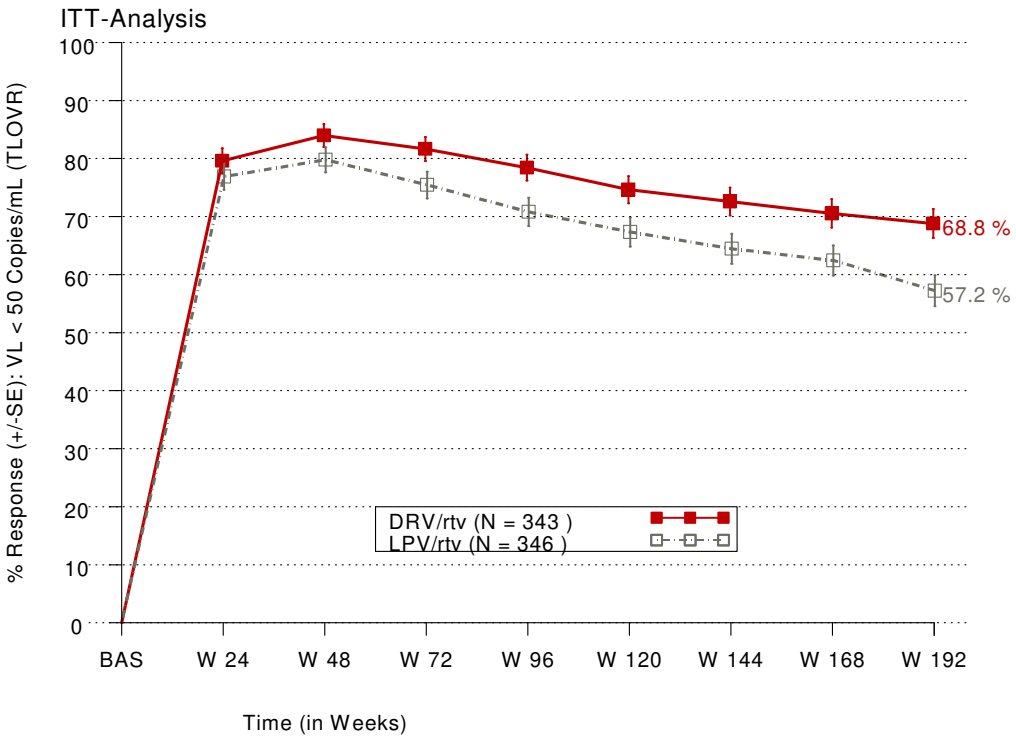


Figure 4: Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL Over Time (ITT – TLOVR)

Source: Display EFF.18

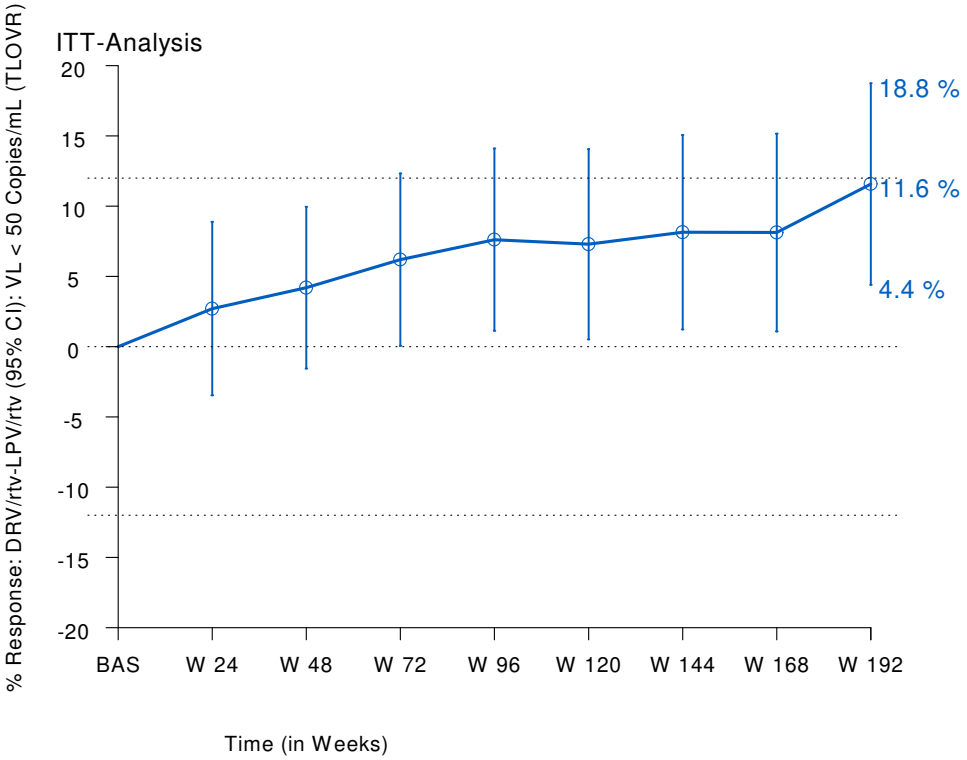


Figure 5: Difference Between the DRV/rtv and LPV/rtv Treatment Groups[a] in Virologic Response Defined as the Percentage of Subjects With < 50 Copies/mL Over Time (ITT – TLOVR)

[a] Based on a normal approximation of the difference in % response

Source: Display EFF.18

Table 13: Statistical Comparisons (Logistic Regression) for Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL From Baseline at Week 192 (ITT– TLOVR)

Analysis Population	Treatment Group	Estimated % Response[a]	Estimated Difference in % Response	95% CI of Difference in % Response[b]	p-Value of Noninferiority	p-Value of Superiority
ITT	DRV/rtv LPV/rtv	69.0 57.3	11.7	4.5; 18.9	< 0.001	0.002
OP	DRV/rtv LPV/rtv	69.3 57.2	12.1	4.9; 19.3	< 0.001	0.001

[a] Percent response estimated from logistic regression analysis including baseline $\log_{10}$ viral load and baseline CD4+ cell count as covariates and treatment as factor.

[b] Confidence limits based on standard error obtained by application of the delta method and a normal approximation to the difference in % response.

Source: Display EFF.25, Display EFF.26

In addition to the TLOVR analyses, the following sensitivity analyses were performed (see Section 3.6.4.1.3): 1) observed case analysis on the ITT population, 2) TLOVR analysis on the population excluding all major protocol deviations, 3) a TLOVR non-VF-censored analysis on the ITT population, 4) LOCF analysis for LPV/rtv subjects (ITT population) discontinuing due to subject wish while TLOVR for DRV/rtv subjects, 5) a NC = F analysis (ITT population), 6) a M = F (ITT population) analysis, and 7) a longitudinal mixed effects model.

Descriptive statistics for virologic response defined as the percentage of subjects with confirmed viral load < 50 copies/mL from these analyses are provided in Display EFF.16 (ITT - Observed Case), Display EFF.20 (ITT excluding all major protocol deviations - TLOVR), Display EFF.21 (ITT - TLOVR Non-VF-censored), Display EFF.22 (ITT - LOCF - DCPW for LPV/rtv, TLOVR for DRV/rtv), Display EFF.24 (ITT - NC = F), Display EFF.23 (ITT - M = F), and Display EFF.29 (longitudinal mixed effects model). The descriptive statistics at Week 192 from these sensitivity analyses are summarized in Table 14, together with the TLOVR results discussed above.

The different sensitivity analyses demonstrated that the results for virologic response defined as the percentage of subjects with confirmed viral load < 50 copies/mL were robust and consistent across the different populations and imputation methods used. Virologic response at Week 192 was consistently higher with DRV/rtv treatment than with LPV/rtv treatment. The lower limit of the 95% CI of the difference between the treatment groups was consistently > -12%, confirming noninferiority of DRV/rtv versus LPV/rtv. In addition, superiority of DRV/rtv versus LPV/rtv was concluded across the different imputation methods, except when using observed case data, the LOCF-DCPW for LPV/rtv / TLOVR for DRV/rtv imputation, and the longitudinal mixed model.

Table 14: Sensitivity Analyses for Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL at Week 192

Population Analysis	DRV/rtv		LPV/rtv		DRV/rtv – LPV/rtv	
	N	Number of Responders[a], n (%)	N	Number of Responders[a], n (%)	Difference in % Response	95% CI of Difference in % Response[b]
ITT - TLOVR	343	236 (68.8)	346	198 (57.2)	11.6	4.4; 18.8
OP - TLOVR	340	235 (69.1)	345	197 (57.1)	12.0	4.8; 19.2
ITT - Observed case	253	235 (92.9)	229	208 (90.8)	2.1	-2.8; 6.9
ITT excluding all major PVs - TLOVR	316	224 (70.9)	327	193 (59.0)	11.9	4.5; 19.2
ITT – TLOVR Non-VF-censored	270	236 (87.4)	245	198 (80.8)	6.6	0.3; 12.9
ITT - LOCF-DCPW for LPV/rtv, TLOVR for DRV/rtv	343	236 (68.8)	346	220 (63.6)	5.2	-1.8; 12.3
ITT - NC = F	343	242 (70.6)	346	211 (61.0)	9.6	2.5; 16.6
ITT - M = F	343	235 (68.5)	346	208 (60.1)	8.4	1.3; 15.5
Longitudinal mixed model[c]	NA	93.2	NA	90.7	2.5	-2.4; 7.3

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

[a] Observed proportion of responders.

[b] Based on a normal approximation to the difference in % response.

[c] Estimated from a longitudinal mixed model (GLIMMIX) including baseline $\log_{10}$ viral load and baseline CD4 count as covariate, treatment and time as factors and the interaction between time and treatment. Serial correlation : assuming an unstructured covariance matrix to account for the correlations between all time points

Source: Display EFF.18, Display EFF.19, Display EFF.16, Display EFF.20, Display EFF.21, Display EFF.22, Display EFF.24, Display EFF.23, Display EFF.29

An overview of subjects' outcome at Week 192, as defined per the FDA Guidance is provided in Table 15 and Display EFF.37. Note that the numbers represented in Table 15 reflect only the status at Week 192 and should not be compared with the number of virologic failures and number of discontinued subjects presented in the virology and safety sections of this report, as in these sections, subjects over the entire treatment period are considered.

Table 15: Outcome Table (Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL, Snapshot Analysis) at Week 192[a] as per FDA Guidance

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)

Source: Display EFF.37

The proportion of subjects with a viral load < 50 copies/mL at Week 192 versus Week 48 and Week 96 is presented in Table 16 and Display EFF.30, and demonstrates the durability of the virologic response.

Virologic response was well sustained in both treatment groups, and a higher percentage of DRV/rtv subjects with a confirmed virologic response at Week 48 retained virologic response at Week 192 compared with subjects receiving LPV/rtv. Of the DRV/rtv subjects with a confirmed virologic response of < 50 copies/mL (undetectable) at Week 48, 81.3% remained undetectable at Week 192. Of the LPV/rtv subjects with a confirmed virologic response < 50 copies/mL at Week 48, 68.5% remained undetectable at Week 192. When comparing the Week-96 and Week-192 results, 87.7% of DRV/rtv subjects and 80.0% of LPV/rtv subjects remained undetectable at Week 192 if they were undetectable at Week 96.

Table 16: Durability of Response: Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL at Week 192 Versus Weeks 48 and 96 (ITT – TLOVR)

	Responder at Week 192							
	DRV/rtv				LPV/rtv			
	No		Yes		No		Yes	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Responder at Week 48								
No	55	53 (96.4)	55	2 (3.6)	70	61 (87.1)	70	9 (12.9)
Yes	288	54 (18.8)	288	234 (81.3)	276	87 (31.5)	276	189 (68.5)
Responder at Week 96								
No	74	74 (100)	74	0 (0.0)	101	99 (98.0)	101	2 (2.0)
Yes	269	33 (12.3)	269	236 (87.7)	245	49 (20.0)	245	196 (80.0)

N = number of subjects; n = number of observations

Source: Display EFF.30

Subgroup analyses for virologic response defined as the percentage of subjects with confirmed viral load < 50 copies/mL at Week 192 by selected baseline parameters are summarized in Table 17 (ITT - TLOVR). A comprehensive overview of the subgroup analyses performed is provided in Display EFF.53.

In all subgroups, virologic response at Week 192 was greater for subjects receiving DRV/rtv than for subjects receiving LPV/rtv except for subjects with a baseline CD4+ cell count < 50 x 10^6/L, and Hispanic subjects (response rates comparable between the treatment groups).

Stratification variables were evaluated for differences in responses. In both subgroups for the stratification factor viral load (< 100,000 and ≥ 100,000 copies/mL) subjects receiving DRV/rtv had a statistically superior virologic response compared to subjects receiving LPV/rtv (< 100,000 copies/mL: 69.5% versus 60.2%, p = 0.038; ≥ 100,000 copies/mL: 67.5% versus 51.7%, p = 0.012). In addition, subjects with baseline CD4+ cell counts ≥ 200 x 10^6 cells/L receiving DRV/rtv demonstrated statistical superiority in virologic responses compared with LPV/rtv (71.3% versus 59.6%, p = 0.014). In subjects with baseline CD4+ cell counts < 200 x 10^6 cells/L, DRV/rtv was shown to be noninferior compared to LPV/rtv (65.2% versus 54.1%, p < 0.001).

Table 17: Subgroup Analyses for Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL at Week 192 (ITT – TLOVR)

	DRV/rtv		LPV/rtv		DRV/rtv - LPV/rtv	
Baseline Parameter	**N**	**n (%)**	**N**	**n (%)**	**Difference in % Response**	**95 % CI of Difference in % Response[a]**
Baseline viral load[b] (copies/mL)						
< 100,000	226	157 (69.5)	226	136 (60.2)	9.3	0.5; 18.1
≥ 100,000	117	79 (67.5)	120	62 (51.7)	15.9	3.5; 28.3
Baseline CD4+ cell count[b] (x 10^6/L)						
< 200	141	92 (65.2)	148	80 (54.1)	11.2	-0.1; 22.5
≥ 200	202	144 (71.3)	198	118 (59.6)	11.7	2.4; 21.0
Gender						
Female	104	74 (71.2)	105	59 (56.2)	15.0	2.0; 27.9
Male	239	162 (67.8)	241	139 (57.7)	10.1	1.5; 18.7
Region						
Asia	37	33 (89.2)	34	24 (70.6)	18.6	0.3; 36.9
Australia	18	16 (88.9)	20	13 (65.0)	23.9	-3.0; 50.8
Europe	100	62 (62.0)	90	47 (52.2)	9.8	-4.3; 23.9
Latin America	60	43 (71.7)	64	40 (62.5)	9.2	-7.5; 25.8
North America	93	56 (60.2)	88	46 (52.3)	7.9	-6.6; 22.4
South Africa	35	26 (74.3)	50	28 (56.0)	18.3	-2.4; 39.0
Race						
Black	80	47 (58.8)	71	34 (47.9)	10.9	-5.1; 26.8
Caucasian/White	137	92 (67.2)	153	84 (54.9)	12.3	1.0; 23.5
Hispanic	77	53 (68.8)	77	51 (66.2)	2.6	-12.3; 17.5
Oriental/Asian	44	39 (88.6)	38	26 (68.4)	20.2	2.9; 37.5
Other	4	4 (100)	5	2 (40.0)	60.0	1.3; 118.7
Not allowed to ask per local regulations	1	1 (100)	2	1 (50.0)	50.0	-728.1; 828.1
Age						
≤ 30	115	72 (62.6)	124	67 (54.0)	8.6	-4.0; 21.1
30 - ≤ 45	175	122 (69.7)	172	104 (60.5)	9.2	-0.8; 19.3
45 - ≤ 55	44	33 (75.0)	40	22 (55.0)	20.0	-0.2; 40.2
55 - ≤ 65	8	8 (100)	9	4 (44.4)	55.6	18.0; 93.1
> 65	1	1 (100)	1	1 (100)	0.0	-
Clade						
B	210	139 (66.2)	208	122 (58.7)	7.5	-1.7; 16.8
C	39	27 (69.2)	51	27 (52.9)	16.3	-4.1; 36.7
CRF01_AE	62	48 (77.4)	55	34 (61.8)	15.6	-1.0; 32.2
Other	31	22 (71.0)	32	15 (46.9)	24.1	0.0; 48.1

N = number of subjects; n = number of observations
[a] Based on a normal approximation of the difference in % response
[b] Stratification factor
Source: Display EFF.53, Display ADD.1

An additional ITT analysis was performed comparing virologic response (< 50 copies/mL, TLOVR) in subjects receiving the DRV/rtv 800/100 mg q.d. regimen with those receiving LPV/rtv 800/200 mg b.i.d. or q.d. with respect to the same noninferiority delta of -12% as for the primary efficacy variable.

The percentage of subjects with confirmed plasma viral load < 50 copies/mL and the differences between the treatment groups are shown in Table 18 (see also Display EFF.38).

In the subgroup of 260 subjects who received LPV/rtv b.i.d. up to Week 192, the virologic response was 58.5% compared with 68.8% for the DRV/rtv q.d. group. The difference in virologic response [95% CI] between the treatment groups was 10.3 [2.7; 18.0]. The lower limit of the 95% CI of the difference between the treatment groups was > -12%. Statistical analysis of the difference in virologic response showed noninferiority of DRV/rtv q.d. versus LPV/rtv b.i.d. (p-value < 0.001). Furthermore, the test for superiority indicated that DRV/rtv q.d. was statistically superior to LPV/rtv b.i.d. (p-value = 0.008).

In the subgroup of 50 subjects who received LPV/rtv q.d. up to Week 192, the virologic response at Week 192 was 52.0%. The difference in virologic response between the treatment groups at Week 192 was 16.8 [2.9; 30.7] showing noninferiority (p-value < 0.001). The test for superiority indicated that DRV/rtv q.d. was statistically superior to LPV/rtv q.d. (p-value = 0.018).

Table 18: Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL at Week 192 by LPV/rtv Dosing Frequency (ITT - TLOVR)

	DRV/rtv		LPV/rtv		DRV/rtv - LPV/rtv	
Analysis Time Point	**N**	**n (%)**	**N**	**N**	**n (%)**	**N**
b.i.d.						
Week 48	343	288 (84.0)	267	219 (82.0)	1.9 [-4.1; 7.9]	< 0.001
Week 96	343	271 (79.0)	258	185 (71.7)	7.3 [0.4; 14.2]	< 0.001
Week 192	343	236 (68.8)	260	152 (58.5)	10.3 [2.7; 18.0]	< 0.001
b.i.d. + q.d.						
Week 48	343	288 (84.0)	27	20 (74.1)	9.9 [-4.7; 24.5]	0.003
Week 96	343	271 (79.0)	37	25 (67.6)	11.4 [-2.6; 25.5]	0.001
Week 192	343	236 (68.8)	36	20 (55.6)	13.2 [-2.8; 29.3]	0.002
q.d.						
Week 48	343	288 (84.0)	52	37 (71.2)	12.8 [1.7; 23.9]	< 0.001
Week 96	343	271 (79.0)	51	35 (68.6)	10.4 [-1.9; 22.6]	< 0.001
Week 192	343	236 (68.8)	50	26 (52.0)	16.8 [2.9; 30.7]	< 0.001

N = number of subjects; n = number of observations
[a] Based on a normal approximation of the difference in % response
Source: Display EFF.28 (Week96), Display EFF.38

4.2.5 Secondary Efficacy Variables

The analyses for the secondary efficacy variables were performed on the ITT population.

4.2.5.1 VIROLOGIC RESPONSE - OTHER PARAMETER

Secondary virologic response parameter was the percentage of subjects with confirmed plasma viral load < 400 copies/mL at all time points, calculated according to the FDA TLOVR algorithm (see Section 3.6.4.1.2).

Descriptive statistics for virologic response defined as the percentage of subjects with confirmed plasma viral load < 400 copies/mL are provided in Display EFF.18 for the ITT population and Display EFF.19 for the OP population. Statistical comparisons between the treatment groups for these virologic response parameters using a logistic regression model (including baseline CD4+ cell count and baseline $\log_{10}$ viral load as covariates and treatment as as factor, see Section

3.6.4.1.3) are provided in Display EFF.25 (ITT population) and Display EFF.26 (OP population). Individual subject data for virologic response are provided in Listing EFF.1.

Virologic response for virologic response defined as the percentage of subjects with confirmed plasma viral load < 400 copies/mL per time point is summarized in Table 19 (ITT - TLOVR). Statistical comparisons between the treatment groups at Week 192 (logistic regression model, ITT - TLOVR) are summarized in Table 20.

At Week 192, virologic response in the ITT population was 75.2% and 65.0% for the DRV/rtv and LPV/rtv treatment groups, respectively. The difference in virologic response [95% CI] between the treatment groups was 10.2 [3.4; 17.0]. Statistical comparison using the logistic regression model showed an estimated difference [95% CI] in virologic response between treatment groups of 10.1 [3.2; 16.9], which demonstrated noninferiority (p-value < 0.001), and also superiority (p = 0.004). Similar results (TLOVR) were obtained for the OP population.

Table 19: Virologic Response Defined as the Percentage of Subjects With Viral Load < 400 Copies/mL per Time Point (ITT – TLOVR)

	DRV/rtv		LPV/rtv		DRV/rtv - LPV/rtv	
Time Point	N	n (%)	N	n (%)	Difference in % Response	95 % CI of Difference in % Response[a]
Week 2	343	72 (21.0)	346	73 (21.1)	-0.1	-6.2; 6.0
Week 4	343	146 (42.6)	346	152 (43.9)	-1.4	-8.8; 6.0
Week 8	343	239 (69.7)	346	233 (67.3)	2.3	-4.6; 9.3
Week 12	343	293 (85.4)	346	292 (84.4)	1.0	-4.3; 6.4
Week 16	343	314 (91.5)	346	313 (90.5)	1.1	-3.2; 5.4
Week 24	343	315 (91.8)	346	306 (88.4)	3.4	-1.1; 7.9
Week 36	343	308 (89.8)	346	303 (87.6)	2.2	-2.5; 7.0
Week 48	343	299 (87.2)	346	294 (85.0)	2.2	-3.0; 7.4
Week 60	343	293 (85.4)	346	287 (82.9)	2.5	-3.0; 7.9
Week 72	343	291 (84.8)	346	279 (80.6)	4.2	-1.4; 9.9
Week 84	343	289 (84.3)	346	273 (78.9)	5.4	-0.4; 11.1
Week 96	343	285 (83.1)	346	268 (77.5)	5.6	-0.3; 11.6
Week 108	343	280 (81.6)	346	257 (74.3)	7.4	1.2; 13.5
Week 120	343	273 (79.6)	346	254 (73.4)	6.2	-0.1; 12.5
Week 132	343	271 (79.0)	346	250 (72.3)	6.8	0.4; 13.2
Week 144	343	267 (77.8)	346	247 (71.4)	6.5	-0.0; 12.9
Week 156	343	264 (77.0)	346	243 (70.2)	6.7	0.2; 13.3
Week 168	343	262 (76.4)	346	238 (68.8)	7.6	0.9; 14.2
Week 180	343	261 (76.1)	346	228 (65.9)	10.2	3.5; 16.9
Week 192	343	258 (75.2)	346	225 (65.0)	10.2	3.4; 17.0

N = number of subjects; n = number of observations

[a] Based on a normal approximation of the difference in % response

Source: Display EFF.18

Table 20: Statistical Comparisons (Logistic Regression) for Virologic Response Defined as the Percentage of Subjects With Viral Load < 400 Copies/mL From Baseline at Week 192 (ITT– TLOVR)

Analysis Population	Treatment Group	Estimated % Response[a]	Estimated Difference in % Response	95% CI of Difference in % Response[b]	p-Value of Noninferiority	p-Value of Superiority
ITT	DRV/rtv LPV/rtv	75.2 65.2	10.1	3.2; 16.9	< 0.001	0.004
OP	DRV/rtv LPV/rtv	75.3 65.1	10.2	3.4; 17.1	< 0.001	0.003

[a] Percent response estimated from logistic regression analysis including baseline $\log_{10}$ viral load and baseline CD4+ cell count as covariates and treatment as factor.
[b] Confidence limits based on standard error obtained by application of the delta method and a normal approximation to the difference in % response.
Source: Display EFF.25, Display EFF.26

In addition to the TLOVR analyses, the same sensitivity analyses as for the primary virologic response parameter were performed for virologic response < 400 copies/ml (TLOVR). Descriptive statistics of the sensitivity analyses for this virologic response parameter are provided together with those for the primary virologic response parameter in Display EFF.16 (ITT - Observed Case), Display EFF.20 (ITT excluding all major protocol deviations - TLOVR), Display EFF.21 (ITT - TLOVR Non-VF Censored), Display EFF.22 (ITT - LOCF - DCPW for LPV/rtv, TLOVR for DRV/rtv), Display EFF.24 (ITT - NC = F), Display EFF.23 (ITT - M = F), and Display EFF.29 (longitudinal mixed effects model). The descriptive statistics at Week 192 from these sensitivity analyses are summarized in Table 21, together with the TLOVR results discussed above.

The different sensitivity analyses demonstrated that the results for virologic response defined as the percentage of subjects with confirmed viral load < 400 copies/mL were robust and consistent across the different populations and imputation methods used. Noninferiority of DRV/rtv versus LPV/rtv was consistently concluded.

Table 21: Sensitivity Analyses for Virologic Response Defined as the Percentage of Subjects With Viral Load < 400 Copies/mL at Week 192

Population Analysis	DRV/rtv		LPV/rtv		DRV/rtv – LPV/rtv	
	N	Number of Responders[a], n (%)	N	Number of Responders[a], n (%)	Difference in % Response	95% CI of Difference in % Response[b]
ITT - TLOVR	343	258 (75.2)	346	225 (65.0)	10.2	3.4; 17.0
OP - TLOVR	340	256 (75.3)	345	224 (64.9)	10.4	3.5; 17.2
ITT - Observed case	253	246 (97.2)	229	222 (96.9)	0.3	-2.7; 3.3
ITT excluding all major PVs - TLOVR	316	245 (77.5)	327	220 (67.3)	10.3	3.4; 17.1
ITT - TLOVR Non-VF-censored	267	258 (96.6)	240	225 (93.8)	2.9	-0.8; 6.6
ITT - LOCF-DCPW for LPV/rtv, TLOVR for DRV/rtv	343	258 (75.2)	346	256 (74.0)	1.2	-5.3; 7.7
ITT - NC = F	343	253 (73.8)	346	225 (65.0)	8.7	1.9; 15.6
ITT - M = F	343	246 (71.7)	346	222 (64.2)	7.6	0.6; 14.5
Longitudinal mixed model[c]	NA	99.6	NA	99.8	-0.15	-2.8; 2.4

N = number of subjects; n = number of observations.
[a] Observed proportion of responders.
[b] Based on a normal approximation to the difference in % response.
[c] Estimated from a longitudinal mixed model (GLIMMIX) including baseline log10 viral load and baseline CD4 count as covariate, treatment and time as factors and the interaction between time and treatment. Serial correlation : assuming an unstructured covariance matrix to account for the correlations between all time points

Source: Display EFF.18, Display EFF.19, Display EFF.16, Display EFF.20, Display EFF.21, Display EFF.22, Display EFF.24, Display EFF.23, Display EFF.29

4.2.5.2 CHANGE IN PLASMA VIRAL LOAD VERSUS BASELINE

The change in plasma $\log_{10}$ viral load from baseline was calculated using the NC = F algorithm (see Section 3.6.4.1.2).

Descriptive statistics for the change in $\log_{10}$ viral load from baseline are provided in Display EFF.5 for the ITT population, and Display EFF.6 for the OP population. Statistical comparisons between the treatment groups using an ANCOVA (including the factors treatment group, and baseline CD4+ cell count and baseline $\log_{10}$ viral load as covariates) are provided in Display EFF.11 (ITT population) and Display EFF.12 (OP population). Individual subject data for the change in $\log_{10}$ viral load from baseline are provided in Listing EFF.1.

The observed mean and median change in $\log_{10}$ viral load from baseline per time point are summarized in Table 22 (ITT - NC=F). Graphical presentations of the mean change in $\log_{10}$ viral load from baseline over time, and of the difference between the DRV/rtv and LPV/rtv treatment groups in mean change in $\log_{10}$ viral load from baseline over time (ITT - NC=F) are provided in Figure 6 and Figure 7, respectively. The statistical comparison between the treatment groups at Week 192 (ANCOVA) for the change in $\log_{10}$ viral load from baseline (ITT - NC=F) is summarized in Table 23.

A decrease in $\log_{10}$ viral load from baseline was observed for both treatment groups at all time points. The mean decrease in $\log_{10}$ viral load was slightly larger for the DRV/rtv group than for

the LPV/rtv group at all time points and after Week 60 the difference in means between the treatment groups became more pronounced over time.

At Week 192, the mean change in $\log_{10}$ viral load from baseline in the ITT population was -2.35 and -2.03 $\log_{10}$ copies/mL for the DRV/rtv and LPV/rtv treatment groups, respectively. The difference in mean change in $\log_{10}$ viral load from baseline [95% CI] between the treatment groups was -0.32 [-0.55; 0.09]. Statistical comparison (ANCOVA - ITT) showed an estimated difference [95% CI] between the DRV/rtv and LPV/rtv treatment groups at Week 192 of -0.30 [-0.52, 0.08] ($p = 0.007$).

Similar results were obtained for the OP population.

Table 22: Mean and Median Change in log_{10} Viral Load from Baseline per Time Point (ITT – NC = F)

Time Point	DRV/rtv N	DRV/rtv Mean[a] (SE) Median (Range)	LPV/rtv N	LPV/rtv Mean[a] (SE) Median (Range)	DRV/rtv - LPV/rtv Difference[b] (SE)	DRV/rtv - LPV/rtv 95 % CI of Difference[c]
Baseline Log_{10} Viral Load (Copies/mL)						
Baseline	343	4.86 (0.034) 4.85 (2.9; 6.7)	346	4.84 (0.032) 4.79 (2.8; 6.7)	0.02 (0.047)	-0.07; 0.11
Change Versus Baseline in Log_{10} Viral Load (Copies/mL)						
Week 2	343	-1.76 (0.027) -1.79 (-3.2; 0.3)	346	-1.69 (0.030) -1.74 (-3.3; 0.3)	-0.07 (0.040)	-0.15; 0.01
Week 4	343	-2.14 (0.030) -2.15 (-4.1; 0.5)	346	-2.07 (0.035) -2.10 (-3.8; 0.3)	-0.07 (0.046)	-0.16; 0.02
Week 8	343	-2.52 (0.038) -2.56 (-4.2; 0.4)	346	-2.46 (0.043) -2.60 (-4.1; 0.4)	-0.07 (0.057)	-0.18; 0.05
Week 12	343	-2.76 (0.043) -2.83 (-4.7; 0.4)	346	-2.69 (0.047) -2.84 (-4.4; 0.2)	-0.08 (0.064)	-0.20; 0.05
Week 16	343	-2.90 (0.047) -3.02 (-5.0; 0.0)	346	-2.80 (0.052) -2.98 (-4.6; 0.8)	-0.10 (0.070)	-0.24; 0.04
Week 24	343	-2.91 (0.054) -3.07 (-5.1; 0.1)	346	-2.79 (0.059) -3.00 (-4.6; 0.8)	-0.12 (0.080)	-0.28; 0.03
Week 36	343	-2.83 (0.059) -3.04 (-5.1; 0.0)	346	-2.76 (0.062) -3.00 (-5.0; 0.0)	-0.07 (0.086)	-0.24; 0.10
Week 48	343	-2.77 (0.064) -3.04 (-5.1; 0.8)	346	-2.65 (0.068) -2.98 (-5.0; 1.0)	-0.12 (0.093)	-0.30; 0.07
Week 60	343	-2.71 (0.066) -3.01 (-5.1; 0.9)	346	-2.58 (0.070) -2.92 (-4.7; 0.3)	-0.13 (0.096)	-0.32; 0.06
Week 72	343	-2.70 (0.068) -3.02 (-5.1; 0.8)	346	-2.52 (0.073) -2.90 (-5.0; 0.4)	-0.18 (0.099)	-0.37; 0.02
Week 84	343	-2.66 (0.068) -2.99 (-5.1; 0.0)	346	-2.49 (0.073) -2.89 (-5.0; 0.4)	-0.18 (0.100)	-0.37; 0.02
Week 96	343	-2.64 (0.070) -2.99 (-5.1; 0.0)	346	-2.45 (0.075) -2.87 (-5.0; 0.4)	-0.20 (0.102)	-0.40; 0.01
Week 108	343	-2.60 (0.071) -3.00 (-5.1; 0.0)	346	-2.33 (0.079) -2.82 (-5.0; 1.3)	-0.28 (0.106)	-0.49; -0.07
Week 120	343	-2.52 (0.074) -2.93 (-5.1; 0.0)	346	-2.33 (0.079) -2.82 (-5.0; 0.0)	-0.19 (0.108)	-0.40; 0.03
Week 132	343	-2.49 (0.076) -2.94 (-5.1; 0.6)	346	-2.28 (0.080) -2.81 (-5.0; 0.2)	-0.21 (0.110)	-0.43; 0.00
Week 144	343	-2.48 (0.076) -2.92 (-5.1; 0.0)	346	-2.25 (0.081) -2.80 (-5.0; 0.3)	-0.23 (0.111)	-0.45; -0.02
Week 156	343	-2.45 (0.077) -2.92 (-5.1; 0.0)	346	-2.22 (0.081) -2.76 (-5.0; 0.1)	-0.23 (0.112)	-0.45; -0.01
Week 168	343	-2.42 (0.078) -2.92 (-5.1; 0.8)	346	-2.17 (0.082) -2.74 (-4.7; 0.0)	-0.26 (0.113)	-0.48; -0.03
Week 180	343	-2.42 (0.078) -2.91 (-5.1; 0.0)	346	-2.07 (0.083) -2.65 (-5.0; 0.4)	-0.35 (0.114)	-0.57; -0.13
Week 192	343	-2.35 (0.079) -2.84 (-5.1; 0.0)	346	-2.03 (0.084) -2.65 (-5.0; 0.3)	-0.32 (0.115)	-0.55; -0.09

n = number of subjects

[a] Observed mean and median change

[b] Difference in means

[c] Based on normal approximation of the difference

Source: Display GEN.10 (Week 96), Display EFF.5

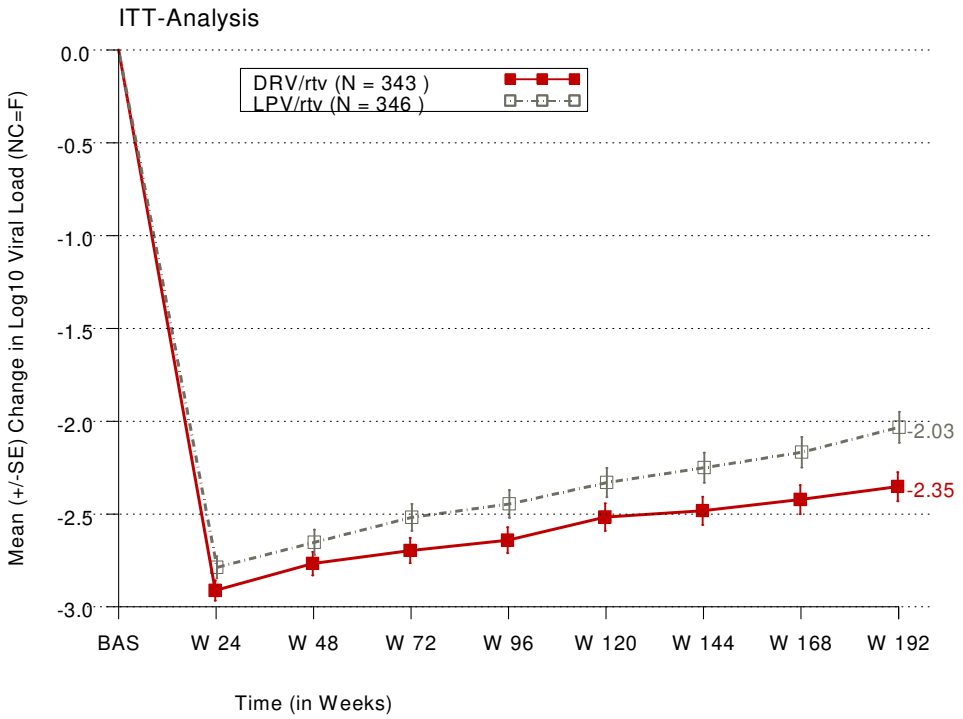


Figure 6: Mean Change from Baseline in log_{10} Viral Load Over Time (ITT – NC = F)

Source: Display GEN.10 (Week 96), Display EFF.5

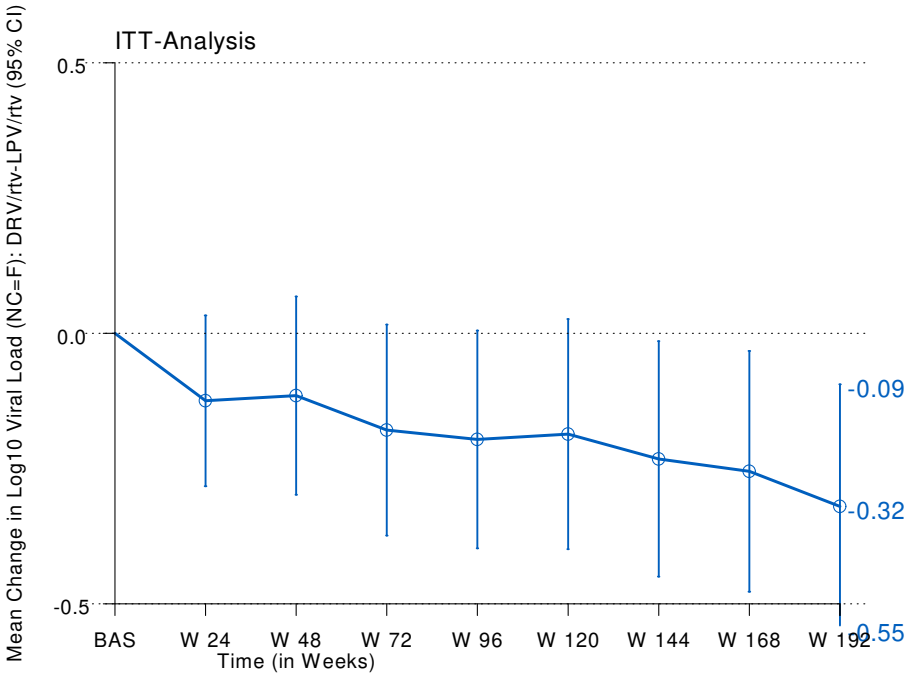


Figure 7: Difference Between DRV/rtv and LPV/rtv Treatment Groups in Mean Change in log_{10} Viral Load Over Time (ITT – NC = F)

Source: Display GEN.10 (Week 96), Display EFF.5

Table 23: Statistical Comparison (ANCOVA) for Change in log_{10} Viral Load at Week 192 (ITT – NC = F)

Analysis Population	Treatment Group	LS-means[a] (SE)	Difference in LS-Means (95% CI[b])
ITT	DRV/rtv LPV/rtv	-2.34 (0.08) -2.04 (0.08)	-0.30 (-0.52; -0.08)
OP	DRV/rtv LPV/rtv	-2.34 (0.08) -2.04 (0.08)	-0.31 (-0.53; -0.09)

[a] Least square means estimated from an ANCOVA model including baseline log_{10} viral load and baseline CD4+ cell count as covariates and treatment as factor.
[b] Based on a normal approximation to the difference
Source: Display EFF.11, Display EFF.12

In addition to the NC = F analyses on the ITT and OP populations, the following sensitivity analyses were performed: 1) observed case analysis on the ITT population, 2) a NC = F non-VF censored analysis (ITT population), 3) a LOCF analysis for control subjects (ITT population) discontinuing due to subject wish while NC = F for DRV/rtv subjects, 4) a Missing = Failure analysis (ITT Population), and 5) a longitudinal mixed effects model analysis. Descriptive statistics for the change in log_{10} viral load from these analyses are provided in Display EFF.3 (ITT - Observed Case), Display EFF.8 (ITT – NC = F Non-VF Censored), Display EFF.9 (ITT - LOCF - DCPW for LPV/rtv, NC = F for DRV/rtv), Display EFF.10 (ITT- M = F), and Display EFF.13 (longitudinal mixed effects model). The descriptive statistics at Week 192 from the sensitivity analyses are summarized in Table 24, together with the NC = F results discussed above.

The different sensitivity analyses demonstrated that the results for the change in log_{10} viral load from baseline were robust and consistent across the different populations and imputation methods used. The mean decrease in log_{10} viral load from baseline at Week 192 was consistently larger for the DRV/rtv group than for the LPV/rtv group, and noninferiority of DRV/rtv versus LPV/rtv was consistently concluded.

Table 24: Sensitivity Analyses for Mean Change in Log_{10} Viral Load at Week 192

Analysis	DRV/rtv N	DRV/rtv Mean[a] (SE) Median (range)	LPV/rtv N	LPV/rtv Mean[a] (SE) Median (range)	DRV/rtv – LPV/rtv Difference[b] (SE)	DRV/rtv – LPV/rtv 95% CI[c] of Difference
ITT - NC = F	343	-2.35 (0.079) -2.84 (-5.1; 0.0)	346	-2.03 (0.084) -2.65 (-5.0; 0.3)	-0.32	-0.55; -0.09
OP - NC = F	340	-2.35 (0.079) -2.84 (-5.1; 0.0)	345	-2.03 (0.084) -2.65 (-5.0; 0.3)	-0.32	-0.55; -0.10
ITT Observed case	253	-3.11 (0.043) -3.12 (-5.1; -0.2)	229	-3.03 (0.051) -3.04 (-5.0; 0.3)	-0.08	-0.20; 0.06
ITT - NC = F Non-VF-Censored	265	-3.04 (0.049) -3.10 (-5.1; 0.0)	241	-2.92 (0.061) -3.01 (-5.0; 0.3)	-0.13	-0.28; 0.03
ITT - LOCF-DCPW for LPV/rtv, NC = F for DRV/rtv	343	-2.35 (0.079) -2.84 (-5.1; 0.0)	346	-2.32 (0.077) -2.80 (-5.0; 0.8)	-0.03	-0.25; 0.18
ITT - M = F	343	-2.29 (0.080) -2.80 (-5.1; 0.0)	346	-2.01 (0.084) -2.63 (-5.0; 0.3)	-0.28	-0.51; -0.06
Longitudinal mixed model	NA	-3.08 (0.026)	NA	-3.02 (0.027)	-0.07	-0.14; 0.01

N = number of subjects.
[a] Observed mean and median change.
[b] Difference in means.
[c] Based on normal approximation of the difference
[d] Estimated from a longitudinal mixed model (GLIMMIX) including baseline log_{10} viral load and baseline CD4+ count as covariates, treatment and time as factors and the interaction between time and treatment. Serial correlation: assuming an unstructured covariance matrix to account for the correlation between all time points.

Source: Display EFF.5, Display EFF.6, Display EFF.3, Display EFF.8, Display EFF.9, Display EFF.10, Display EFF.13

4.2.5.3 TIME TO FIRST VIROLOGIC RESPONSE

The time to first virologic response was calculated according to the FDA-TLOVR algorithm (see Section 3.6.4.1.2). Subjects who never achieved virologic response were censored at their last available assessment time point during the treatment period.

Descriptive statistics for the time to virologic response (TLOVR) are provided in Display EFF.32. Statistical comparisons between the treatment groups (Cox proportional hazards model including the factors baseline CD4+ cell count, and baseline log_{10} viral load as covariates) are provided in Display EFF.33. Individual subject data for the time to virologic response are provided in Listing EFF.1.

A Kaplan-Meier estimate of the time to first virologic response is provided in Figure 8. The difference between the treatment groups in time to virologic response defined as plasma viral load < 50 copies/mL was not statistically significant (p = 0.5197).

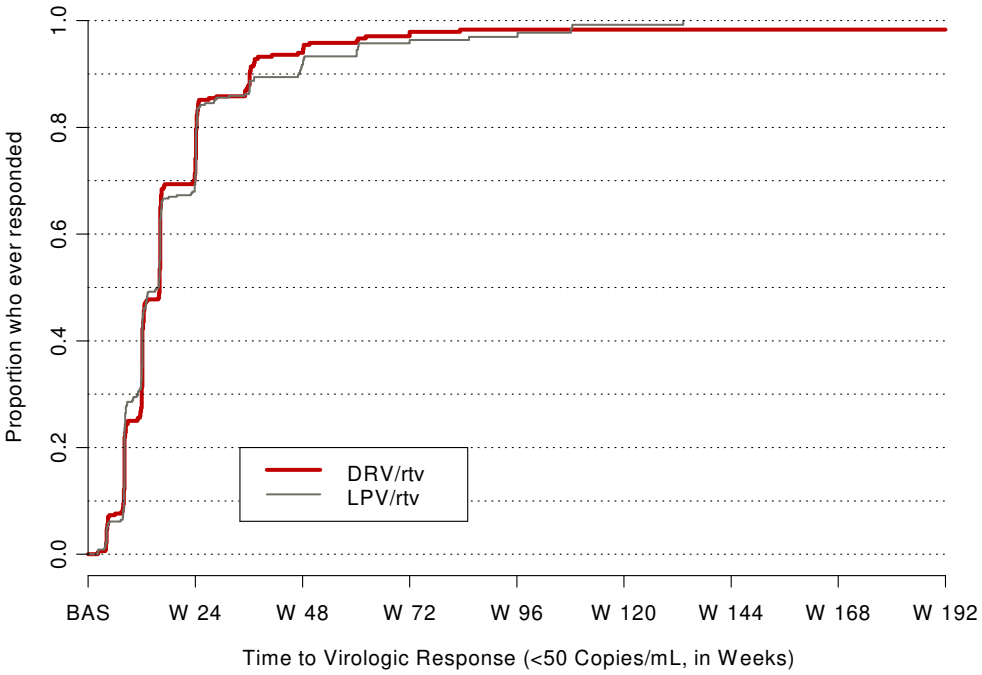


Figure 8: Time to Virologic Response Defined as the Percentage of Subjects Achieving Plasma Viral Load < 50 Copies/mL (ITT – TLOVR)

Source: Display GEN.32

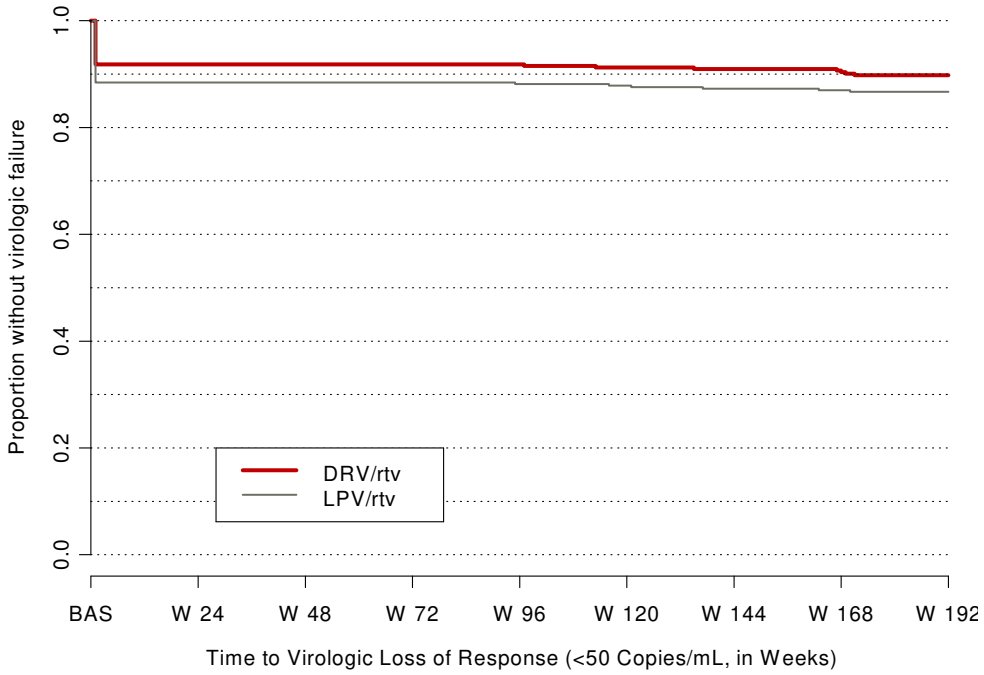
4.2.5.4 TIME TO LOSS OF VIROLOGIC RESPONSE

The time to virologic failure was calculated according to the TLOVR algorithm (see Section 3.6.4.1.2). Subjects who never achieved virologic response were defined as nonresponders and were considered as failures on Day 1.

Descriptive statistics for the time to virologic failure (TLOVR) are provided in Display EFF.34. Statistical comparisons between the treatment groups (Cox proportional hazards model including the factors baseline CD4+ cell count and baseline $\log_{10}$ viral load as covariates) are provided in Display EFF.35. Individual subject data for the time to virologic failure are provided in Listing EFF.1.

The Kaplan-Meier estimate provided in Figure 9 shows that the proportion of subjects not achieving a plasma viral load < 50 copies/mL was lower in the DRV/rtv group than in the LPV/rtv group, and that loss of virologic response over time occurred slightly less frequently in the DRV/rtv group than in the LPV/rtv group.

The difference between the DRV/rtv and LPV/rtv treatment groups in time to virologic failure (parameter plasma viral load < 50 copies/mL) was statistically significant (p = 0.0034), with a smaller probability of failing under DRV/rtv treatment compared to LPV/rtv treatment (hazard ratio [95% CI]: 0.69 [0.54; 0.88]).



Note: Subjects who never achieved virologic response were defined as nonresponders and were considered as failures on Day 1.

Figure 9: Time to Loss of Virologic Response Defined as the Percentage of Subjects Achieving Plasma Viral Load < 50 Copies/mL (ITT – TLOVR)

Source: Display GEN.34

4.2.5.5 VIRAL LOAD DAVG

Descriptive statistics for the DAVG of $\log_{10}$ plasma viral load (observed) are provided in Display EFF.14. Statistical comparison between the treatment groups using an ANCOVA (including the factor treatment group and baseline CD4+ cell count and baseline $\log_{10}$ viral load as covariates) is provided in Display EFF.15, and summarized in Table 25.

The mean viral load DAVG at Week 192 was -2.56 and -2.38 $\log_{10}$ copies/mL for the DRV/rtv and LPV/rtv treatment groups, respectively.

Statistical comparison (ANCOVA) showed an estimated difference [95% CI] in viral load DAVG at Week 192 between the treatment groups of -0.17 [-0.33; -0.01], which was statistically significant ($p = 0.041$).

These results are in line with the findings for the virologic response rates and for the change in $\log_{10}$ plasma viral load from baseline.

Table 25: Statistical Comparison (ANCOVA) for Viral Load DAVG at Week 192 (ITT – Observed)

Treatment Group	LS Means[a] (SE)	Difference in LS Means	95% CI of Difference in LS Means	p-Value
DRV/rtv	-2.55 (0.058)	-0.17	-0.33; -0.01	0.041
LPV/rtv	-2.39 (0.058)			

[a] Least square means estimated from an ANCOVA model including the factors treatment group and baseline CD4+ cell count and baseline $\log_{10}$ viral load as covariates.

Source: Display EFF.15

4.2.6 Immunologic Change

CD4+ cell count was calculated using the NC = F algorithm.

Descriptive statistics for the change from baseline in absolute CD4+ cell count, CD8+ cell count, and the CD4/CD8 ratio are provided in Display EFF.43 (NC = F – ITT). Statistical comparisons between the treatment groups using an ANCOVA (including factors for treatment and baseline CD4+ cell count and baseline $\log_{10}$ viral load as covariates) are provided in Display EFF.47 (ITT population). Individual subject data for the change in CD4+ cell count and CD8+ cell count from baseline are provided in Listing EFF.3. Conclusions based on CD8+ cell count and CD4/CD8 ratio were generally consistent with those for CD4+ cell count.

The mean and median change in CD4+ cell count from baseline per time point is summarized in Table 26 (ITT - NC = F). A graphical presentation of the mean change in CD4+ cell count from baseline over time (ITT - NC = F) is provided in Figure 10. Statistical comparison between the treatment groups at Week 192 (ANCOVA) for the change in CD4+ cell count from baseline over time (ITT - NC = F) is summarized in Table 27.

A mean increase in CD4+ cell count from baseline was observed for both treatment groups at all time points with similar increases being observed in both treatment groups.

At Week 192, the mean change in CD4+ cell count from baseline (NC = F) was 266 x 10^6/L for the DRV/rtv group and 269 x 10^6/L for the LPV/rtv group, while the median change was 258 and 263 x 10^6/L, respectively. The difference in mean change in CD4+ cell count from baseline [95% CI] between the treatment groups (-3 [-38; 33]) was not statistically significant (lower limit of the 95% CI < 0). Statistical comparison (ANCOVA) for the change in CD4+ cell count from baseline at Week 192 showed an estimated difference [95% CI] between the DRV/rtv and LPV/rtv treatment groups of -5 [-40; 31], which was also not statistically significant (p = 0.795).

Table 26: Mean and Median Change in CD4+ Cell Count from Baseline per Time Point (ITT – NC = F)

Time Point	DRV/rtv N	DRV/rtv Mean[a] (SE) Median (Range)	LPV/rtv N	LPV/rtv Mean[a] (SE) Median (Range)	DRV/rtv - LPV/rtv Difference[b] (SE)	DRV/rtv - LPV/rtv 95 % CI of Difference[c]
Baseline CD4+ Cell Count (x10⁶/L)						
Baseline	343	245 (8.0) 228 (4; 750)	346	231 (7.1) 218 (2; 714)	13.8 (10.74)	-7; 35
Change Versus Baseline in CD4+ Cell Count (x10⁶/L)						
Week 2	343	64 (6.7) 48 (-264; 1438)	346	65 (5.0) 45 (-215; 624)	-1.7 (8.36)	-18.1; 14.7
Week 4	343	87 (5.3) 74 (-182; 578)	346	86 (4.9) 76 (-250; 833)	0.5 (7.28)	-13.8; 14.8
Week 8	343	97 (5.4) 85 (-227; 548)	346	106 (5.9) 91 (-286; 803)	-8.6 (7.98)	-24.3; 7.1
Week 12	343	106 (5.8) 96 (-242; 605)	346	111 (5.5) 91 (-89; 685)	-4.6 (7.98)	-20.30; 11.0
Week 16	343	117 (6.0) 107 (-134; 720)	346	117 (5.1) 103 (-136; 412)	0.4 (7.85)	-15.0; 15.8
Week 24	343	132 (6.2) 118 (-157; 658)	346	133 (6.0) 117 (-146; 574)	-1.3 (8.60)	-18.2; 15.6
Week 36	343	152 (7.6) 137 (-209; 859)	346	154 (7.2) 139 (-285; 598)	-2.6 (10.44)	-23.1; 17.9
Week 48	343	153 (7.4) 136 (-182; 725)	346	161 (7.1) 141 (-95; 684)	-7.5 (10.25)	-27.7; 12.6
Week 60	343	171 (8.1) 158 (-221; 857)	346	187 (7.9) 174 (-156; 766)	-16.1 (11.30)	-38.3; 6.1
Week 72	343	182 (8.9) 162 (-168; 885)	346	186 (8.0) 172 (-89; 743)	-4.1 (11.94)	-27.5; 19.4
Week 84	343	184 (8.5) 172 (-183; 1135)	346	202 (9.5) 185 (-117; 960)	-17.8 (12.80)	-43.0; 7.3
Week 96	343	189 (9.2) 171 (-278; 921)	346	195 (8.6) 190 (-179; 782)	-5.6 (12.60)	-30.4; 19.1
Week 108	343	212 (9.6) 194 (-169; 958)	346	212 (9.8) 203 (-75; 1067)	-0.0 (13.74)	-27.0; 27.0
Week 120	343	202 (9.6) 185 (-106; 808)	346	216 (9.8) 205 (-47; 863)	-14.1 (13.7)	-41.0; 12.9
Week 132	343	212 (9.7) 198 (-143; 727)	346	232 (11.3) 223 (-87; 1244)	-20.0 (14.9)	-49.3; 9.3
Week 144	343	227 (10.5) 208 (-143; 1080)	346	229 (10.8) 228 (-145; 895)	-1.6 (15.0)	-31.1; 27.0
Week 156	343	240 (11.1) 229 (-279; 1162)	346	249 (11.9) 241 (-70; 1002)	-9.2 (16.3)	-41.1; 22.8
Week 168	343	265 (11.8) 260 (-22; 1156)	346	268 (12.7) 270 (-8; 1416)	-2.8 (17.3)	-36.8; 31.2
Week 180	343	274 (12.2) 270 (-49; 1141)	346	264 (13.5) 269 (-287; 1539)	10.0 (18.2)	-25.8; 45.7
Week 192	343	266 (11.9) 258 (-15; 1287)	346	269 (13.6) 263 (-128; 1206)	-3 (18.10)	-38.4; 32.7

N = number of subjects.

[a] Observed mean and median change.

[b] Difference in means

[c] Based on normal approximation of the difference

Source: Display GEN.10 (Week 96), Display EFF.43

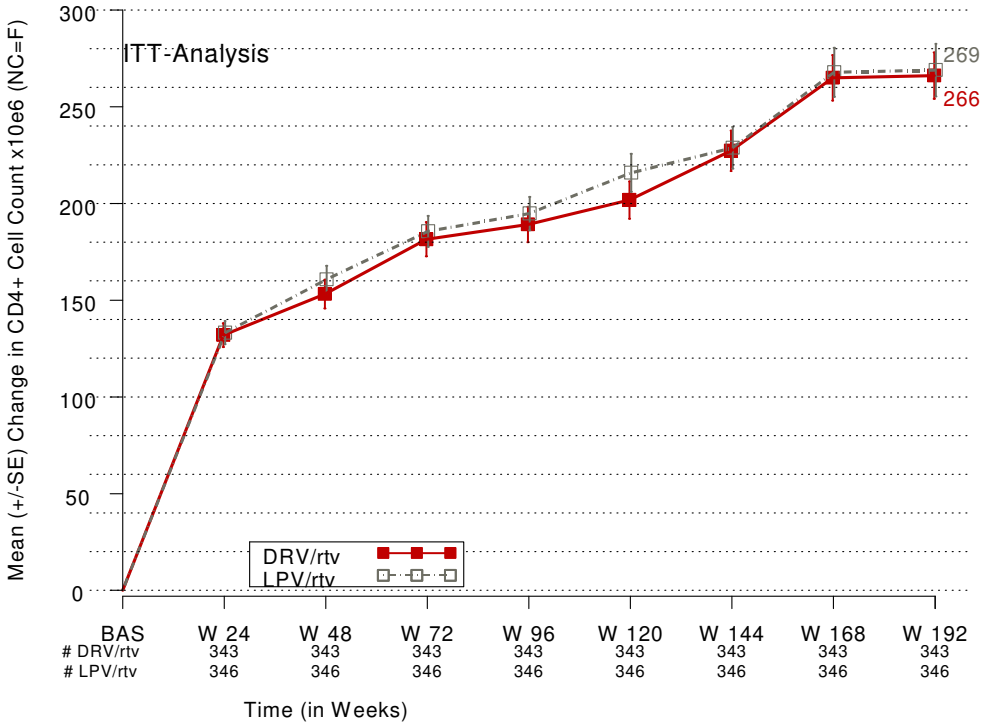


Figure 10: Mean Change in CD4+ Cell Count from Baseline Over Time (ITT – NC = F)

Source: Display GEN.10 (Week 96), Display EFF.43

Table 27: Statistical Comparison (ANCOVA) for Change in CD4+ Cell Count at Week 192

Analysis Population - Imputation	Treatment Group	LS-means[a] (SE)	Difference in LS-Means (95% CI[b])
ITT - NC = F	DRV/rtv LPV/rtv	265 (12.8) 270 (12.8)	-5 (-40; 31)
ITT - Observed case	DRV/rtv LPV/rtv	351 (12.5) 405 (13.1)	-53 (-89; -18)
OP - NC = F	DRV/rtv LPV/rtv	265 (12.9) 270 (12.8)	-4 (-40; 31)
Longitunidinal mixed model	DRV/rtv LPV/rtv	345 (11.8) 397 (12.1)	-51 (-84; -18)

[a] Least square means estimated from an ANCOVA model including baseline $\log_{10}$ viral load and baseline CD4+ cell counts as covariates and treatment as factors.

[b] Based on a normal approximation to the difference

Source: Display EFF.47, Display EFF.46, Display EFF.48, Display EFF.49

In addition to the NC = F analysis on the ITT population, the following sensitivity analyses were performed: 1) observed case analysis on the ITT population, 2) NC = F analysis on the OP population, and 3) longitudinal mixed model analysis. Statistical comparisons (ANCOVA, same model as for the NC = F analysis) between the treatment groups from these analyses are provided in Display EFF.46 (ITT - Observed Case), Display EFF.48 (OP - NC = F), and Display EFF. 49 (longitudinal mixed model), and are summarized in Table 27, together with the NC = F results for the ITT population.

The different sensitivity analyses demonstrated that the results for the change in CD4+ cell count from baseline were robust and consistent across the different populations and imputation methods used.

Immunologic response (ITT – NC = F) by CD4+ cell count categories at Week 192 is summarized in Figure 11; a complete overview is provided in Display EFF.50. A crosstabulation of immunologic response following DRV/rtv and LPV/rtv treatment versus baseline CD4+ cell count category is provided in Display EFF.51.

At baseline, 8.7% of subjects in both the DRV/rtv and LPV/rtv treatment groups had CD4+ cell count < 50 x 10^6/L; 21.0% and 17.6%, respectively, had a CD4+ cell count ≥ 350 x 10^6/L. At Week 96, the proportion of subjects had decreased in the lower CD4+ cell count categories and increased in the highest CD4+ cell count category in both treatment groups: no subjects in either treatment group had a CD4+ cell count < 50 x 10^6/L while 71.0% and 73.5%, respectively, had a CD4+ cell count ≥ 350 x 10^6/L. At Week 192, the proportion of subjects in the highest CD4+ cell count category had increased further in both treatment groups: 90.2% and 90.1%, respectively.

There were no relevant differences between the DRV/rtv and LPV/rtv treatment groups with respect to immunologic response as defined per CD4+ cell count category at any time point.

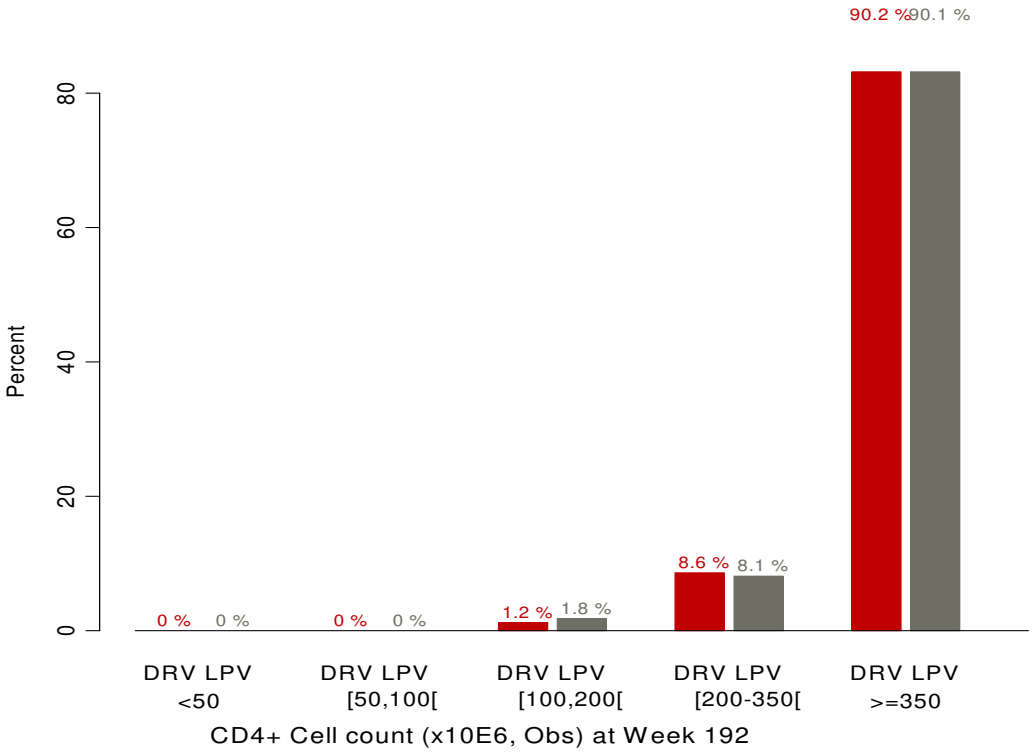


Figure 11: Immunologic Response (Observed) at Week 192 by CD4+ Cell Count Category

Source: Display EFF.50

4.3 RESISTANCE DETERMINATIONS

4.3.1 Influence of Baseline Genotype on Response

Most subjects did not show any evidence of resistance at baseline (see Section 4.1.4.2) and no influence of baseline genotype on response could therefore be observed (see also Display EFF.53).

In the DRV/rtv group, 4 subjects had 1 DRV RAM at baseline (L33F in 3 subjects, I84V in 1 subject), and 1 subject had 2 DRV RAMs at baseline (I54L and I84V). Four of these 5 subjects showed confirmed virologic response (defined as viral load < 50 copies/mL, TLOVR) at Week 192, including the subject with 2 DRV RAMs (CRF ID 211-0803). Subject 211-0064 was classified as a virologic failure based on a plasma viral load > 50 copies/mL at Weeks 48 and 60 (57 and 62 copies/mL, respectively), after having had consecutive plasma viral load values < 50 copies/mL at Weeks 16, 24 and 36. This subject again achieved a plasma viral load < 50 copies/mL from Week 84 onwards up to Week 192 (Listing VIR.3 and Listing EFF.1).

4.3.2 Development of Resistance

Analysis of the development of resistance at endpoint (i.e., the last available time point with a genotype and/or phenotype during the treatment period) compared to baseline was performed in subjects from both treatment groups, who experienced virologic failure. Initially, phenotypic and genotypic determinations were only performed on plasma samples with HIV-1 RNA ≥ 1,000 copies/mL. Additional testing was performed on samples from virologic failures with HIV-1 RNA ≥ 50 copies/mL, to better assess the relationship between virologic failure and resistance.

The TLOVR (non-VF censored) algorithm was used for the identification of virologic failures, which means that for subjects who discontinued for reasons other than virologic failure, the changes or responses at time points after discontinuation were not imputed, except for subjects whose viral load rebounded before discontinuation. Moreover, subjects who discontinued before Week 12 (i.e., who did not have the full opportunity to show virologic response) were not taken into account to determine virologic failures. The virologic failures group consisted of rebounders and subjects who were never suppressed:

- rebounders: subjects who were still in the trial at Week 12 and first achieved 2 consecutive viral load values < 50 copies/mL, followed by 2 consecutive viral load values of ≥ 50 copies/mL, or discontinuation with a last observed viral load value on treatment of ≥ 50 copies/mL;
- subjects who were never suppressed: subjects who were still in the trial at Week 12 and never achieved 2 consecutive viral load values of < 50 copies/mL.

An overview of the number of rebounders and subjects who were never suppressed is provided in Table 28 (see also Display EFF.36). The percentage of virologic failures (based on plasma viral load < 50 copies/mL) 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 (viral load > 50 copies/mL) versus 71 (20.5%) of the 346 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. Nineteen (48.7%) of the 39 rebounders in the DRV/rtv group and 23 (46.9%) of the 49 rebounders in the LPV/rtv group were transient viral load elevations > 50 copies/mL, but became undetectable again at endpoint (Listing EFF.1).

Table 28: Number of Rebounders, Subjects who Where Never Suppressed, and Virologic Failures for Virologic Response Defined as the Percentage of Subjects With Plasma Viral Load < 50 Copies/mL (ITT – TLOVR non-VF Censored)

Number of Subjects, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Virologic failure	55 (16.0)	71 (20.5)
Rebounder	39 (11.4)	49 (14.2)
Never supressed	16 (4.7)	22 (6.4)

N = number of subjects; n = number of observations

Source: Display EFF.36

An overview of the development of mutations in virologic failures at endpoint is provided in Table 29. An overview of the loss of susceptibility to ARVs in virologic failures at endpoint is provided in Table 30.

The development of mutations was evaluated in virologic failures (TLOVR non-VF censored) from both treatment groups. The development of a mutation was defined as a mutation that could be detected by resistance testing (population sequencing) at endpoint while not present at (pre)baseline. Genotyping was performed when viral load was ≥ 50 copies/mL. Paired baseline/endpoint genotypes were available for 43 and 57 virologic failure subjects (defined using a viral load > 50 copies/mL) in the DRV/rtv and LPV/rtv groups, respectively. In the virologic failures of the DRV/rtv group, 4 (9.3%) subjects with developing PI RAMs at endpoint were identified*. In the virologic failures of the LPV/rtv group, 9 (15.8%) subjects with developing PI RAMs (3 of these 9 subjects developed LPV RAMs) at endpoint were identified. None of the developing PI RAMs were primary (major) PI mutations (see Table 29). All virologic failures (DRV/rtv and LPV/rtv), for which paired baseline/endpoint phenotypes were available, remained susceptible to DRV, LPV, amprenavir, atazanavir, indinavir, saquinavir, and tipranavir (see Table 30).

In 4 (9.3%) virologic failures of the DRV/rtv group and 7 (12.3%) of the LPV/rtv group, 1 or 2 developing NRTI RAMs were identified at endpoint. Based on Antivirogram® phenotype, out of all virologic failures with available phenotypes at baseline and endpoint (39 for the DRV/rtv group, 52 for the LPV/rtv group), HIV isolates from 4 (10.5%) subjects in the DRV/rtv group and 5 (9.8%) in the LPV/rtv group lost susceptibility to FTC. Loss of susceptibility to FTC was associated with the development of the M184I and/or V mutation in all these subjects. Two other subjects (CRF ID 211-0309, 211-0119) in the LPV/rtv group developed M184I or V without loss susceptibility to FTC (1 was already resistant to FTC at baseline and endpoint, and 1 had no susceptibility data at endpoint).

A listing of subjects experiencing virologic failure, including the genotype and phenotype at screening, baseline, and endpoint is provided in Listing VIR.1 and Listing VIR.2.

* Subject 211-0631 (DRV/rtv) developed a V11I (DRV RAM) after treatment stop; no loss of susceptibility was observed for any PI. This subject discontinued due to noncompliance and scored ‘nonadherent’ according to M-MASRI across the treatment phase (≤ 95% adherent in 11 out of 13 visits). Further genotypic (post-database lock) analyses revealed that the V11I was also present at Week 132 (genotype not included in Week-192 locked database).

Table 29: Development of Mutations in Virologic Failures (Plasma Viral Load < 50 Copies/mL – TLOVR Non-VF-Censored) at Endpoint

	DRV/rtv N = 55	**LPV/rtv N = 71**
Total number of virologic failures with baseline and endpoint genotype[a]	***43***[e]	***57***
Subjects developing mutations at endpoint, n (%)		
IAS PI RAMs[b]	4 (9.3)[c] L10V (n =1) **V11I** (n=1)[c] I13V + G16E (n = 1)[d] I13V (n = 1)	9 (15.8) I13V (n = 1) L33V (n = 1) M36I (n = 1) I62V (n = 1) **A71V** (n = 2) **A71T** + V77I (n = 1) V77I (n = 1) I93L (n = 1)
IAS NRTI RAMs[b]	4 (9.3) M184I/V (n = 1)[d] M184V (n = 2) M184V + K70E (n = 1)	7 (12.3) M184I/V (n = 1) M184I (n = 2) M184V (n = 4)

[a] Genotype was determined if viral load ≥ 50 copies/mL
[b] IAS-USA 2009[29]
[c] Subject 211-0631 (DRV/rtv) developed a V11I after treatment stop. This subject discontinued due to noncompliance.Further genotypic (post database lock) analyses revealed that the V11I was also present at Week 132 (genotype not included in Week-192 locked database).
[d] I13V+G16E and M184I/V developed in the same subject (CRF ID 211-0653)
[e] 1 genotype that was obtained post-database lock (see footnote [c]) was added to the Week-192 analysis data
Note: Mutations in bold are IAS USA 2009 DRV/LPV RAMs
Source: Display VIR.8, Display VIR.9, Listing VIR.1, Listing VIR.2

Table 30: Loss of Susceptibility to ARVs in Virologic Failures (Plasma Viral Load < 50 Copies/mL – TLOVR Non-VF-Censored) at Endpoint

	DRV/rtv N = 55	**LPV/rtv N = 71**
Total number of virologic failures with baseline and endpoint phenotype[a]	***39***	***52***
Subjects who lost susceptibility to ARVs at Endpoint Compared to Baseline, n (%)		
Loss of susceptibility to trial PI	**0**	**0**
Loss of susceptibility to any PI	**1 (2.6)**[b]	**1 (1.9)**[b]
Loss of susceptibility to FTC[c]	**4 (10.5)**[d]	**5 (9.8)**[c,d]
Loss of susceptibility TDF[c]	**2 (5.1)**[e]	**0**

[a] Phenotype determined by Antivirogram® if viral load ≥ 50 copies/mL.
[b] FC nelfinavir 0.9 to 2.7 and 1.6 to 2.6, respectively (not correlated with developing PI RAMs)
[c] 1 subject had baseline viruses with no susceptibility to FTC.
[d] All subjects developed M184I and/or V.
[e] FC TDF 0.7 to 2.7 and 0.3 to 1.8 (not correlated with developing NRTI RAMs)
Source: Display VIR.2, Display VIR.3, Listing VIR.1, Listing VIR.2

4.4 PATIENT-REPORTED OUTCOMES

4.4.1 M-MASRI

The M-MASRI questionnaire asked subjects to report adherence to DRV/rtv and LPV/rtv respectively by means of a horizontal VAS that generates a self-rated percentage of doses of DRV/rtv and LPV/rtv taken during the past month. Subject-reported adherence rates are transformed to binary variables using a 95% cut-off to define adherent (> 95%) and nonadherent (≤ 95%) subjects.

Descriptive statistics of the actual adherence rates throughout the trial to Week 192 are provided in Display PRO.1 and a tabulation of the percent of adherent subjects provided in Display PRO.2. A graphical presentation of the proportion of adherent subjects as determined by the M-MASRI scores is shown in Figure 12. Descriptive statistics of the confirmed virologic response (TLOVR) at Week 192 and mean change from baseline (NC = F) in viral load at Week 192 versus adherence at Week 192 are provided Display PRO.3 and Display PRO.4, respectively.

The percentage of adherent subjects ranged from 82.0% to 89.4% for DRV/rtv subjects and 78.3% to 86.1% for LPV/rtv subjects. Up to Week 20 the adherence rate were comparable between the treatment groups. From Week 144 onwards, there was a statistically significant higher adherence rate with DRV/rtv compared to LPV/rtv ($p < 0.05$).

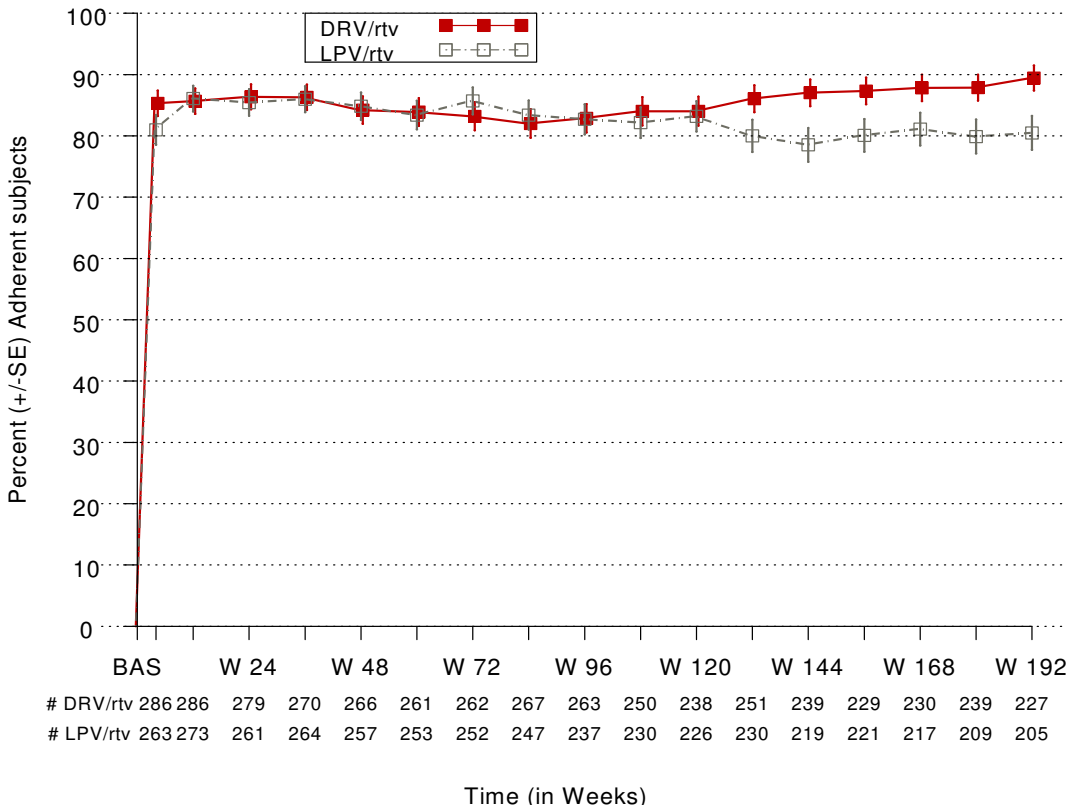


Figure 12: Proportion of Adherent Subjects as Assessed by M-MASRI Over Time

Source: Display PRO.2

Virologic response by adherence as assessed by the M-MASRI is presented in Display PRO.3. Virologic response defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL per time point is summarized in Table 31.

As assessed by the M-MASRI, virologic response at Week 192 (plasma viral load < 50 copies/mL) was greater in adherent subjects than in nonadherent subjects (adherence based on the overall assessment). In adherent subjects, virologic response was greater in the DRV/rtv group than in the and LPV/rtv group, and superiority in virologic response of DRV/rtv versus LPV/rtv was established (lower limit of the 95% CI of the difference between the treatment groups 12.2 [4.2; 20.2] was > 0%). In nonadherent subjects, noninferiority in virologic response of DRV/rtv versus LPV/rtv was established (lower limit of the 95% CI of the difference between the treatment groups 10.3 [-7.6; 28.1] was > -12%). Of note, for nonadherent subjects the sample size of the subgroups was relatively limited and conclusions should be drawn with caution.

Table 31: Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 copies/mL (ITT – TLOVR) at Week 192 by Adherence[a]

	DRV/rtv		LPV/rtv		DRV/rtv - LPV/rtv	
Baseline Parameter	**N**	**n (%)**	**N**	**n (%)**	**Difference in % Response**	**95 % CI of Difference in % Response[b]**
Adherence						
Adherent	270	198 (73.3)	252	154 (61.1)	12.2	(4.2; 20.2)
Nonadherent	54	31 (57.4)	70	33 (47.1)	10.3	(-7.6; 28.1)

N = number of subjects; n = number of observations
[a] Overall assessment
[b] Based on a normal approximation of the difference in % response
Source: Display PRO.3

4.5 EFFICACY CONCLUSIONS

The Week-192 efficacy results of this trial in treatment-naïve subjects demonstrated statistically significant noninferiority in confirmed virologic response (plasma viral load < 50 copies/mL) at Week 192 with DRV/rtv 800/100 mg q.d. compared to LPV/rtv 800/200 mg total daily dose, both in combination with a fixed background regimen of TDF/FTC, in view of the predefined delta of 12%. At Week 192, virologic response defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL (ITT - TLOVR) was 68.8% for the DRV/rtv group and 57.2% for the LPV/rtv group. The lower limit of the 95% CI of the difference between the treatment groups was > -12% (i.e., delta, the maximum allowable difference). The estimated difference [95% CI] between the treatment groups was 11.6 [4.4; 18.8] and was statistically significant, thereby demonstrating noninferiority (p-value < 0.001). The lower limit of the 95% CI for the difference in virologic response was above 0, and the secondary objective to test for superiority of DRV/rtv over LPV/rtv showed a statistically significant difference between the treatments, thus superiority of DRV/rtv over LPV/rtv in this patient population could be concluded (p = 0.002).

The results for virologic response (plasma viral load < 50 copies/mL) were robust and consistent as confirmed by different sensitivity analyses.

Subgroup analyses consistently showed a higher virologic response with DRV/rtv compared to LPV/rtv at Week 192 across subgroups by baseline viral load, gender, region, age, and clade. In both subgroups by the stratification factor baseline viral load (< 100,000 and ≥ 100,000 copies/mL), subjects receiving DRV/rtv had a statistically superior virologic response compared with subjects receiving LPV/rtv (< 100,000 copies/mL: 69.5% versus 60.2%, p = 0.038; ≥ 100,000 copies/mL: 67.5% versus 51.7%, p = 0.012). In addition, subjects with CD4+ cell counts ≥ 200 x 10^6 cells/L at baseline receiving DRV/rtv demonstrated statistical superiority in virologic responses compared with LPV/rtv (71.3% versus 59.6%, p = 0.014). In subjects with baseline CD4+ cell counts < 200 x 10^6 cells/L, DRV/rtv was shown to be noninferior compared to LPV/rtv (65.2% versus 54.1%, p < 0.001).

Virologic response was well sustained in both treatment groups. Of the DRV/rtv subjects with a confirmed virologic response of < 50 copies/mL (undetectable) at Week 48, 81.3% remained undetectable at Week 192 versus 68.5% with LPV/rtv. When comparing the Weeks-96 and -192

results, 87.7% of DRV/rtv subjects and 80.0% of LPV/rtv subjects remained undetectable at Week 192 if they were undetectable at Week 96.

The results for virologic response defined as the percentage of subjects with confirmed plasma viral load < 400 copies/mL were in line with those for the primary virologic response parameter. At Week 192, virologic response (ITT - TLOVR) was 75.2% and 65.0% for the DRV/rtv and LPV/rtv groups, respectively (estimated difference [95% CI]: 10.2 [3.4; 17.0]; lower limit of the 95% CI > -12%). The between-group difference was statistically significant, demonstrating noninferiority ($p < 0.001$). The lower limit of the 95% CI for the difference in virologic response was also above 0, and thus superiority of DRV/rtv over LPV/rtv for this parameter could be concluded ($p = 0.002$).

The results for the other secondary efficacy parameters were also supportive of those for the primary virologic response parameter.

The mean change in $\log_{10}$ viral load from baseline (ITT - NC = F) at Week 192 was -2.35 and -2.03 $\log_{10}$ copies/mL for the DRV/rtv and LPV/rtv groups, respectively (difference [95% CI]: -0.32 [-0.55; 0.09]. The between-group difference was statistically significant (ANCOVA, $p = 0.007$).

There was no statistically significant difference between the treatment groups with respect to the time to virologic response (viral load < 50 copies/mL) ($p = 0. 5197$). In contrast, statistical analysis of the time to loss of virologic response showed a between-group difference that was statistically significant for < 50 copies/mL (TLOVR) ($p = 0.0034$), with a smaller probability of failing under DRV/rtv treatment compared to LPV/rtv treatment (hazard ratio [95% CI]: 0.69 [0.54; 0.88]).

Immunologic response was similar in the DRV/rtv and LPV/rtv treatment groups. The median change in CD4+ cell count from baseline (ITT - NC = F) at Week 192 was 258 and 263 x 10^6/L for the DRV/rtv and LPV/rtv groups, respectively. Mean change at Week 192 was 266 x 10^6 cells/L and 269 x 10^6 cells/L, respectively. Also when considering immunologic results by CD4+ cell count category, there were no relevant differences between the DRV/rtv and LPV/rtv groups both at baseline and at Week 192.

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.

The percentage of adherent subjects determined by the M-MASRI questionnaire for DRV/rtv subjects ranged from 82.0% to 89.4% and for LPV/rtv subjects ranged from 78.3% to 86.1% at the successive time points. There was no statistically significant difference between the treatment groups with respect to the percentage of adherent subjects during the trial.

Overall, the efficacy responses observed in subjects receiving DRV/rtv 800/100 mg q.d., the consistently higher response rates compared with LPV/rtv 800/200 mg (total daily dose) and low number of virologic failures provide further evidence of the durable potency of a DRV/rtv-containing regimen in the treatment-naïve HIV-1 infected population.

4.6 SAFETY RESULTS

The safety analysis was performed on the ITT population, unless otherwise specified.

4.6.1 Adverse Events

The AEs discussed in this section are those that were reported during the treatment period, unless otherwise specified. All AEs are reported by preferred term, unless otherwise specified. Where a relationship to investigational medication (DRV/rtv or LPV/rtv) is provided, this assessment is based on the judgement of the investigator unless otherwise specified. All AE summary tables are ordered alphabetically, both by System Organ Class (SOC) and by preferred term (unless otherwise specified).

4.6.1.1 SUMMARY OF ALL ADVERSE EVENTS

A summary of the AEs reported during the treatment period in this trial is provided in Table 32; a more extensive summary table is provided in Display SAF.1. The incidence of AEs reported in ≥ 5% of subjects in any treatment group during the treatment period by SOC and preferred term is summarized in Table 33. An overview of the incidence of all AEs in this trial is provided in Display SAF.2. Individual subject data for AEs are provided in Listing SAF.1.

In total, 95.0% of subjects in the DRV/rtv treatment group and 96.2% of subjects in the LPV/rtv treatment group experienced ≥ 1 AE.

The most frequent AEs (preferred term) were diarrhea (39.4% and 54.9% with DRV/rtv and LPV/rtv, respectively), upper respiratory tract infection (24.5% and 23.1%), headache (22.4% and 17.6%), nausea (18.4% and 30.3%), nasopharyngitis (17.2% and 14.5%), abdominal pain (12.8% and 14.5%), cough (12.2% and 14.7%), bronchitis (11.1% and 11.8%), back pain (11.1% and 8.1%), rash (10.2% and 8.7%), influenza (8.7% and 12.7%), fatigue (8.7% and 10.7%), and vomiting (8.2% and 13.3%). All other AEs were reported in < 10% of subjects in any treatment group. Diarrhea, nausea and vomiting were reported less frequently with DRV/rtv than with LPV/rtv.

Display SAF.7 provides an overview of the incidence of the most frequent AEs (i.e., list above, in ≥ 10%) over time. For most of these AEs, the incidence was highest during the first 24 weeks of treatment and decreased beyond Week 24 in both treatment groups. This was most apparent for diarrhea, nausea, abdominal pain and vomiting, and upper respiratory tract infection, headache, and rash (preferred term). For the other AEs, the difference in the incidence during the first 24 weeks of treatment compared to the weeks beyond that time point was generally smaller, and for cough and influenza, this was only seen for the LPV/rtv treatment group. Only for back

pain, the incidence was fairly constant over time in both treatment groups.

Table 32: Adverse Events: Summary Table

n (%)	DRV/rtv N = 343	LPV/rtv N = 346
≥ 1 AE	326 (95.0)	333 (96.2)
≥ 1 SAE	55 (16.0)	72 (20.8)
≥ 1 grade 3 or 4 AE	103 (30.0)	110 (31.8)
≥ 1 AE at least possibly related to the PI[a]	194 (56.6)	259 (74.9)
≥ 1 AE ≥ grade 2 and at least possibly related to the PI[a]	96 (28.0)	124 (35.8)
≥ 1 AE leading to permanent discontinuation	26 (7.6)[b,c]	50 (14.5)[b]

N = total number of subjects with data; n = number of observations
[a] DRV/rtv or LPV/rtv
[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.
Source: Display SAF.1, Display SAF.28

Table 33: Adverse Events Reported in > 5% of Subjects of any Treatment Group During the Treatment Period (Regardless of Severity and Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any AE	***326 (95.0)***	***333 (96.2)***
Blood and Lymphatic System Disorders	**37 (10.8)**	**38 (11.0)**
Cardiac Disorders	**17 (5.0)**	**21 (6.1)**
Ear and Labyrinth Disorders	**15 (4.4)**	**19 (5.5)**
Eye Disorders	**48 (14.0)**	**35 (10.1)**
Gastrointestinal Disorders	**226 (65.9)**	**267 (77.2)**
Abdominal pain	44 (12.8)	50 (14.5)
Diarrhea	135 (39.4)	190 (54.9)
Dyspepsia	15 (4.4)	18 (5.2)
Flatulence	13 (3.8)	19 (5.5)
Hemorrhoids	18 (5.2)	15 (4.3)
Nausea	63 (18.4)	105 (30.3)
Vomiting	28 (8.2)	46 (13.3)
General Disorders and Administration Site Conditions	**86 (25.1)**	**98 (28.3)**
Fatigue	30 (8.7)	37 (10.7)
Pyrexia	21 (6.1)	24 (6.9)
Infections and Infestations	**274 (79.9)**	**276 (79.8)**
Bronchitis	38 (11.1)	41 (11.8)
Gastroenteritis	15 (4.4)	31 (9.0)
Herpes simplex	30 (8.7)	20 (5.8)
Herpes zoster	18 (5.2)	17 (4.9)
Influenza	30 (8.7)	44 (12.7)
Nasopharyngitis	59 (17.2)	50 (14.5)
Pharyngitis	19 (5.5)	24 (6.9)
Sinusitis	27 (7.9)	30 (8.7)

Table 33: Adverse Events Reported in > 5% of Subjects of any Treatment Group During the Treatment Period (Regardless of Severity and Causality), Cont'd

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Syphilis	22 (6.4)	8 (2.3)
Upper respiratory tract infection	84 (24.5)	80 (23.1)
Urinary tract infection	34 (9.9)	32 (9.2)
Injury, Poisoning and Procedural Complications	**52 (15.2)**	**49 (14.2)**
Investigations	**90 (26.2)**	**103 (29.8)**
ALT increased	9 (2.6)	20 (5.8)
AST increased	10 (2.9)	18 (5.2)
Metabolism and Nutrition Disorders	**62 (18.1)**	**88 (25.4)**
Hypercholesterolemia	13 (3.8)	23 (6.6)
Hypertriglyceridemia	8 (2.3)	29 (8.4)
Musculoskeletal and Connective Tissue Disorders	**105 (30.6)**	**108 (31.2)**
Arthralgia	31 (9.0)	27 (7.8)
Back pain	38 (11.1)	28 (8.1)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**23 (6.7)**	**36 (10.4)**
Nervous System Disorders	**129 (37.6)**	**121 (35.0)**
Dizziness	21 (6.1)	22 (6.4)
Headache	77 (22.4)	61 (17.6)
Psychiatric Disorders	**73 (21.3)**	**73 (21.1)**
Depression	22 (6.4)	28 (8.1)
Insomnia	25 (7.3)	30 (8.7)
Renal and Urinary Disorders	**33 (9.6)**	**34 (9.8)**
Reproductive System and Breast Disorders	**44 (12.8)**	**46 (13.3)**
Respiratory, Thoracic and Mediastinal Disorders	**80 (23.3)**	**92 (26.6)**
Cough	42 (12.2)	51 (14.7)
Skin and Subcutaneous Tissue Disorders	**158 (46.1)**	**139 (40.2)**
Pruritus	21 (6.1)	10 (2.9)
Rash	35 (10.2)	30 (8.7)
Vascular Disorders	**31 (9.0)**	**36 (10.4)**
Hypertension	24 (7.0)	17 (4.9)

N = total number of subjects with data; n = number of observations
[a] Preferred term, for all rash-related events, see Section 4.6.1.3.4.1
Source: Display SAF.2

An overview of the incidence of **AEs by LPV/rtv dosing frequency** (b.i.d. versus q.d.) is provided in Display SAF.3. A summary of the incidence of AEs reported in ≥ 5% of subjects by dosing frequency of LPV/rtv is provided in Table 34. It should be noted that the sample size for the group of subjects receiving LPV/rtv q.d. is too small to allow drawing reliable conclusions.

Table 34: Adverse Events Reported in ≥ 5% of Subjects in any Treatment Group During the Treatment Period (Regardless of Severity and Causality) by Dosing Frequency of LPV/rtv

System Organ Class Dictionary-Derived Term, n (%)	LPV/rtv b.i.d. N = 260	LPV/rtv q.d. N = 50
Any AE	***248 (95.4)***	***49 (98.0)***
Blood and Lymphatic System Disorders	**30 (11.5)**	**6 (12.0)**
Anemia	7 (2.7)	4 (8.0)
Lymphadenopathy	13 (5.0)	2 (4.0)
Cardiac Disorders	**15 (5.8)**	**1 (2.0)**
Ear and Labyrinth Disorders	**13 (5.0)**	**3 (6.0)**
Eye Disorders	**27 (10.4)**	**3 (6.0)**
Gastrointestinal Disorders	**191 (73.5)**	**45 (90.0)**
Abdominal pain	33 (12.7)	7 (14.0)
Diarrhea	136 (52.3)	34 (68.0)
Dyspepsia	15 (5.8)	1 (2.0)
Flatulence	13 (5.0)	5 (10.0)
Hemorrhoids	10 (3.8)	4 (8.0)
Nausea	76 (29.2)	18 (36.0)
Toothache	5 (1.9)	3 (6.0)
Vomiting	34 (13.1)	7 (14.0)
General Disorders and Administration Site Conditions	**66 (25.4)**	**17 (34.0)**
Fatigue	20 (7.7)	9 (18.0)
Pain	8 (3.1)	3 (6.0)
Pyrexia	18 (6.9)	4 (8.0)
Infections and Infestations	**211 (81.2)**	**36 (72.0)**
Abscess	1 (0.4)	3 (6.0)
Bronchitis	32 (12.3)	4 (8.0)
Cellulitis	2 (0.8)	3 (6.0)
Folliculitis	7 (2.7)	4 (8.0)
Gastroenteritis	27 (10.4)	1 (2.0)
Herpes simplex	17 (6.5)	3 (6.0)
Herpes zoster	10 (3.8)	4 (8.0)
Influenza	41 (15.8)	1 (2.0)
Nasopharyngitis	40 (15.4)	5 (10.0)
Onychomycosis	3 (1.2)	4 (8.0)
Oral candidiasis	9 (3.5)	3 (6.0)
Papilloma viral infection	1 (0.4)	3 (6.0)
Pharyngitis	19 (7.3)	3 (6.0)
Rhinitis	14 (5.4)	1 (2.0)
Sinusitis	20 (7.7)	4 (8.0)
Upper respiratory tract infection	61 (23.5)	12 (24.0)
Urinary tract infection	29 (11.2)	2 (4.0)
Injury, Poisoning and Procedural Complications	**34 (13.1)**	**6 (12.0)**
Investigations	**79 (30.4)**	**13 (26.0)**
ALT increased	18 (6.9)	0
AST increased	16 (6.2)	0

Table 34: Adverse Events Reported in ≥ 5% of Subjects in any Treatment Group During the Treatment Period (Regardless of Severity and Causality) by Dosing Frequency of LPV/rtv, Cont'd

System Organ Class Dictionary-Derived Term, n (%)	LPV/rtv b.i.d. N = 260	LPV/rtv q.d. N = 50
Metabolism and Nutrition Disorders	**65 (25.0)**	**14 (28.0)**
Anorexia	13 (5.0)	1 (2.0)
Hypercholesterolemia	18 (6.9)	2 (4.0)
Hyperlipidemia	10 (3.8)	4 (8.0)
Hypertriglyceridemia	20 (7.7)	5 (10.0)
Musculoskeletal and Connective Tissue Disorders	**76 (29.2)**	**18 (36.0)**
Arthralgia	20 (7.7)	3 (6.0)
Back pain	22 (8.5)	4 (8.0)
Myalgia	15 (5.8)	2 (4.0)
Pain in extremity	11 (4.2)	4 (8.0)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**21 (8.1)**	**6 (12.0)**
Nervous System Disorders	**85 (32.7)**	**21 (42.0)**
Dizziness	15 (5.8)	2 (4.0)
Headache	43 (16.5)	14 (28.0)
Hypoesthesia	4 (1.5)	3 (6.0)
Psychiatric Disorders	**46 (17.7)**	**15 (30.0)**
Depression	19 (7.3)	7 (14.0)
Insomnia	19 (7.3)	6 (12.0)
Renal and Urinary Disorders	**22 (8.5)**	**7 (14.0)**
Hematuria	6 (2.3)	4 (8.0)
Reproductive System and Breast Disorders	**30 (11.5)**	**11 (22.0)**
Erectile dysfunction	4 (1.5)	4 (8.0)
Respiratory, Thoracic and Mediastinal Disorders	**64 (24.6)**	**16 (32.0)**
Cough	37 (14.2)	8 (16.0)
Dyspnea	3 (1.2)	3 (6.0)
Pharyngolaryngeal pain	12 (4.6)	4 (8.0)
Skin and Subcutaneous Tissue Disorders	**111 (42.7)**	**14 (28.0)**
Dermatitis	9 (3.5)	3 (6.0)
Eczema	13 (5.0)	1 (2.0)
Rash	23 (8.8)	3 (6.0)
Seborrheic dermatitis	7 (2.7)	4 (8.0)
Vascular Disorders	**24 (9.2)**	**7 (14.0)**
Hypertension	11 (4.2)	4 (8.0)

N = total number of subjects with data; n = number of observations
Source: Display SAF.3

The incidence of **AIDS-defining illnesses reported as an AE** during the treatment period is summarized in Table 35 (see also Display SAF.22). Individual subject data for AIDS-defining illnesses are provided in Listing SAF.7.

In total, 5.2% of subjects in the DRV/rtv group and 3.8% in the LPV/rtv group had an AE that was an AIDS-defining illnesses. AEs that were an AIDS-defining illness were reported in at most 4 subjects in any treatment group. The majority of these were from the SOC Infections and Infestations (4.4% and 2.6% with DRV/rtv and LPV/rtv, respectively).

Table 35: AIDS-Defining Illnesses Reported as an Adverse Event During the Treatment Period (Regardless of Severity and Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
AnyAIDS Defining Illness Reported as an AE	***18 (5.2)***	***13 (3.8)***
Infections and Infestations	**15 (4.4)**	**9 (2.6)**
Candidiasis	4 (1.2)	2 (0.6)
Cerebral toxoplasmosis	0	1 (0.3)
Cytomegalovirus chorioretinitis	2 (0.6)	0
Disseminated tuberculosis	1 (0.3)	1 (0.3)
HIV wasting syndrome	1 (0.3)	0
Meningitis cryptococcal	0	2 (0.6)
Mycobacterium avium complex infection	1 (0.3)	0
Esophageal candidiasis	2 (0.6)	1 (0.3)
Progressive multifocal leukoencephalopathy	1 (0.3)	0
Pulmonary tuberculosis	4 (1.2)	2 (0.6)
Tuberculosis	1 (0.3)	0
Neoplasms, Benign, Malignant, and Unspecified (incl Cysts and Polyps)	**3 (0.9)**	**4 (1.2)**
B-cell lymphoma	0	1 (0.3)
Diffuse large B-cell lymphoma	1 (0.3)	0
Kaposi's sarcoma	1 (0.3)	3 (0.9)
Lymphoma	1 (0.3)	0
Plasmablastic lymphoma	1 (0.3)	0

N = total number of subjects with data; n = number of observations
Source: Display SAF.22

The **incidence by gender of the most frequent AEs** during the treatment period (by preferred term, in ≥ 10%) is summarized inTable 36. An overview of the incidence of all AEs in this trial by gender is provided in Display SAF.4. Approximately 1 third (30.3%) of the trial population was female.

The incidence of diarrhea was lower in female subjects than in male subjects in both treatment groups. The incidence of vomiting was higher in female subjects than in male subjects in both treatment groups. Abdominal pain and nausea were reported with similar frequency in male and female subjects in the DRV/rtv group, but were more frequent in female subjects than in male subjects in the LPV/rtv group. Back pain was reported with similar frequency in male and female subjects in the DRV/rtv group, but was less frequent in female subjects than in male subjects in the LPV/rtv group. Nasopharyngitis was less frequent in female subjects than in male subjects in the DRV/rtv group, but was reported with similar frequency in male and female subjects in the LPV/rtv group. There were no relevant differences between male and female subjects in both treatment groups with respect to the incidence of bronchitis, cough, fatigue, headache, rash, and upper respiratory tract infection.

Table 36: Most Frequent Adverse Events[a] Reported During the Treatment Period by Gender (Regardless of Severity or Causality)

Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	Female N = 104	Male N = 239	Female N = 105	Male N = 241
Abdominal pain	17 (16.3)	27 (11.3)	21 (20.0)	29 (12.0)
Back pain	11 (10.6)	27 (11.3)	4 (3.8)	24 (10.0)
Bronchitis	11 (10.6)	27 (11.3)	12 (11.4)	29 (12.0)
Cough	11 (10.6)	31 (13.0)	13 (12.4)	38 (15.8)
Diarrhea	31 (29.8)	104 (43.5)	51 (48.6)	139 (57.7)
Fatigue	8 (7.7)	22 (9.2)	8 (7.6)	29 (12.0)
Headache	26 (25.0)	51 (21.3)	17 (16.2)	44 (18.3)
Influenza	11 (10.6)	19 (7.9)	17 (16.2)	27 (11.2)
Nasopharyngitis	13 (12.5)	46 (19.2)	17 (16.2)	33 (13.7)
Nausea	20 (19.2)	43 (18.0)	43 (41.0)	62 (25.7)
Rash	9 (8.7)	26 (10.9)	12 (11.4)	18 (7.5)
Upper respiratory tract infection	28 (26.9)	56 (23.4)	27 (25.7)	53 (22.0)
Vomiting	15 (14.4)	13 (5.4)	27 (25.7)	19 (7.9)

N = total number of subjects with data; n = number of observations
[a] AEs reported in ≥ 10% of subjects
Source: Display SAF.4

4.6.1.2 SEVERITY AND RELATEDNESS

The incidence of **grade 2 to 4 AEs** reported in ≥ 2% of subjects in either treatment group during the treatment period is summarized in Table 37. An overview of all grade 2 to 4 AEs in this trial is provided in Display SAF.24.

Overall, grade 2 to 4 AEs were reported with comparable frequency in the DRV/rtv group (70.0%) and the LPV/rtv group (74.6%). The majority of grade 2 to 4 AEs (preferred term) occurred in ≤ 2% of subjects in either treatment group. The most frequent grade 2 to 4 AEs were diarrhea (8.7% and 15.9% with DRV/rtv and LPV/rtv, respectively), headache (6.7% and 5.5%), upper respiratory tract infection (6.4% and 6.1%), abdominal pain (5.8% and 6.1%), bronchitis (4.7% and 8.7%), hypercholesterolemia (2.9% and 5.5%), and hypertriglyceridemia (2.3% and 6.1%), ALT increased (2.3% and 5.5%). All other grade 2 to 4 AEs were observed in < 5% in either treatment group.

The incidence of **grade 3 or 4 AEs** reported in ≥ 2 subjects in either treatment group during the treatment period is summarized in Table 38. An overview of all grade 3 or 4 AEs in this trial is provided in Display SAF.25. For the incidence of all grade 3 AEs in this trial, refer to Supporting Data Display 1 and Display SAF.26, and for the incidence of all grade 4 AEs in this trial refer to Supporting Data Display 2 and Display SAF.27. Individual subject data for AEs of grade 3 and 4 are provided in Listing SAF.4.

Overall, grade 3 or 4 AEs were reported with comparable frequency in the DRV/rtv group (30.0%) and the LPV/rtv group (31.8%). The majority of grade 3 or 4 AEs (preferred term) occurred in ≤ 1% of subjects in either treatment group and there were no relevant differences between the treatment groups. The most frequent grade 3 or 4 AEs were LDL increased (3.2% and 1.4% with DRV/rtv and LPV/rtv, respectively), AST increased (2.0% and 2.0%), blood amylase increased (2.0% and 2.0%), hypertriglyceridemia (1.5% and 3.5%), and ALT increased

(1.5% and 2.6%), hypercholesterolemia (0.6% and 2.0%), and abdominal pain (0.6% and 1.2%). All other grade 3 or 4 AEs were observed in < 1% in either treatment group.

Table 37: Grade 2 to 4 Adverse Events Reported in ≥ 2% of Subjects in any Treatment Group During the Treatment Period (Regardless of Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any Grade 2 to 4 AE	***240 (70.0)***	***258 (74.6)***
Blood and Lymphatic System Disorders	**12 (3.5)**	**10 (2.9)**
Cardiac Disorders	**7 (2.0)**	**10 (2.9)**
Ear and Labyrinth Disorders	**4 (1.2)**	**7 (2.0)**
Eye Disorders	**9 (2.6)**	**7 (2.0)**
Gastrointestinal Disorders	**85 (24.8)**	**105 (30.3)**
Abdominal pain	20 (5.8)	21 (6.1)
Diarrhea	30 (8.7)	55 (15.9)
Nausea	14 (4.1)	13 (3.8)
Vomiting	7 (2.0)	12 (3.5)
General Disorders and Administration Site Conditions	**27 (7.9)**	**33 (9.5)**
Fatigue	3 (0.9)	10 (2.9)
Pyrexia	9 (2.6)	6 (1.7)
Hepatobiliary Disorders	**4 (1.2)**	**8 (2.3)**
Immune System Disorders	**3 (0.9)**	**10 (2.9)**
Infections and Infestations	**139 (40.5)**	**154 (44.5)**
Bronchitis	16 (4.7)	30 (8.7)
Herpes simplex	8 (2.3)	10 (2.9)
Herpes zoster	9 (2.6)	14 (4.0)
Influenza	10 (2.9)	14 (4.0)
Nasopharyngitis	16 (4.7)	14 (4.0)
Pharyngitis	6 (1.7)	12 (3.5)
Respiratory tract infection viral	6 (1.7)	7 (2.0)
Secondary syphilis	8 (2.3)	1 (0.3)
Sinusitis	12 (3.5)	17 (4.9)
Syphilis	10 (2.9)	4 (1.2)
Upper respiratory tract infection	22 (6.4)	21 (6.1)
Urinary tract infection	12 (3.5)	8 (2.3)
Injury, Poisoning and Procedural Complications	**28 (8.2)**	**26 (7.5)**
Investigations	**59 (17.2)**	**66 (19.1)**
ALT increased	8 (2.3)	19 (5.5)
AST increased	8 (2.3)	16 (4.6)
Blood amylase increased	7 (2.0)	8 (2.3)
Blood cholesterol increased	9 (2.6)	5 (1.4)
LDL increased	14 (4.1)	6 (1.7)
Metabolism and Nutrition Disorders	**35 (10.2)**	**60 (17.3)**
Anorexia	4 (1.2)	3 (0.9)
Hypercholesterolemia	10 (2.9)	19 (5.5)
Hyperlipidemia	4 (1.2)	12 (3.5)
Hypertriglyceridemia	8 (2.3)	21 (6.1)
Musculoskeletal and Connective Tissue Disorders	**41 (12.0)**	**48 (13.9)**
Arthralgia	9 (2.6)	9 (2.6)
Back pain	15 (4.4)	13 (3.8)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**8 (2.3)**	**16 (4.6)**

Table 37: Grade 2 to 4 Adverse Events Reported in ≥ 2% of Subjects in any Treatment Group During the Treatment Period (Regardless of Causality), Cont'd

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Nervous System Disorders	**49 (14.3)**	**45 (13.0)**
Headache	23 (6.7)	19 (5.5)
Psychiatric Disorders	**31 (9.0)**	**37 (10.7)**
Depression	11 (3.2)	15 (4.3)
Insomnia	5 (1.5)	12 (3.5)
Renal and Urinary Disorders	**7 (2.0)**	**11 (3.2)**
Reproductive System and Breast Disorders	**20 (5.8)**	**19 (5.5)**
Respiratory, Thoracic and Mediastinal Disorders	**27 (7.9)**	**26 (7.5)**
Cough	11 (3.2)	14 (4.0)
Skin and Subcutaneous Tissue Disorders	**46 (13.4)**	**43 (12.4)**
Rash	8 (2.3)	12 (3.5)
Vascular Disorders	**17 (5.0)**	**17 (4.9)**
Hypertension	14 (4.1)	8 (2.3)

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

Source: Display SAF.24

Table 38: Grade 3 or 4 Adverse Events Reported in ≥ 2 Subjects in any Treatment Group During the Treatment Period (Regardless of Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any Grade 3 or 4 AE	***103 (30.0)***	***110 (31.8)***
Blood and Lymphatic System Disorders	**4 (1.2)**	**4 (1.2)**
Neutropenia	1 (0.3)	2 (0.6)
Cardiac Disorders	**4 (1.2)**	**5 (1.4)**
Gastrointestinal Disorders	**12 (3.5)**	**15 (4.3)**
Abdominal pain	2 (0.6)	4 (1.2)
Diarrhea	2 (0.6)	1 (0.3)
Nausea	3 (0.9)	1 (0.3)
Vomiting	2 (0.6)	2 (0.6)
General Disorders and Administration Site Conditions	**4 (1.2)**	**6 (1.7)**
Non-cardiac chest pain	1 (0.3)	3 (0.9)
Pyrexia	2 (0.6)	0
Hepatobiliary Disorders	**2 (0.6)**	**4 (1.2)**
Infections and Infestations	**16 (4.7)**	**28 (8.1)**
Bronchitis	1 (0.3)	3 (0.9)
Gastroenteritis	3 (0.9)	0
Hepatitis A	0	2 (0.6)
Hepatitis C	0	2 (0.6)
Herpes zoster	3 (0.9)	3 (0.9)
Meningitis cryptococcal	0	2 (0.6)
Pneumonia	2 (0.6)	2 (0.6)
Pulmonary tuberculosis	2 (0.6)	1 (0.3)
Injury, Poisoning and Procedural Complications	**6 (1.7)**	**7 (2.0)**

Table 38: Grade 3 or 4 Adverse Events Reported in ≥ 2 Subjects in any Treatment Group During the Treatment Period (Regardless of Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Investigations	**36 (10.5)**	**40 (11.6)**
ALT Increased	5 (1.5)	9 (2.6)
AST Increased	7 (2.0)	7 (2.0)
Blood amylase increased	7 (2.0)	7 (2.0)
Blood bilirubin increased	1 (0.3)	2 (0.6)
Blood cholesterol increased	1 (0.3)	2 (0.6)
Blood HIV RNA increased	2 (0.6)	0
Blood triglycerides increased	0	2 (0.6)
Hepatic enzyme increased	3 (0.9)	2 (0.6)
Lipase increased	1 (0.3)	3 (0.9)
Liver function test abnormal	0	2 (0.6)
LDL increased	11 (3.2)	5 (1.4)
Transaminases increased	1 (0.3)	3 (0.9)
Metabolism and Nutrition Disorders	**11 (3.2)**	**23 (6.6)**
Hypercholesterolemia	2 (0.6)	7 (2.0)
Hyperlipidemia	1 (0.3)	2 (0.6)
Hypertriglyceridemia	5 (1.5)	12 (3.5)
Musculoskeletal and Connective Tissue Disorders	**5 (1.5)**	**5 (1.4)**
Intervertebral disc protrusion	2 (0.6)	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**4 (1.2)**	**5 (1.4)**
Hodgkin's disease	1 (0.3)	2 (0.6)
Nervous System Disorders	**9 (2.6)**	**8 (2.3)**
Cerebrovascular accident	0	2 (0.6)
Headache	1 (0.3)	3 (0.9)
Syncope	2 (0.6)	0
Psychiatric Disorders	**5 (1.5)**	**3 (0.9)**
Depression	1 (0.3)	2 (0.6)
Suicide attempt	2 (0.6)	1 (0.3)
Renal and Urinary Disorders	**1 (0.3)**	**2 (0.6)**
Reproductive System and Breast Disorders	**3 (0.9)**	**0**
Respiratory, Thoracic and Mediastinal Disorders	**4 (1.2)**	**3 (0.9)**
Skin and Subcutaneous Tissue Disorders	**5 (1.5)**	**0**
Rash	2 (0.6)	0
Vascular Disorders	**5 (1.5)**	**3 (0.9)**
Hypertension	3 (0.9)	2 (0.6)

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

Source: Display SAF.25

The incidence of **AEs considered at least possibly related to the PI** (DRV/rtv or LPV/rtv, investigator-assessed causality) in ≥ 1% of subjects in either treatment group during the treatment period is summarized in Table 39. An overview of all AEs considered at least possibly related to the PI in this trial is provided in Display SAF.29.

Overall, AEs considered at least possibly related to the PI were reported less frequently in the DRV/rtv group (56.6%) than in the LPV/rtv group (74.9%). The majority of AEs at least possibly related to the PI (preferred term) occurred in ≤ 1% of subjects in any treatment group. The most frequent AEs (preferred term) considered at least possibly related to DRV/rtv or LPV/rtv, respectively, were diarrhea (24.5% and 48.6%), nausea (14.0% and 25.7%), headache (6.4% and 8.1%), abdominal pain (3.5% and 6.9%), vomiting (3.2% and 8.1%), hypercholesterolemia (2.9% and 5.8%), and hypertriglyceridemia (2.0% and 7.5%). All other AEs considered at least possibly related to the PI occurred in < 5% of subjects in any treatment group.

The incidence of **AEs ≥ grade 2 and considered at least possibly related to the PI** in ≥ 2 subjects in any treatment group during the treatment period is summarized in Table 40. An overview of all AEs ≥ grade 2 and considered at least possibly related to the PI is provided in Display SAF.30.

Overall, the incidence of AEs ≥ grade 2 and considered by the investigator at least possibly related to the PI was lower in the DRV/rtv group (28.0%) than in the LPV/rtv group (35.8%). The majority of grade ≥ 2 AEs at least possibly related to the PI (preferred term) occurred in ≤ 1% of subjects in any treatment group. The most frequent AEs ≥ grade 2 and considered at least possibly related to DRV/rtv or LP/rtv, respectively, were diarrhea (5.0% and 11.3%), LDL increased (3.2% and 1.7%), hypercholesterolemia (2.3% and 4.9%), hypertriglyceridemia (2.0% and 5.8%), ALT increased (1.5% and 3.2%), and hyperlipidemia (0.6% and 3.2%). All other AEs ≥ grade 2 and considered at least possibly related to the PI occurred in < 3% in any treatment group.

An overview of all **grade 3 or 4 AEs considered at least possibly related to the PI** in this trial is provided in Display SAF.31.

Overall, grade 3 or 4 AEs considered at least possibly related to the PI were reported with comparable frequency in the DRV/rtv group (11.1%) and the LPV/rtv group (12.1%). The majority of grade ≥ 3 AEs at least possibly related to the PI (preferred term) occurred in < 1% of subjects in any treatment group. The most frequent AEs ≥ grade 3 and considered at least possibly related to DRV/rtv or LPV/rtv, respectively, were LDL increased (2.3% and 1.4%), hypertriglyceridemia (1.5% and 3.2%), ALT increased (1.2% and 1.7%), AST increased (1.2% and 1.2%), blood amylase increased (1.2% and 0.3%), and hypercholesterolemia (0.6% and 1.7%). All other AEs ≥ grade 3 and considered at least possibly related to the PI occurred in < 1% in any treatment group.

For an overview of **grade 4 AEs considered at least possibly related to the PI** in this trial, refer to Display SAF.32.

Table 39: Adverse Events Considered at Least Possibly Related to the PI in ≥ 1% of Subjects in any Treatment Group During the Treatment Period (Regardless of Severity, Investigator-Assessed Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any AE at Least Possibly Related to the PI	***194 (56.6)***	***259 (74.9)***
Blood and Lymphatic System Disorders	**4 (1.2)**	**3 (0.9)**
Gastrointestinal Disorders	**128 (37.3)**	**212 (61.3)**
Abdominal distension	7 (2.0)	7 (2.0)
Abdominal pain	12 (3.5)	24 (6.9)
Diarrhea	84 (24.5)	168 (48.6)
Dyspepsia	5 (1.5)	10 (2.9)
Flatulence	8 (2.3)	16 (4.6)
Gastritis	2 (0.6)	5 (1.4)
Nausea	48 (14.0)	89 (25.7)
Vomiting	11 (3.2)	28 (8.1)
General Disorders and Administration Site Conditions	**18 (5.2)**	**21 (6.1)**
Asthenia	2 (0.6)	4 (1.2)
Fatigue	12 (3.5)	11 (3.2)
Hepatobiliary Disorders	**2 (0.6)**	**1 (0.3)**
Infections and Infestations	**6 (1.7)**	**8 (2.3)**
Investigations	**32 (9.3)**	**39 (11.3)**
ALT increased	6 (1.7)	12 (3.5)
AST increased	4 (1.2)	10 (2.9)
Blood amylase increased	4 (1.2)	2 (0.6)
Blood cholesterol increased	7 (2.0)	5 (1.4)
LDL increased	11 (3.2)	7 (2.0)
Metabolism and Nutrition Disorders	**30 (8.7)**	**63 (18.2)**
Anorexia	5 (1.5)	9 (2.6)
Decreased appetite	1 (0.3)	4 (1.2)
Hypercholesterolemia	10 (2.9)	20 (5.8)
Hyperlipidemia	4 (1.2)	13 (3.8)
Hypertriglyceridemia	7 (2.0)	26 (7.5)
Musculoskeletal and Connective Tissue Disorders	**7 (2.0)**	**11 (3.2)**
Arthralgia	1 (0.3)	4 (1.2)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**2 (0.6)**	**2 (0.6)**
Nervous System Disorders	**40 (11.7)**	**52 (15.0)**
Dizziness	6 (1.7)	6 (1.7)
Dysgeusia	5 (1.5)	9 (2.6)
Headache	22 (6.4)	28 (8.1)
Paresthesia	1 (0.3)	5 (1.4)
Psychiatric Disorders	**10 (2.9)**	**8 (2.3)**
Insomnia	4 (1.2)	5 (1.4)
Skin and Subcutaneous Tissue Disorders	**50 (14.6)**	**35 (10.1)**
Alopecia	6 (1.7)	5 (1.4)
Dry skin	4 (1.2)	4 (1.2)
Lipodystrophy acquired	4 (1.2)	2 (0.6)
Pruritus	7 (2.0)	4 (1.2)
Rash	9 (2.6)	5 (1.4)

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

Source: Display SAF.29

Table 40: Adverse Events ≥ Grade 2 and Considered at Least Possibly Related to the PI in ≥ 2 Subjects in any Treatment Group During the Treatment Period (Investigator-Assessed Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any AE ≥ Grade 2 and at Least Possibly Related to the PI	***96 (28.0)***	***124 (35.8)***
Blood and Lymphatic System Disorders	**2 (0.6)**	**0**
Cardiac Disorders	**2 (0.6)**	**0**
Gastrointestinal Disorders	**28 (8.2)**	**53 (15.3)**
Abdominal distension	0	2 (0.6)
Abdominal pain	3 (0.9)	6 (1.7)
Diarrhea	17 (5.0)	39 (11.3)
Flatulence	1 (0.3)	2 (0.6)
Gastritis	0	4 (1.2)
Gastroesophageal reflux disease	0	2 (0.6)
Nausea	8 (2.3)	10 (2.9)
Vomiting	4 (1.2)	4 (1.2)
General Disorders and Administration Site Conditions	**3 (0.9)**	**6 (1.7)**
Fatigue	1 (0.3)	4 (1.2)
Hepatobiliary Disorders	**2 (0.6)**	**1 (0.3)**
Infections and Infestations	**1 (0.3)**	**3 (0.9)**
Injury, Poisoning and Procedural Complications	**2 (0.6)**	**0**
Investigations	**29 (8.5)**	**31 (9.0)**
ALT increased	5 (1.5)	11 (3.2)
AST increased	4 (1.2)	9 (2.6)
Blood amylase increased	4 (1.2)	2 (0.6)
Blood cholesterol increased	7 (2.0)	4 (1.2)
Blood triglycerides increased	1 (0.3)	2 (0.6)
Hepatic enzyme increased	1 (0.3)	2 (0.6)
Lipase increased	2 (0.6)	1 (0.3)
LDL increased	11 (3.2)	6 (1.7)
Weight increased	2 (0.6)	1 (0.3)
Metabolism and Nutrition Disorders	**19 (5.5)**	**45 (13.0)**
Anorexia	1 (0.3)	2 (0.6)
Hypercholesterolemia	8 (2.3)	17 (4.9)
Hyperlipidemia	2 (0.6)	11 (3.2)
Hypertriglyceridemia	7 (2.0)	20 (5.8)
Musculoskeletal and Connective Tissue Disorders	**1 (0.3)**	**2 (0.6)**
Nervous System Disorders	**9 (2.6)**	**8 (2.3)**
Headache	4 (1.2)	4 (1.2)
Psychiatric Disorders	**2 (0.6)**	**3 (0.9)**
Insomnia	0	2 (0.6)
Reproductive System and Breast Disorders	**2 (0.6)**	**1 (0.3)**
Erectile dysfunction	2 (0.6)	1 (0.3)
Skin and Subcutaneous Tissue Disorders	**19 (5.5)**	**10 (2.9)**
Dermatitis allergic	3 (0.9)	0
Lipohypertrophy	1 (0.3)	3 (0.9)
Pruritus	2 (0.6)	0
Rash	2 (0.6)	3 (0.9)
Rash maculopapular	2 (0.6)	0

N = total number of subjects with data; n = number of observations
Source: Display SAF.30

4.6.1.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

Narratives for deaths, other SAEs (if considered at least possibly drug related), AEs leading to discontinuation, and AEs of interest that are either an SAE or grade 3 or 4 in severity are provided in TMC114-C211-W192-narratives. The data presented in the narratives principally reflect those available in the 192-weeks analysis. Nevertheless, whenever the pharmacovigilance database (i.e., the Council for International Organizations of Medical Sciences [CIOMS] reports) contained additional information that was considered relevant to understand the events leading to death or other SAEs, this information was added to the narratives. Consequently, the narratives included with this report can contain more information compared to the data included in the Week-192 analysis with cut-off date of 29 March 2010.

4.6.1.3.1 Deaths

Four subjects in the DRV/rtv group and 7 subjects in the LPV/rtv group died during the treatment period. This resulted in a mortality rate of 0.4 per 100 patient years of exposure for treatment with DRV/rtv, and 0.7 with LPV/rtv. In addition, 1 subject of the DRV/rtv group and 1 subject of the LPV/rtv group died posttrial.

None of the deaths were considered related to the trial treatment by the investigator.

A summary of the deaths during the treatment period is provided in Table 41 (and Listing SAF.3). A summary of the deaths posttrial is provided in Listing SAF.8. Detailed subject narratives of the deaths in this trial are provided in TMC114-C211-W192-narratives.

Table 41: Summary Table of Deaths During the Treatment Period

CRF ID	Gender	Age	Time of Death (Date) Days Since Treatment Start)	Cause of Death (Preferred Term)	Time of Onset (Date) (Days Since Treatment Start)	Duration of Treatment Phase (Start - Stop)	Baseline and Last[a] log_{10} Viral Load / Baseline CD4+ Cell Count[b]	Concomitant AEs
DRV/rtv								
211-0212	Male	47	24 Jul 2008 (839 days)	Lymphoma Doubtfully related	2 Jun 2008 (787 days)	8 Apr 2006 - 14 Jun 2008	5.88 / 75 1.69 / 94	Alopecia, renal impairment, vith nerve paralysis
211-0584	Male	40	5 Feb 2007 (265 days)	Diffuse large B-cell lymphoma Not related	6 Oct 2006 (143 days)	17 May 2006 - 11 Oct 2006	5.43 / 110 1.69 / 230	Abdominal discomfort, abdominal pain, cystitis, diarrhea, dysuria, food poisoning, nausea, pharyngolaryngeal pain, toothache
211-0611	Male	49	1 Sep 2008 (834 days)	Drug toxicity Not related	1 Sep 2008 (834 days)	22 May 2006 - 1 Sep 2008	4.96 / 202 1.69 / 383	Hematuria, hydronephrosis, nephrolithiasis, oral candidiasis, spinal cord injury lumbar, tinea pedis, urinary incontinence, urinary tract infection, weight increased
211-0746	Male	40	2 Jun 2009 (1094 days)	Meningitis meningococcal Not related	1 Jun 2009 (1093 days)	5 Jun 2006 - 2 Jun 2009	4.81 / 246 1.69 / 653	Diarrhea, gastroesophageal reflux disease, headache, insomnia, umbilical hernia
LPV/rtv								
211-0005	Male	53	4 Mar 2007 (468 days)	Cardiorespiratory arrest Not related	4 Mar 2007 (468 days)	22 Nov 2005 - 04 Mar 2007	4.77 / 165 2.13 / 239	Anemia, arthralgia, blood cholesterol increased, bronchitis, constipation, diarrhea, flank pain, hypernatremia, multi-organ failure, oral candidiasis, septic shock, staphylococcal infection, thrombocytopenia, upper respiratory tract infection

Table 41: Summary Table of Deaths, Cont'd

CRF ID	Gender	Age	Time of Death (Date)	Cause of Death (Preferred Term)	Time of Onset (Date) (Days Since Treatment Start)	Duration of Treatment Phase (Start - Stop)	Baseline and Last[a] log_{10} Viral Load / Baseline CD4+ Cell Count[b]	Concomitant AEs
211-0182	Male	34	24 Jul 2006 (95 days)	Cerebrovascular accident Not related	23 Jul 2006 (94 days)	21 Apr 2006 - 24 Jul 2006	4.99 / 17 1.69 / 63	Anemia, cough, exophthalmos, eye pain, facial palsy, fatigue, hematuria, hypertension, joint injury, meningitis cryptococcal, pain, vomiting
211-0183	Male	52	30 Jan 2008 (658 days)	Dehydration Not related Hepatorenal syndrome Not related	29 Jan 2008 (657 days) 30 Jan 2008 (658 days)	13 Apr 2006 - 30 Jan 2008	4.05 / 145 1.69 / 212	Cyanosis, coma, confusional state, disorientation, oliguria, hypotension, dehydration, melena, vomiting, hepatorenal syndrome
211-0275	Male	28	12 Oct 2009 (1274 days)	Road traffic accident Not related	05 Oct 2009 (1267 days)	18 Apr 2006 - 7 Oct 2009	5.82 / 346 1.69 / 651	-
211-0510	Male	41	27 Jun 2006 (43 days)	Disseminated tuberculosis Not related	20 Jun 2006 (36 days)	16 May 2006 - 27 Jun 2006	5.09 / 134 2.39 / 210	Cough, diarrhea, lipoma, lower respiratory tract infection, lymphangitis, myalgia
211-0635	Male	39	17 Jan 2008 (609 days)	Death Not related	17 Jan 2008 (609 days)	19 May 2006 - 17 Jan 2008	4.93 / 218 1.69/ 404	Diarrhea, folliculitis, facial palsy, headache, fluid retention, death
211-0685	Male	63	12 Jun 2008 (751 days)	Myocardial infarction, pneumonia Doubtfully related	8 Jun 2008 (747 days)	24 May 2006 - 12 Jun 2008	5.26 / 12 1.69 / 83	Atrioventricular block 1st degree, dyspnea exertional, nausea, pruritis generalized

[a] Latest measured time point before death.
[b] Viral load : copies/mL; CD4+ cell count: x 10^6/L

Source: Listing GEN.6 (Week 96), Listing GEN.7 (Week 96), Listing SAF.1, Listing SAF.3

4.6.1.3.2 Serious Adverse Events

An overview of all SAEs in the trial is provided in Display SAF.23, and an overview of all SAEs considered at least possibly related to the PI is provided in Display SAF.33. The incidence of SAEs reported in ≥ 2 subjects in any treatment group during the treatment period is summarized in Table 42, and the incidence of SAEs considered at least possibly related to the PI during the treatment period is provided in Table 43. Individual subject data for SAEs are provided in Listing SAF.2. Narratives on the SAEs that were considered at least possibly related are provided in TMC114-C211-W192-narratives.

Overall, the incidence of SAEs was lower in the DRV/rtv group (16.0%) than in the LPV/rtv group (20.8%). By SOC, the most frequent SAEs (in ≥ 3% of subjects in any treatment group) were Infections and Infestations (4.7% and 8.4%, with DRV/rtv and LPV/rtv, respectively), and Gastrointestinal Disorders (2.6% and 4.0%). The majority of SAEs (preferred term) occurred in ≤ 2 subjects in any treatment group. SAEs occurring in > 2 subjects in any treatment group were non-cardiac chest pain (1 and 3 subjects with DRV/rtv and LPV/rtv, respectively), bronchitis (0 and 3 subjects), and hypertension (3 and 1 subjects).

Three subjects (0.9%) in the DRV/rtv group and 10 subjects (2.9%) in the LPV/rtv group had an SAE considered at least possibly related to the PI (see Table 43). Except ALT increased (which occurred in 2 LPV/rtv subjects), all SAEs considered at least possibly related to the PI occurred in only 1 subject in any treatment group.

In addition to the 11 subjects who died (see Section 4.6.1.3.1), 4 subjects in the DRV/rtv group and 11 subjects in the LPV/rtv group permanently discontinued the trial medication due to an SAE (see below). Except for the pregnancies (4 cases: 2 in each group), all these SAEs were grade 3 or 4 in severity (Listing SAF.5). For 1 subject in the DRV/rtv group and 3 subjects in the LPV/rtv group, the SAE(s) leading to permanent discontinuation were considered at least possibly related to the trial medication.

- CRF ID 211-0339 (DRV/rtv): pregnancy (not related);
- CRF ID 211-0344 (DRV/rtv): Stevens-Johnson Syndrome (grade 4, very likely related);
- CRF ID 211-0645 (DRV/rtv): pregnancy (not related);
- CRF ID 211-0760 (DRV/rtv): suicide attempt, intentional overdose (grade 4, not related);
- CRF ID 211-0177 (LPV/rtv): Hodgkin's disease (grade 4, doubtfully related);
- CRF ID 211-0234 (LPV/rtv): hepatitis acute (grade 4, doubtfully related);
- CRF ID 211-0278 (LPV/rtv): pregnancy (not related);
- CRF ID 211-0318 (LPV/rtv): transaminases increased (grade 4, possibly related);
- CRF ID 211-0458 (LPV/rtv): pregnancy (not related);
- CRF ID 211-0462 (LPV/rtv): abdominal neoplasm (grade 4, not related);
- CRF ID 211-0571 (LPV/rtv): ALT increased (grade 4, possibly related);
- CRF ID 211-0574 (LPV/rtv): ALT increased (grade 4, not related),
  AST increased (grade 4, not related),

hyperurecemia (grade 3, not related);

- CRF ID 211-0633 (LPV/rtv): transaminases increased (grade 4, not related);
- CRF ID 211-0702 (LPV/rtv): hepatitis A (grade 4, not related);
- CRF ID 211-0845 (LPV/rtv): AST increased (grade 4, possibly related); ALT increased (grade 4, possibly related);

Table 42: Serious Adverse Events Reported in ≥ 2 Subjects in any Treatment Group During the Treatment Period (Regardless of Severity or Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any SAE	***55 (16.0)***	***72 (20.8)***
Blood and Lymphatic System Disorders	**3 (0.9)**	**2 (0.6)**
Neutropenia	1 (0.3)	2 (0.6)
Cardiac Disorders	**5 (1.5)**	**6 (1.7)**
Gastrointestinal Disorders	**9 (2.6)**	**14 (4.0)**
Abdominal pain	1 (0.3)	2 (0.6)
Rectal hemorrhage	1 (0.3)	2 (0.6)
Vomiting	1 (0.3)	2 (0.6)
General Disorders and Administration Site Conditions	**5 (1.5)**	**7 (2.0)**
Non-cardiac chest pain	1 (0.3)	3 (0.9)
Pyrexia	2 (0.6)	1 (0.3)
Hepatobiliary Disorders	**2 (0.6)**	**5 (1.4)**
Infections and Infestations	**16 (4.7)**	**29 (8.4)**
Bronchitis	0	3 (0.9)
Condyloma acuminatum	0	2 (0.6)
Gastroenteritis	2 (0.6)	0
Herpes zoster	1 (0.3)	2 (0.6)
Meningitis cryptococcal	0	2 (0.6)
Pneumonia	2 (0.6)	2 (0.6)
Pulmonary tuberculosis	2 (0.6)	1 (0.3)
Secondary syphilis	2 (0.6)	0
Injury, Poisoning and Procedural Complications	**6 (1.7)**	**8 (2.3)**
Contusion	0	2 (0.6)
Rib fracture	0	2 (0.6)
Road traffic accident	1 (0.3)	2 (0.6)
Wound	0	2 (0.6)
Investigations	**2 (0.6)**	**9 (2.6)**
ALT increased	0	3 (0.9)
AST increased	0	2 (0.6)
Transaminases increased	0	2 (0.6)
Metabolism and Nutrition Disorders	**0**	**2 (0.6)**
Musculoskeletal and Connective Tissue Disorders	**2 (0.6)**	**2 (0.6)**
Intervertebral disc protrusion	2 (0.6)	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**6 (1.7)**	**4 (1.2)**
Hodgkin's disease	1 (0.3)	2 (0.6)

Table 42: Serious Adverse Events Reported in ≥ 2 Subjects in any Treatment Group During the Treatment Period (Regardless of Severity or Causality), Cont'd

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Nervous System Disorders	**4 (1.2)**	**4 (1.2)**
Cerebrovascular accident	0	2 (0.6)
Pregnancy, Puerperium and Perinatal Conditions	**2 (0.6)**	**3 (0.9)**
Pregnancy	2 (0.6)	2 (0.6)
Psychiatric Disorders	**6 (1.7)**	**3 (0.9)**
Suicide attempt	2 (0.6)	1 (0.3)
Reproductive System and Breast Disorders	**2 (0.6)**	**0**
Respiratory, Thoracic and Mediastinal Disorders	**4 (1.2)**	**4 (1.2)**
Dyspnea	1 (0.3)	2 (0.6)
Skin and Subcutaneous Tissue Disorders	**2 (0.6)**	**1 (0.3)**
Social Circumstances	**0**	**3 (0.9)**
Pregnancy of partner	0	2 (0.6)
Surgical and Medical Procedures	**1 (0.3)**	**2 (0.6)**
Vascular Disorders	**5 (1.5)**	**2 (0.6)**
Hypertension	3 (0.9)	1 (0.3)

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

Source: Display SAF.23

Table 43: Serious Adverse Events Considered at Least Possibly Related to the PI (DRV/rtv or LPV/rtv) in any Treatment Group During the Treatment Period (Regardless of Severity, Investigator-Assessed Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any SAE at least Possibly Related to the PI	***3 (0.9)***	***10 (2.9)***
Cardiac Disorders	**1 (0.3)**	**0**
Arrhythmia	1 (0.3)	0
Gastrointestinal Disorders	**1 (0.3)**	**2 (0.6)**
Diarrhea	0	1 (0.3)
Nausea	1 (0.3)	0
Pancreatitis acute	0	1 (0.3)
Vomiting	0	1 (0.3)
General Disorders and Administration Site Conditions	**1 (0.3)**	**0**
Drug interaction	1 (0.3)	0
Hepatobiliary Disorders	**0**	**1 (0.3)**
Hepatitis	0	1 (0.3)
Immune System Disorders	**0**	**1 (0.3)**
Immune reconstitution syndrome	0	1 (0.3)
Investigations	**1 (0.3)**	**5 (1.4)**
ALT increased	0	2 (0.6)
AST increased	0	1 (0.3)
Blood bilirubin increased	0	1 (0.3)
Electrocardiogram QT prolonged	1 (0.3)	0
Hepatic enzyme increased	0	1 (0.3)
Neutrophil count decreased	0	1 (0.3)
Transaminases increased	0	1 (0.3)

Table 43: Serious Adverse Events Considered at Least Possibly Related to the PI (DRV/rtv or LPV/rtv) in any Treatment Group During the Treatment Period (Regardless of Severity, Investigator-Assessed Causality), Cont'd

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Nervous System Disorders	**1 (0.3)**	**1 (0.3)**
Headache	1 (0.3)	0
Intracranial aneurysm	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	**1 (0.3)**	**1 (0.3)**
Rash	0	1 (0.3)
Stevens-Johnson syndrome	1 (0.3)	0

N = total number of subjects with data; n = number of observations
Source: Display SAF.33

4.6.1.3.3 Adverse Events Leading to Treatment Discontinuation

An overview of all AEs leading to permanent discontinuation in the trial is provided in Display SAF.28, and an overview of all AEs leading to permanent discontinuation and considered at least possibly related to the PI is provided in Display SAF.34. The incidence of AEs leading to permanent discontinuation in ≥ 2 subjects in any treatment group during the treatment period is summarized in Table 44, and the incidence of AEs leading to permanent discontinuation and considered at least possibly related to the PI in any treatment group during the treatment period is provided in Table 45. Individual subject data for AEs leading to permanent discontinuation are provided in Listing SAF.5. Narratives on the AEs leading to permanent discontinuation are provided in TMC114-C211-W192-narratives.

Overall, AEs leading to permanent discontinuation were reported less frequently in the DRV/rtv group (7.6%) compared to the LPV/rtv group (14.5%). By SOC, the most frequent AEs leading to permanent discontinuation (in ≥ 2% of subjects in any treatment group) were Pregnancy, Puerperium and Perinatal Conditions (2.6% and 1.4% with DRV/rtv and LPV/rtv, respectively), Infections and Infestations (0.9% and 2.0%), Investigations (0.6% and 2.6%), and Gastrointestinal Disorders (0.3% and 2.9%). The majority of AEs leading to permanent discontinuation (preferred term) occurred in ≤ 2 subjects in any treatment group. AEs leading to permanent discontinuation in > 2 subjects in any treatment group were pregnancy (9 and 5 subjects), ALT increased (1 and 4 subjects), AST increased (1 and 3 subjects), and diarrhea (0 and 7 subjects).

Overall, 1.7% of subjects in the DRV/rtv group and 6.6% in the LPV/rtv group had ≥ 1 AE leading to permanent discontinuation that was considered by the investigator at least possibly related to the PI. In the DRV/rtv group, all AEs leading to permanent discontinuation and considered at least possibly related occurred in only 1 subject. In the LPV/rtv group, diarrhea occurred in 7 subjects, ALT increased in 3 subjects, hypercholesterolemia, hypertriglyceridemia, and rash each in 2 subjects. No other subjects in the LPV/rtv group discontinued for the same related AE.

In addition to the 11 subjects who died (see Section 4.6.1.3.1), the AE leading to permanent discontinuation was reported as an SAE for 4 subjects in the DRV/rtv group and 11 subjects in the LPV/rtv group (see Section 4.6.1.3.2).

Table 44: Adverse Events Leading to Permanent Discontinuation in ≥ 2 Subjects in any Treatment Group During the Treatment Period (Regardless of Severity or Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any AE Leading to Permanent Discontinuation	***26 (7.6)[a,b]***	***50 (14.5)[a]***
Cardiac Disorders	**0**	**2 (0.6)**
Gastrointestinal Disorders	**1 (0.3)**	**10 (2.9)**
Diarrhea	0	7 (2.0)
Nausea	1 (0.3)	2 (0.6)
Hepatobiliary Disorders	**1 (0.3)**	**3 (0.9)**
Infections and Infestations	**3 (0.9)**	**7 (2.0)**
Hepatitis A	0	2 (0.6)
Pulmonary tuberculosis	2 (0.6)	1 (0.3)
Injury, Poisoning and Procedural Complications	**3 (0.9)**	**2 (0.6)**
Investigations	**2 (0.6)**	**9 (2.6)**
ALT increased	1 (0.3)	4 (1.2)
AST increased	1 (0.3)	3 (0.9)
Transaminases increased	0	2 (0.6)
Metabolism and Nutrition Disorders	**1 (0.3)**	**5 (1.4)**
Hypercholesterolemia	0	2 (0.6)
Hypertriglyceridemia	0	2 (0.6)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**2 (0.6)**	**3 (0.9)**
Nervous System Disorders	**0**	**3 (0.9)**
Pregnancy, Puerperium and Perinatal Conditions	**9 (2.6)**	**5 (1.4)**
Pregnancy	9 (2.6)	5 (1.4)
Skin and Subcutaneous Tissue Disorders	**4 (1.2)**	**6 (1.7)**
Rash	2 (0.6)	2 (0.6)

N = total number of subjects with data; n = number of observations
[a] Also including pregnancies (9 and 6 subjects with DRV/rtv and LPV/rtv, respectively).
[b] Including Subject 211-0837, who discontinued due to an AE in the follow-up phase.
Source: Display SAF.28

Table 45: Adverse Events Leading to Permanent Discontinuation and Considered at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity, Investigator-Assessed Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any AE Leading to Permanent Discontinuation at Least Possibly Related to the PI	***6 (1.7)***	***23 (6.6)***
Gastrointestinal Disorders	**0**	**8 (2.3)**
Abdominal pain	0	1 (0.3)
Diarrhea	0	7 (2.0)
Flatulence	0	1 (0.3)
Nausea	0	1 (0.3)
Pancreatitis	0	1 (0.3)
Hepatobiliary Disorders	**1 (0.3)**	**0**
Hepatitis	1 (0.3)	0

Table 45: Adverse Events Leading to Permanent Discontinuation and Considered at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity, Investigator-Assessed Causality), Cont'd

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Investigations	**1 (0.3)**	**5 (1.4)**
ALT increased	1 (0.3)	3 (0.9)
AST increased	1 (0.3)	1 (0.3)
Transaminases increased	0	1 (0.3)
Weight increased	0	1 (0.3)
Metabolism and Nutrition Disorders	**1 (0.3)**	**3 (0.9)**
Anorexia	1 (0.3)	0
Hypercholesterolemia	0	2 (0.6)
Hypertriglyceridemia	0	2 (0.6)
Nervous System Disorders	**0**	**2 (0.6)**
Headache	0	1 (0.3)
Paresthesia	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	**3 (0.9)**	**6 (1.7)**
Leukocytoclastic vasculitis	1 (0.3)	0
Lipoatrophy	0	1 (0.3)
Lipodystrophy acquired	0	1 (0.3)
Rash	1 (0.3)	2 (0.6)
Rash macular	0	1 (0.3)
Stevens-Johnson syndrome	1 (0.3)	0
Urticaria	0	1 (0.3)

N = total number of subjects with data; n = number of observations
Source: Display SAF.35

4.6.1.3.4 Other Adverse Events of Interest

In this section, attention is focused on AEs that 1) are considered relevant in the DRV target population, 2) are considered class effects of ARVs, or 3) were identified as being of potential importance based on earlier clinical data. These are rash-related, cardiac, GI, liver-related, lipid-related, and glucose-related AEs. Summary tables of the AEs of interest discussed in the following sections are provided in Display SAF.17.

Overviews of the incidence of all the AEs of interest in this trial described in the following sections are provided in Display SAF.8 (rash-related AEs), Display SAF.10 (cardiac AEs), Display SAF.11 (GI AEs), Display SAF.12 (pancreatic events), Display SAF.13 (liver-related AEs), Display SAF.15 (lipid-related AEs), and Display SAF.16 (glucose-metabolism-related AEs). An overview of the incidence of the AEs of interest over time is provided in Display SAF.21.

Individual subject data for AEs of interest are provided in Listing SAF.1 and Listing SAF.6.

Narratives on AEs of interest that are either SAEs or grade 3 or 4 AEs, and all other SAEs of interest if at least possibly drug related, and AEs of interest leading to discontinuation are provided in TMC114-C211-W192-narratives.

Details on laboratory abnormalities of interest are provided in Section 4.6.1.

4.6.1.3.4.1 *Rash-Related Adverse Events of Interest*

A summary table of the rash-related AEs in this trial is provided in Table 46. The incidence of rash-related AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 47 (see also Display SAF.8 and Display SAF.19, respectively). An overview of the incidence of rash-related AEs over time is provided in Table 48 and Display SAF.21. Individual subject data for rash-related AEs are provided in Listing SAF.6 and Listing SAF.1.

The incidence of rash-related AEs was 21.6% in the DRV/rtv group and 16.5% in the LPV/rtv group. The most frequent rash-related AEs (preferred term) were rash (10.2% and 8.7% with DRV/rtv and LPV/rtv, respectively), rash papular (3.8% and 1.7%), urticaria (2.0% and 1.7%), and dermatitis allergic (2.0% and 1.2%). All other rash-related AEs occurred in < 2% of subjects in any treatment group.

The incidence of rash-related AEs was highest during the first 24 weeks of treatment and decreased beyond that time point in both treatment groups.

The incidence of rash-related AEs considered at least possibly related to the PI was 5.2% in the DRV/rtv group compared to 3.2% in the LPV/rtv group. Rash (2.6% and 1.4% with DRV/rtv and LPV/rtv, respectively) was the most frequent related rash-related AE. All other rash-related AEs considered at least possibly related to the PI occurred in < 1% of subjects in any treatment group.

All except 4 rash-related AEs were grade 1 or 2 in severity.

Grade 3 rash-related AEs were reported in 3 DRV/rtv subjects: rash (CRF ID 211-0219, doubtfully related; CRF ID 211-0454, very likely related) and dermatitis allergic (CRF ID 211-0521, not related). The rash in Subject 211-0219 was considered reason for permanent discontinuation of the trial medication. The rash in Subject 211-0454 resolved following DRV/rtv dose reduction, and later, the subject discontinued DRV/rtv. The allergic dermatitis did not result in a change with respect to the investigational medication.

There was 1 grade 4 rash-related AE: Stevens Johnson syndrome (CRF ID 211-0344, DRV/rtv, very likely related). The event was reported as an SAE and was considered reason for permanent discontinuation of trial medication.

In addition, a rash-related AE was reported as an SAE in 1 LPV/rtv subject: rash (grade 2, probably related). This subject later discontinued due to grade 1 rash (probably related).

In addition, 3 subjects in the LPV/rtv group permanently discontinued treatment due to a rash-related AE: rash macular (CRF ID 211-0114, grade 2), rash (CRF ID 211-0117, grade 2; CRF ID 211-0683, grade 1), urticaria (CRF ID 211-0208, grade 2). All these AE were considered at least possibly related.

An overview of the incidence of rash-related AEs by recorded history of sulfonamide allergy is provided in Display SAF.9. In total 11 subjects (3.2%) in the DRV/rtv group and 11 (3.2%) in the LPV/rtv group had a history of sulfonamide allergy. Of these subjects, 1 in the DRV/rtv q.d. group and 2 in the DRV/rtv b.i.d. group experienced a rash-related AE.

Table 46: Rash-Related AEs: Summary Table

Rash-Related AEs, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
≥ 1 AE	74 (21.6)	57 (16.5)
≥ 1 AE with a worst grade 1	53 (15.5)	37 (10.7)
≥ 1 AE with a worst grade 2	17 (5.0)	20 (5.8)
≥ 1 AE with a worst grade 3	3 (0.9)	0
≥ 1 AE with a worst grade 4	1 (0.3)	0
≥ 1 AE at least possibly related to the PI	18 (5.2)	11 (3.2)
≥ 1 AE at least possibly related to the PI and at least grade 2	9 (2.6)	5 (1.4)
≥ 1 AE at least possibly related to the PI and at least grade 3	2 (0.6)	0
≥ 1 SAE	1 (0.3)	1 (0.3)
≥ 1 SAE and at least possibly related	1 (0.3)	1 (0.3)
≥ 1 AE leading to permanent discontinuation	3 (0.9)	4 (1.2)
≥ 1 AE leading to permanent discontinuation and at least possibly related	2 (0.6)	4 (1.2)

N = number of subjects; n = number of observations

Source: Display SAF.17

Table 47: Rash-Related Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity)

System Organ Class Preferred Term, n (%)	DRV/rtv All N = 343	DRV/rtv Related N = 343	LPV/rtv All N = 346	LPV/rtv Related N = 346
Any Rash-Related AE	***74 (21.6)***	***18 (5.2)***	***57 (16.5)***	***11 (3.2)***
Dermatitis allergic	7 (2.0)	3 (0.9)	4 (1.2)	1 (0.3)
Dermatitis bullous	1 (0.3)	0	0	0
Drug eruption	2 (0.6)	0	1 (0.3)	1 (0.3)
Eosinophilic pustular folliculitis	0	0	2 (0.6)	0
Erythema	3 (0.9)	0	2 (0.6)	0
Prurigo	4 (1.2)	0	0	0
Rash	35 (10.2)	9 (2.6)	30 (8.7)	5 (1.4)
Rash erythematous	1 (0.3)	0	2 (0.6)	0
Rash follicular	1 (0.3)	0	1 (0.3)	0
Rash macular	4 (1.2)	0	5 (1.4)	2 (0.6)
Rash maculopapular	4 (1.2)	2 (0.6)	3 (0.9)	0
Rash morbilliform	1 (0.3)	1 (0.3)	0	0
Rash papular	13 (3.8)	2 (0.6)	6 (1.7)	0
Skin exfoliation	0	0	1 (0.3)	0
Skin reaction	0	0	2 (0.6)	1 (0.3)
Stevens-Johnson syndrome	1 (0.3)	1 (0.3)	0	0
Urticaria	7 (2.0)	2 (0.6)	6 (1.7)	1 (0.3)

N = number of subjects; n = number of observations

Source: Display SAF.8, Display SAF.19

Table 48: Rash-Related Events Over Time

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
DRV/rtv														
Any Rash-Related AE	***343***	***40 (11.7)***	***321***	***4 (1.2)***	***305***	***5 (1.6)***	***296***	***4 (1.4)***	***288***	***3 (1.0)***	***276***	***2 (0.7)***	***268***	***3 (1.1)***
Dermatitis allergic	343	4 (1.2)	321	0	305	1 (0.3)	296	1 (0.3)	288	0	276	0	268	0
Dermatitis bullous	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Drug eruption	343	1 (0.3)	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Erythema	343	1 (0.3)	321	0	305	0	296	0	288	1 (0.3)	276	1 (0.4)	268	0
Prurigo	343	0	321	0	305	2 (0.7)	296	0	288	0	276	0	268	0
Rash	343	20 (5.8)	321	1 (0.3)	305	2 (0.7)	296	1 (0.3)	288	0	276	1 (0.4)	268	1 (0.4)
Rash macular	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Rash maculopapular	343	2 (0.6)	321	0	305	0	296	1 (0.3)	288	1 (0.3)	276	0	268	0
Rash morbilliform	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Rash papular	343	7 (2.0)	321	1 (0.3)	305	0	296	1 (0.3)	288	1 (0.3)	276	0	268	2 (0.7)
Stevens-Johnson syndrome	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Urticaria	343	4 (1.2)	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
LPV/rtv														
Any Rash-Related AE	***346***	***35 (10.1)***	***315***	***4 (1.3)***	***302***	***6 (2.0)***	***286***	***3 (1.0)***	***273***	***3 (1.1)***	***256***	***3 (1.2)***	***251***	***1 (0.4)***
Dermatitis allergic	346	3 (0.9)	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
Drug eruption	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Eosinophilic pustular folliculitis	346	2 (0.6)	315	0	302	0	286	0	273	0	256	0	251	0
Erythema	346	1 (0.3)	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
Rash	346	17 (4.9)	315	3 (1.0)	302	1 (0.3)	286	1 (0.3)	273	2 (0.7)	256	2 (0.8)	251	0
Rash erythematous	346	1 (0.3)	315	1 (0.3)	302	0	286	0	273	0	256	0	251	0
Rash follicular	346	0	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
Rash macular	346	2 (0.6)	315	0	302	0	286	1 (0.3)	273	0	256	0	251	0
Rash maculo-papular	346	2 (0.6)	315	0	302	0	286	0	273	0	256	1 (0.4)	251	0
Rash papular	346	4 (1.2)	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
Skin exfoliation	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Skin reaction	346	2 (0.6)	315	0	302	0	286	0	273	0	256	0	251	0
Urticaria	346	1 (0.3)	315	0	302	1 (0.3)	286	1 (0.3)	273	1 (0.4)	256	0	251	1 (0.4)

Source: Display ADD.6

4.6.1.3.4.2 *Cardiac Adverse Events of Interest*

A summary table of the cardiac AEs in this trial is provided in Table 49. The incidence of cardiac AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 50 (see also Display SAF.10 and Display SAF.19, respectively). The incidence of grade 3 or 4 cardiac AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 51 (see also Display SAF.18 and Display SAF.20, respectively). An overview of the incidence of cardiac AEs over time is provided in Table 52 and Display SAF.21. Individual subject data for cardiac AEs are provided in Listing SAF.6 and Listing SAF.1.

Cardiac AEs were reported with similar frequency in the DRV/rtv group (5.8%) and LPV/rtv group (6.1%). Heart-failure-related AEs were reported in 0.6% and 1.2% of subjects in the respective treatment groups, ischemia-related AEs in 1.5% and 1.4%, and rhythm-disturbance-related AEs in 3.8% and 4.0%. The most frequent cardiac AE by preferred term were atrioventricular block first degree and tachycardia (both in 0.3% and 1.2%, respectively), and bradycardia (0.6% and 0.9%). All other cardiac AEs occurred in ≤ 2 subjects (0.6%) in either treatment group.

There was no increase of time in the incidence of cardiac AEs.

Cardiac AEs considered at least possibly related to the PI were very in infrequent in both treatment groups (0.9% and 0.6% of subjects with DRV/rtv and LPV/rtv, respectively). All cardiac AEs considered at least possibly related to the PI except 1 (atrioventricular block first degree) occurred in only 1 subject.

Cardiac AEs were mostly grade 1 or 2 in severity.

Grade 3 cardiac AEs were reported in 2 subjects in the DRV/rtv group and 4 subjects in the LPV/rtv group: pericardial effusion (CRF ID 211-0212, DRV/rtv, doubtfully related), angina pectoris (CRF ID 211-0045, DRV/rtv, not related), right ventricular failure (CRF ID 211-0595, LPV/rtv, not related), cardiopulmonary failure (CRF ID 211-0792, LPV/rtv, not related), myocardial infarction (CRF ID 211-0685, LPV/rtv, doubtfully related) and ECG corrected QT interval prolonged (CRF ID 211-0686, LPV/rtv, doubtfully related; myocardial ischemia [no severity grading available, not related] was later also reported in this subject). The events in Subjects 211-0212, 211-0595, 211-0792, 211-0685, and 211-0686 were reported as an SAE. The event in Subjects 211-0212 led to interruption of the trial medication, and Subject 211-0685 died (pneumonia was reported as concomitant cause of death, see Section 4.6.1.3.1). The remaining events did not result in a change with respect to the investigational medication.

Grade 4 cardiac AEs were reported in 1 subject in the DRV/rtv group and 2 subjects in the LPV/rtv group: coronary artery disease and myocardial infarction (CRF ID 221-0216, DRV/rtv, not related), cardiorespiratory arrest (CRF ID 211-0005, LPV/rtv, not related; this subject died [see Section 4.6.1.3.1]), angina unstable (CRF ID 211-0269, LPV/rtv, not related). All these grade 4 events were reported as an SAE.

In addition, cardiac AEs were reported as an SAE in 2 more subjects in the DRV/rtv group: cardiac enzymes increased and myocardial ischemia (both in CRF ID 211-0418, grade 1, doubtfully related), arrhythmia and electrocardiogram QT prolonged (both in CRF ID 211-0336, grade 2, possibly related). These latter 2 events occurred in a subject who took illicit drugs during the trial (methamphetamine and GHB). No action was taken with respect to the trial medication for these events.

Table 49: Cardiac AEs: Summary Table

Cardiac AEs, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
≥ 1 AE	20 (5.8)	21 (6.1)
≥ 1 AE with a worst grade 1	14 (4.1)	11 (3.2)
≥ 1 AE with a worst grade 2	3 (0.9)	4 (1.2)
≥ 1 AE with a worst grade 3	2 (0.6)	4 (1.2)
≥ 1 AE with a worst grade 4	1 (0.3)	2 (0.6)
≥ 1 AE at least possibly related to the PI	3 (0.9)	2 (0.6)
≥ 1 AE at least possibly related to the PI and at least grade 2	2 (0.6)	0
≥ 1 AE at least possibly related to the PI and at least grade 3	0	0
≥ 1 SAE	4 (1.2)	6 (1.7)
≥ 1 SAE and at least possibly related	1 (0.3)	0
≥ 1 AE leading to permanent discontinuation	0	2 (0.6)
≥ 1 AE leading to permanent discontinuation and at least possibly related	0	0

N = number of subjects; n = number of observations

Source: Display SAF.17

Table 50: Cardiac Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity)

System Organ Class Preferred Term, n (%)	DRV/rtv All N = 343	DRV/rtv Related N = 343	LPV/rtv All N = 343	LPV/rtv Related N = 343
Any Cardiac-Related AE	***20 (5.8)***	***3 (0.9)***	***21 (6.1)***	***2 (0.6)***
Cardiac Events: Heart Failure	**2 (0.6)**	**0**	**4 (1.2)**	**0**
Cardiac murmur	1 (0.3)	0	1 (0.3)	0
Cardiomyopathy	0	0	1 (0.3)	0
Cardiopulmonary failure	0	0	1 (0.3)	0
Pericardial effusion	1 (0.3)	0	0	0
Right ventricular failure	0	0	1 (0.3)	0
Cardiac Related Events: Ischemic	**5 (1.5)**	**0**	**5 (1.4)**	**0**
Angina pectoris	1 (0.3)	0	1 (0.3)	0
Angina unstable	0	0	1 (0.3)	0
Cardiac enzymes increased	1 (0.3)	0	0	0
Coronary artery disease	1 (0.3)	0	0	0
Electrocardiogram T-wave abnormal	2 (0.6)	0	0	0
Myocardial infarction	1 (0.3)	0	1 (0.3)	0
Myocardial ischemia	1 (0.3)	0	2 (0.6)	0
Cardiac Related Events: Rhythm Disturbance	**13 (3.8)**	**3 (0.9)**	**14 (4.0)**	**2 (0.6)**
Arrhythmia	1 (0.3)	1 (0.3)	0	0
Arrhythmia supraventricular	0	0	1 (0.3)	0
Atrioventricular block first degree	1 (0.3)	0	4 (1.2)	2 (0.6)
Atrioventricular block second degree	0	0	1 (0.3)	0
Bradycardia	2 (0.6)	1 (0.3)	3 (0.9)	0
Bundle branch block right	2 (0.6)	0	0	0
Cardiorespiratory arrest	0	0	1 (0.3)	0
Electrocardiogram QT corrected interval prolonged	1 (0.3)	0	1 (0.3)	0
Electrocardiogram QT prolonged	1 (0.3)	1 (0.3)	0	0

Table 50: Cardiac Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity), Cont'd

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All N = 343	Related N = 343	All N = 343	Related N = 343
Palpitations	2 (0.6)	0	2 (0.6)	0
Sinus bradycardia	1 (0.3)	1 (0.3)	1 (0.3)	0
Sinus tachycardia	1 (0.3)	0	0	0
Tachycardia	1 (0.3)	0	4 (1.2)	0
Wolff-Parkinson-White syndrome	1 (0.3)	0	0	0

N = number of subjects; n = number of observations

Source: Display SAF.10, Display SAF.19

Table 51: Grade 3 or 4 Cardiac Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity)

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All N = 343	Related N = 343	All N = 343	Related N = 343
Any Grade 3 or 4 Cardiac-Related AE	***3 (0.9)***	***0***	***6 (1.7)***	***0***
Cardiac Events: Heart Failure	**1 (0.3)**	**0**	**2 (0.6)**	**0**
Cardiopulmonary failure	0	0	1 (0.3)	0
Pericardial effusion	1 (0.3)	0	0	0
Right ventricular failure	0	0	1 (0.3)	0
Cardiac Events: Ischemic	**2 (0.6)**	**0**	**2 (0.6)**	**0**
Angina pectoris	1 (0.3)	0	0	0
Angina unstable	0	0	1 (0.3)	0
Coronary artery disease	1 (0.3)	0	0	0
Myocardial infarction	1 (0.3)	0	1 (0.3)	0
Cardiac Events: Rhythm Disturbance	**0**	**0**	**2 (0.6)**	**0**
Cardio-respiratory arrest	0	0	1 (0.3)	0
Electrocardiogram QT corrected interval prolonged	0	0	1 (0.3)	0

N = number of subjects; n = number of observations

Source: Display SAF.18, Display SAF.20

Table 52: Cardiac Events Over Time

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
DRV/rtv														
Any Cardiac AE: Heart Failure	***343***	***40 (11.7)***	***321***	***4 (1.2)***	***305***	***5 (1.6)***	***296***	***4 (1.4)***	***288***	***3 (1.0)***	***276***	***2 (0.7)***	***268***	***3 (1.1)***
Pericardial effusion	343	0	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
Any Cardiac AE: Ischemic	***343***	***2 (0.6)***	***321***	***1 (0.3)***	***305***	***1 (0.3)***	***296***	***0***	***288***	***1 (0.3)***	***276***	***0***	***268***	***0***
Angina pectoris	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Cardiac enzymes increased	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Coronary artery disease	343	0	321	0	305	0	296	0	288	1 (0.3)	276	0	268	0
Electrocardiogram T wave abnormal	343	1 (0.3)	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
Myocardial infarction	343	0	321	0	305	0	296	0	288	1 (0.3)	276	0	268	0
Myocardial ischemia	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Any Cardiac AE: Rhythm Disturbance	***343***	***5 (1.5)***	***321***	***5 (1.6)***	***305***	***0***	***296***	***3 (1.0)***	***288***	***1 (0.3)***	***276***	***0***	***268***	***0***
Arrhythmia	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Atrioventricular block first degree	343	0	321	1 (0.3)	305	0	296	1 (0.3)	288	0	276	0	268	0
Bradycardia	343	0	321	1 (0.3)	305	0	296	1 (0.3)	288	1 (0.3)	276	0	268	0
Bundle branch block right	343	1 (0.3)	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
ECG QT corrected interval prolonged	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
ECG QT prolonged	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Palpitations	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Sinus bradycardia	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Sinus tachycardia	343	0	321	0	305	0	296	1 (0.3)	288	0	276	0	268	0
Tachycardia	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Wolff-Parkinson-White syndrome	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
LPV/rtv														
Any Cardiac AE: Heart Failure	***346***	***1 (0.3)***	***315***	***0***	***302***	***0***	***286***	***0***	***273***	***1 (0.4)***	***256***	***0***	***251***	***0***
Cardiac murmur	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Cardiopulmonary failure	346	0	315	0	302	0	286	0	273	1 (0.4)	256	0	251	0

Table 52: Cardiac Events Over Time, Cont'd

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Any Cardiac AE: Ischemic	***346***	***1 (0.3)***	***315***	***0***	***302***	***1 (0.3)***	***286***	***0***	***273***	***2 (0.7)***	***256***	***0***	***251***	***0***
Angina pectoris	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Angina unstable	346	0	315	0	302	0	286	0	273	1 (0.4)	256	0	251	0
Myocardial infarction	346	0	315	0	302	0	286	0	273	1 (0.4)	256	0	251	0
Myocardial ischaemia	346	0	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
Any Cardiac AE: Rhythm Disturbance	***346***	***4 (1.2)***	***315***	***2 (0.6)***	***302***	***4 (1.3)***	***286***	***1 (0.3)***	***273***	***4 (1.5)***	***256***	***1 (0.4)***	***251***	***0***
Arrhythmia supraventricular	346	0	315	0	302	0	286	0	273	1 (0.4)	256	0	251	0
Atrioventricular block first degree	346	3 (0.9)	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
Atrioventricular block second degree	346	0	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
Bradycardia	346	0	315	1 (0.3)	302	0	286	1 (0.3)	273	1 (0.4)	256	0	251	0
Cardiorespiratory arrest	346	0	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
ECG QT corrected interval prolonged	346	0	315	0	302	0	286	0	273	0	256	1 (0.4)	251	0
Palpitations	346	0	315	1 (0.3)	302	0	286	0	273	0	256	0	251	0
Sinus bradycardia	346	0	315	0	302	1 (0.3)	286	0	273	0	256	0	251	0
Tachycardia	346	1 (0.3)	315	0	302	0	286	0	273	2 (0.7)	256	0	251	0

Source: Display ADD.6

4.6.1.3.4.3 *GI Adverse Events of Interest*

A summary table of the GI AEs in this trial is provided in Table 53. The incidence of GI AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 54 (see also Display SAF.11 and Display SAF.19, respectively). The incidence of grade 3 or 4 GI AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 55 (see also Display SAF.18 and Display SAF.20, respectively). An overview of the incidence of GI AEs over time is provided in Table 56 and Display SAF.21. Individual subject data for GI AEs are provided in Listing SAF.6 and Listing SAF.1.

The incidence of GI AEs was lower in the DRV/rtv group (54.8%) than in the LPV/rtv group (69.4%). The most frequent GI AEs (preferred term) were diarrhea (39.4% and 54.9% with DRV/rtv and LPV/rtv, respectively), nausea (18.4% and 30.3%), abdominal pain (12.8% and 14.5%), and vomiting (8.2% and 13.3%). All other GI AEs occurred in ≤ 6% of subjects in either treatment group. Diarrhea, nausea and vomiting all occurred less frequently in the DRV/rtv group than in the LPV/rtv group, while the incidence of the other individual GI AEs was generally comparable between the treatment groups.

The incidence of GI AEs was highest during the first 24 weeks of treatment and decreased beyond that time point in both treatment groups.

The incidence of GI AEs considered at least possibly related to the PI was also lower in the DRV/rtv group (35.9%) than in the LPV/rtv group (59.2%). The most frequent GI AEs considered at least possibly related to the PI were diarrhea (24.5% and 48.6%), nausea (14.0% and 25.7%), abdominal pain (3.5% and 6.9%), and vomiting (3.2% and 8.1%). All other related GI AEs occurred in ≤ 5% of subjects in either treatment group.

GI AEs grade 3 in severity were reported in 7 (2.0%) subjects in the DRV/rtv group and 8 (2.3%) subjects in the LPV/rtv group. These grade 3 GI AEs were considered at least possibly related to the PI in 3 DRV/rtv subjects and 2 LPV/rtv subjects: diarrhea (CRF ID 221-0010, DRV/rtv, possibly related), nausea and vomiting (both in CRF ID 221-0447, DRV/rtv, possibly related), nausea (CRF ID 221-0185, DRV/rtv, probably related), abdominal pain (CRF ID 221-0249, LPV/rtv, probably related; concomitant AE was diarrhea, grade 2, probably related), nausea (CRF ID 221-0347, LPV/rtv, very likely related), and. In Subject 221-0249, the grade 3 event led to permanent treatment discontinuation, and none of the events were reported as an SAE.

Grade 4 GI AEs were reported in 1 LPV/rtv subject: diarrhea and vomiting (CRF ID 211-0234, very likely related). These events were reported as an SAE and no action with respect to the trial medication was taken (this subject later permanently discontinued treatment due to constipation and vomiting, see below).

In addition, GI AEs were reported as an SAE in 3 subjects in the DRV/rtv group and 3 subjects in the LPV/rtv group: abdominal pain (CRF ID 221-0252, DRV/rtv, grade 3, doubtfully related), diarrhea and vomiting (both in CRF ID 221-0369, DRV/rtv, grade 2, not related), and nausea (CRF ID 221-0539, DRV/rtv, grade 2, probably related), abdominal pain (CRF ID 221-0033, LPV/rtv, grade 3, not related; CRF ID 221-0536, LPV/rtv, grade 3, doubtfully related), vomiting (CRF ID 221-0183, LPV/rtv, grade 3, not related), and intestinal perforation (CRF ID 221-0527, LPV/rtv, grade 3, not related [this subject later permanently discontinued treatment due to nausea, see below]). Treatment was interrupted for the GI event in Subject 211-0536, and no action was taken with respect to the trial medication for the other events.

In addition, GI AEs led to permanent treatment discontinuation in 1 subject in the DRV/rtv group and 8 subjects in the LPV/rtv group: nausea and vomiting (both in CRF ID 221-0580, DRV/rtv, grade 2, not related), diarrhea (CRF ID 221-0017, LPV/rtv, grade 1, possibly related; CRF ID 221-0167, LPV/rtv, grade 2, probably related; CRF ID 221-0207, LPV/rtv, grade 2, very likely related; CRF ID 221-0361, LPV/rtv, grade 1, probably related; CRF ID 221-0723, LPV/rtv, grade 2, very likely related), constipation and vomiting (CRF ID 221-0234, LPV/rtv, grade 2/not related and grade 1/doubtfully related; concomitant AEs leading to permanent stop were jaundice and hepatitis acute), diarrhea, flatulence and nausea (all 3 in CRF ID 221-0463, LPV/rtv, grade 1, possibly related), nausea (CRF ID 221-0527, LPV/rtv, grade 1, doubtfully related; concomitant AE leading to discontinuation was paresthesia).

Table 53: GI AEs: Summary Table

GI AEs, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
≥ 1 AE	188 (54.8)	240 (69.4)
≥ 1 AE with a worst grade 1	129 (37.6)	163 (47.1)
≥ 1 AE with a worst grade 2	52 (15.2)	68 (19.7)
≥ 1 AE with a worst grade 3	7 (2.0)	8 (2.3)
≥ 1 AE with a worst grade 4	0	1 (0.3)
≥ 1 AE at least possibly related to the PI	123 (35.9)	205 (59.2)
≥ 1 AE at least possibly related to the PI and at least grade 2	28 (8.2)	49 (14.2)
≥ 1 AE at least possibly related to the PI and at least grade 3	3 (0.9)	3 (0.9)
≥ 1 SAE	3 (0.9)	5 (1.4)
≥ 1 SAE and at least possibly related	1 (0.3)	1 (0.3)
≥ 1 AE leading to permanent discontinuation	1 (0.3)	9 (2.6)
≥ 1 AE leading to permanent discontinuation and at least possibly related	0	7 (2.0)

N = number of subjects; n = number of observations

Source: Display SAF.17

Table 54: GI Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity)

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All N = 343	Related N = 343	All N = 346	Related N = 346
Any GI AE	***188 (54.8)***	***123 (35.9)***	***240 (69.4)***	***205 (59.2)***
Gastrointestinal Disorders	**188 (54.8)**	**123 (35.9)**	**240 (69.4)**	**205 (59.2)**
Abdominal discomfort	5 (1.5)	3 (0.9)	4 (1.2)	1 (0.3)
Abdominal distension	11 (3.2)	7 (2.0)	9 (2.6)	7 (2.0)
Abdominal pain	44 (12.8)	12 (3.5)	50 (14.5)	24 (6.9)
Abdominal tenderness	1 (0.3)	0	3 (0.9)	1 (0.3)
Bowel movement irregularity	0	0	1 (0.3)	1 (0.3)
Colitis	2 (0.6)	0	4 (1.2)	1 (0.3)
Constipation	6 (1.7)	1 (0.3)	11 (3.2)	2 (0.6)
Defecation urgency	0	0	1 (0.3)	1 (0.3)
Diarrhea	135 (39.4)	84 (24.5)	190 (54.9)	168 (48.6)
Enteritis	0	0	1 (0.3)	0
Enterocolitis	1 (0.3)	0	1 (0.3)	0
Epigastric discomfort	1 (0.3)	1 (0.3)	0	0
Fecal incontinence	0	0	2 (0.6)	0
Flatulence	13 (3.8)	8 (2.3)	19 (5.5)	16 (4.6)
Frequent bowel movements	3 (0.9)	2 (0.6)	2 (0.6)	2 (0.6)
Gastrointestinal motility disorder	0	0	1 (0.3)	1 (0.3)
Gastrointestinal pain	1 (0.3)	0	0	0
Intestinal perforation	0	0	1 (0.3)	0
Irritable bowel syndrome	0	0	2 (0.6)	1 (0.3)
Nausea	63 (18.4)	48 (14.0)	105 (30.3)	89 (25.7)
Proctitis ulcerative	1 (0.3)	0	0	0
Stomach discomfort	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
Vomiting	28 (8.2)	11 (3.2)	46 (13.3)	28 (8.1)

N = number of subjects; n = number of observations

Source: Display SAF.11, Display SAF.19

Table 55: Grade 3 or 4 GI Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All N = 343	Related N = 343	All N = 346	Related N = 346
Any Grade 3 or 4 GI AE	***7 (2.0)***	***3 (0.9)***	***9 (2.6)***	***3 (0.9)***
Gastrointestinal Disorders	**7 (2.0)**	**3 (0.9)**	**9 (2.6)**	**3 (0.9)**
Abdominal pain	2 (0.6)	0	4 (1.2)	1 (0.3)
Constipation	0	0	1 (0.3)	0
Diarrhea	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)
Intestinal perforation	0	0	1 (0.3)	0
Irritable bowel syndrome	0	0	1 (0.3)	0
Nausea	3 (0.9)	2 (0.6)	1 (0.3)	1 (0.3)
Vomiting	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)

N = number of subjects; n = number of observations

Source: Display SAF.18, Display SAF.20

Table 56: GI Adverse Events Over Time

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
DRV/rtv														
Any GI AE	***343***	***143 (41.7)***	***321***	***31 (9.7)***	***305***	***18 (5.9)***	***296***	***20 (6.8)***	***288***	***19 (6.6)***	***276***	***8 (2.9)***	***268***	***8 (3.0)***
Abdominal discomfort	343	4 (1.2)	321	0	305	0	296	1 (0.3)	288	0	276	0	268	0
Abdominal distension	343	9 (2.6)	321	1 (0.3)	305	0	296	1 (0.3)	288	0	276	0	268	1 (0.4)
Abdominal pain	343	25 (7.3)	321	4 (1.2)	305	10 (3.3)	296	4 (1.4)	288	3 (1.0)	276	2 (0.7)	268	2 (0.7)
Abdominal tenderness	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Colitis	343	0	321	0	305	1 (0.3)	296	0	288	1 (0.3)	276	0	268	0
Constipation	343	2 (0.6)	321	1 (0.3)	305	0	296	1 (0.3)	288	0	276	0	268	1 (0.4)
Diarrhea	343	96 (28.0)	321	20 (6.2)	305	7 (2.3)	296	10 (3.4)	288	11 (3.8)	276	4 (1.4)	268	1 (0.4)
Enterocolitis	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Epigastric discomfort	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Flatulence	343	6 (1.7)	321	2 (0.6)	305	1 (0.3)	296	1 (0.3)	288	0	276	1 (0.4)	268	0
Frequent bowel movements	343	1 (0.3)	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
Gastrointestinal pain	343	0	321	0	305	0	296	1 (0.3)	288	0	276	0	268	0
Nausea	343	47 (13.7)	321	7 (2.2)	305	3 (1.0)	296	2 (0.7)	288	6 (2.1)	276	1 (0.4)	268	3 (1.1)
Proctitis ulcerative	343	0	321	0	305	0	296	1 (0.3)	288	0	276	0	268	0
Stomach discomfort	343	2 (0.6)	321	0	305	0	296	0	288	0	276	0	268	0
Vomiting	343	16 (4.7)	321	4 (1.2)	305	2 (0.7)	296	2 (0.7)	288	2 (0.7)	276	0	268	3 (1.1)
LPV/rtv														
Any GI AE	***346***	***208 (60.1)***	***315***	***22 (7.0)***	***302***	***23 (7.6)***	***286***	***15 (5.2)***	***273***	***8 (2.9)***	***256***	***7 (2.7)***	***251***	***7 (2.8)***
Abdominal discomfort	346	2 (0.6)	315	1 (0.3)	302	0	286	1 (0.3)	273	0	256	0	251	0
Abdominal distension	346	7 (2.0)	315	1 (0.3)	302	0	286	1 (0.3)	273	0	256	0	251	0
Abdominal pain	346	32 (9.2)	315	5 (1.6)	302	4 (1.3)	286	3 (1.0)	273	1 (0.4)	256	2 (0.8)	251	1 (0.4)
Abdominal tenderness	346	3 (0.9)	315	0	302	0	286	0	273	0	256	0	251	0
Bowel movement irregularity	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Colitis	346	1 (0.3)	315	0	302	1 (0.3)	286	0	273	0	256	1 (0.4)	251	0
Constipation	346	6 (1.7)	315	1 (0.3)	302	1 (0.3)	286	1 (0.3)	273	1 (0.4)	256	0	251	0
Defecation urgency	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Diarrhea	346	160 (46.2)	315	10 (3.2)	302	15 (5.0)	286	6 (2.1)	273	3 (1.1)	256	5 (2.0)	251	4 (1.6)
Enteritis	346	0	315	1 (0.3)	302	0	286	0	273	0	256	0	251	0
Enterocolitis	346	0	315	1 (0.3)	302	0	286	0	273	0	256	0	251	0
Flatulence	346	13 (3.8)	315	2 (0.6)	302	1 (0.3)	286	1 (0.3)	273	1 (0.4)	256	0	251	0

Table 56: GI Adverse Events Over Time, Cont'd

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Frequent bowel movements	346	2 (0.6)	315	0	302	0	286	0	273	0	256	0	251	0
Gastrointestinal motility disorder	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Intestinal perforation	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Irritable bowel syndrome	346	2 (0.6)	315	0	302	0	286	0	273	0	256	0	251	0
Nausea	346	88 (25.4)	315	2 (0.6)	302	3 (1.0)	286	1 (0.3)	273	1 (0.4)	256	0	251	1 (0.4)
Stomach discomfort	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Vomiting	346	37 (10.7)	315	3 (1.0)	302	1 (0.3)	286	3 (1.0)	273	3 (1.1)	256	0	251	1 (0.4)

Source: Display ADD.6

4.6.1.3.4.4 *Pancreatic Adverse Events of Interest*

A summary table of the pancreatic AEs in this trial is provided in Table 61. The incidence of liver-related AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 62 (see also Display SAF.12 and Display SAF.19, respectively). The incidence of grade 3 or 4 pancreatic AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 63 (see also Display SAF.18 and Display SAF.20, respectively). An overview of the incidence of pancreatic AEs over time is provided in Table 60 and Display SAF.21. Individual subject data for pancreatic AEs are provided in Listing SAF.6 and Listing SAF.1.

Pancreatic AEs were reported with similar frequency in the DRV/rtv group (3.2%) and LPV/rtv group (3.8%). Pancreatic AEs were most frequently of the SOC Investigations: blood amylase increased (2.3% in both treatment groups), and lipase increased (0.9% and 1.4% with DRV/rtv and LPV/rtv, respectively). All other pancreatic AEs occurred in < 1% of subjects in either treatment group.

There was no increase of time in the incidence of pancreatic AEs.

Pancreatic AEs considered by the investigator at least possibly related to the PI (DRV/rtv or LPV/rtv) were reported in 1.2% of subjects in both treatment groups. The most frequent pancreatic AEs considered at least possibly related to the PI were blood amylase increased (1.2% and 0.6% with DRV/rtv and LPV/rtv, respectively), and lipase increased (0.6% and 0.3%). All other related pancreatic AEs occurred in < 1 subject in either treatment group.

Grade 3 pancreatic AEs were reported in 8 (2.3%) subjects in both treatment groups. These grade 3 or 4 pancreatic AEs were considered at least possibly related to the PI in 4 DRV/rtv subjects and 2 LPV/rtv subjects: blood amylase increased (CRF ID 221-0083, DRV/rtv, possibly related; CRF ID 221-0218, DRV/rtv, possibly related; CRF ID 221-0749, DRV/rtv, possibly related; CRF ID 221-0040, LPV/rtv, probably related), lipase increased (CRF ID 221-0409, LPV/rtv, grade 3, possibly related), and both blood amylase increased and lipase increased (CRF ID 211-0140, DRV/rtv, possibly related).

A grade 4 pancreatic AE was reported in 1 LPV/rtv subject: lipase increased (CRF ID 211-0201, doubtfully related). This subject had concomitantly blood amylase increased (grade 3; doubtfully related). Both events were reported as an SAE. Treatment was interrupted for lipase increased.

In addition, pancreatic SAEs were reported in 1 subject in the DRV/rtv group and 1 subject in the LPV/rtv group: pancreatitis (CRF ID 211-0548, DRV/rtv, grade 2, doubtfully related), and pancreatitis acute (CRF ID 211-0585, LPV/rtv, grade 2, possibly related).

No subjects permanently discontinued the trial medication due to a pancreatic-related grade 3 or 4 AE. However, 1 subject in the LPV/rtv group (CRF ID 211-0099) permanently discontinued trial medication due to grade 2 pancreatitis (possibly related).

Table 57: Pancreatic AEs: Summary Table

Pancreatic AEs, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
≥ 1 AE	11 (3.2)	13 (3.8)
≥ 1 AE with a worst grade 1	2 (0.6)	1 (0.3)
≥ 1 AE with a worst grade 2	1 (0.3)	3 (0.9)
≥ 1 AE with a worst grade 3	8 (2.3)	8 (2.3)
≥ 1 AE with a worst grade 4	0	1 (0.3)
≥ 1 AE at least possibly related to the PI	4 (1.2)	4 (1.2)
≥ 1 AE at least possibly related to the PI and at least grade 2	4 (1.2)	4 (1.2)
≥ 1 AE at least possibly related to the PI and at least grade 3	4 (1.2)	2 (0.6)
≥ 1 SAE	1 (0.3)	2 (0.6)
≥ 1 SAE and at least possibly related	0	1 (0.3)
≥ 1 AE leading to permanent discontinuation	0	1 (0.3)
≥ 1 AE leading to permanent discontinuation and at least possibly related	0	1 (0.3)

N = number of subjects; n = number of observations
Source: Display SAF.17

Table 58: Pancreatic Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity)

System Organ Class Preferred Term, n (%)	DRV/rtv All N = 343	DRV/rtv Related N = 343	LPV/rtv All N = 346	LPV/rtv Related N = 346
Any Pancreatic AE	***11 (3.2)***	***4 (1.2)***	***13 (3.8)***	***4 (1.2)***
Gastrointestinal Disorders	**3 (0.9)**	**0**	**2 (0.6)**	**2 (0.6)**
Pancreatitis	3 (0.9)	0	1 (0.3)	1 (0.3)
Pancreatitis acute	0	0	1 (0.3)	1 (0.3)
Investigations	**8 (2.3)**	**4 (1.2)**	**10 (2.9)**	**2 (0.6)**
Blood amylase increased	8 (2.3)	4 (1.2)	8 (2.3)	2 (0.6)
Lipase increased	3 (0.9)	2 (0.6)	5 (1.4)	1 (0.3)
Metabolism and Nutrition Disorders	**0**	**0**	**1 (0.3)**	**0**
Hyperamylasemia	0	0	1 (0.3)	0

N = number of subjects; n = number of observations
Source: Display SAF.12, Display SAF.19

Table 59: Grade 3 or 4 Pancreatic Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period

System Organ Class Preferred Term, n (%)	DRV/rtv All N = 343	DRV/rtv Related N = 343	LPV/rtv All N = 346	LPV/rtv Related N = 346
Any Grade 3 or 4 Pancreatic AE	***8 (2.3)***	***4 (1.2)***	***9 (2.6)***	***2 (0.6)***
Gastrointestinal Disorders	**1 (0.3)**	**0**	**0**	**0**
Pancreatitis	1 (0.3)	0	0	0
Investigations	**7 (2.0)**	**4 (1.2)**	**8 (2.3)**	**2 (0.6)**
Blood amylase increased	7 (2.0)	4 (1.2)	7 (2.0)	1 (0.3)
Lipase increased	1 (0.3)	1 (0.3)	3 (0.9)	1 (0.3)
Metabolism and Nutrition Disorders	**0**	**0**	**1 (0.3)**	**0**
Hyperamylasemia	0	0	1 (0.3)	0

N = number of subjects; n = number of observations
Source: Display SAF.18, Display SAF.20

Table 60: Pancreatic Events Over Time

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
DRV/rtv														
Any Pancreatic AE	***343***	***6 (1.7)***	***321***	***1 (0.3)***	***305***	***0***	***296***	***2 (0.7)***	***288***	***2 (0.7)***	***276***	***1 (0.4)***	***268***	***2 (0.7)***
Blood amylase increased	343	5 (1.5)	321	0	305	0	296	2 (0.7)	288	2 (0.7)	276	1 (0.4)	268	2 (0.7)
Lipase increased	343	0	321	0	305	0	296	1 (0.3)	288	1 (0.3)	276	1 (0.4)	268	1 (0.4)
Pancreatitis	343	1 (0.3)	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
LPV/rtv														
Any Pancreatic AE	***346***	***6 (1.7)***	***315***	***2 (0.6)***	***302***	***1 (0.3)***	***286***	***1 (0.3)***	***273***	***0***	***256***	***0***	***251***	***4 (1.6)***
Blood amylase increased	346	4 (1.2)	315	0	302	1 (0.3)	286	1 (0.3)	273	0	256	0	251	3 (1.2)
Hyperamylasemia	346	0	315	1 (0.3)	302	0	286	0	273	0	256	0	251	0
Lipase increased	346	2 (0.6)	315	1 (0.3)	302	1 (0.3)	286	0	273	0	256	0	251	2 (0.8)
Pancreatitis	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Pancreatitis acute	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0

Source: Display ADD.6

4.6.1.3.4.5 *Liver-Related Adverse Events of Interest*

A summary table of the liver-related AEs in this trial is provided in Table 61. The incidence of liver-related AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 62 (see also Display SAF.13 and Display SAF.19, respectively). The incidence of grade 3 or 4 liver-related AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 63 (see also Display SAF.18 and Display SAF.20, respectively). An overview of the incidence of liver-related AEs over time is provided in Table 64 and Display SAF.21. Individual subject data for liver-related AEs are provided in Listing SAF.6 and Listing SAF.1.

Liver-related AEs were reported less frequently in the DRV/rtv group (7.6%) than in the LPV/rtv group (14.5%). The most frequent liver-related AEs (preferred term) were AST increased (2.9% and 5.2%), and ALT increased (2.6% and 5.8%). All other liver-related AEs occurred in ≤ 2% of subjects in either treatment group.

The incidence of liver-related AEs was fairly constant over time for the DRV/rtv group. For the LPV/rtv group, the incidence of liver-related AEs was highest during the first 24 weeks of treatment and decrease beyond that time point.

Liver-related AEs considered at least possibly related to the PI were reported in 2.9% of subjects in the DRV/rtv group and in 5.2% of subjects in the LPV/rtv group. The most frequent liver-related AEs (preferred term) at least possibly related to the PI were ALT increased (1.7% and 3.5%), and AST increased (1.2% and 2.9%). All other liver-related AEs considered at least possibly related to the PI occurred in ≤ 1% of subjects in either treatment group.

Grade 3 or 4 liver-related AEs were reported in 5.0% of subjects in the DRV/rtv group and 7.8% of subjects in the LPV/rtv group. These events were most frequently AST increased (2.0% in both groups), and ALT increased (1.5% and 2.6% with DRV/rtv and LPV/rtv, respectively). All other grade 3 or 4 liver-related AEs occurred in < 1% of subjects. In 2.3% and 3.2% of subjects, respectively, grade 3 or 4 liver-related AEs were considered at least possibly related to the PI.

In 2 DRV/rtv subjects and 10 LPV/rtv subjects grade 3 or 4 liver-related AEs were reported as an SAE: ascites (CRF ID 211-0371, DRV/rtv, grade 3, doubtfully related), cholecystitis acute and cholelithiasis (both in CRF ID 211-0835, DRV/rtv, grade 3, not related); hepatorenal syndrome (CRF ID 211-0183, LPV/rtv, grade 3, not related), hepatitis acute (CRF ID 211-0234, LPV/rtv, grade 4, doubtfully related), transaminases increased (CRF ID 211-0318, grade 4, possibly related; in addition, hepatitis, grade 2, possibly related was reported as an SAE in this subject), cholecystitis chronic (CRF ID 211- 0474, LPV/rtv, grade 3, not related), hepatitis A (CRF ID 211-0702, LPV/rtv, grade 4, not related), blood bilirubin increased and hepatic enzyme increased (CRF ID 0448, LPV/rtv, grade 3 and grade 4, respectively, both possibly related [this subject later permanently discontinued due to the AE hepatotoxicity, see below]); ALT increased (CRF ID 211-0571, LPV/rtv, grade 4, possibly related), ALT increased and ALT increased (CRF ID 211-0574, LPV/rtv, grade 4, not related; CRF ID 211-0845, LPV/rtv, grade 4, possibly related), transaminases increased (CRF ID 211-0633, LPV/rtv, grade 4, not related). In 8 LPV/rtv subjects (CRF ID 211-0183, 211-0234, 211-0702, 211-0318, 211-0571, 211-0574, 211-0633, and 211-0845), treatment was permanently discontinued due to the SAEs.

In addition, liver-related AEs led to permanent treatment discontinuation in 3 DRV/rtv subjects and 5 LPV/rtv subjects: hepatitis (CRF ID 221-0080, DRV/rtv, grade 3, probably related); blood

bilirubin increased and hepatic enzyme increased (both in CRF ID 221-0255, DRV/rtv, grade 4, not related), ALT increased and AST increased (both in CRF ID 221-0340, DRV/rtv, grade 3 and grade 4, respectively, probably related), hepatitis A (CRF ID 221-0013, LPV/rtv, grade 3, not related), hepatitis C (CRF ID 221-0237, LPV/rtv, grade 2, not related), AST increased (CRF ID 221-0390, LPV/rtv, grade 4, doubtfully related), hepatotoxicity (CRF ID 211-0448, LPV/rtv, grade 3, doubtfully related), ALT increased (CRF ID 221-0610, LPV/rtv, grade 4, possibly related).

Table 61: Liver-Related AEs: Summary Table

Liver-Related AEs, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
≥ 1 AE	26 (7.6)	50 (14.5)
≥ 1 AE with a worst grade 1	7 (2.0)	7 (2.0)
≥ 1 AE with a worst grade 2	2 (0.6)	16 (4.6)
≥ 1 AE with a worst grade 3	13 (3.8)	15 (4.3)
≥ 1 AE with a worst grade 4	4 (1.2)	12 (3.5)
≥ 1 AE at least possibly related to the PI	10 (2.9)	18 (5.2)
≥ 1 AE at least possibly related to the PI and at least grade 2	9 (2.6)	16 (4.6)
≥ 1 AE at least possibly related to the PI and at least grade 3	8 (2.3)	11 (3.2)
≥ 1 SAE	2 (0.6)	10 (2.9)
≥ 1 SAE and at least possibly related	0	4 (1.2)
≥ 1 AE leading to permanent discontinuation	3 (0.9)	13 (3.8)
≥ 1 AE leading to permanent discontinuation and at least possibly related	2 (0.6)	4 (1.2)

N = number of subjects; n = number of observations

Source: Display SAF.17

Table 62: Liver-Related Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity)

System Organ Class Preferred Term, n (%)	DRV/rtv All N = 343	DRV/rtv Related N = 343	LPV/rtv All N = 346	LPV/rtv Related N = 346
Any Liver-Related AE	***26 (7.6)***	***10 (2.9)***	***50 (14.5)***	***18 (5.2)***
Gastrointestinal Disorders	**1 (0.3)**	**0**	**0**	**0**
Ascites	1 (0.3)	0	0	0
Hepatobiliary Disorders	**6 (1.7)**	**2 (0.6)**	**12 (3.5)**	**1 (0.3)**
Biliary colic	0	0	1 (0.3)	0
Cholecystitis acute	1 (0.3)	0	0	0
Cholecystitis chronic	1 (0.3)	0	1 (0.3)	0
Cholelithiasis	1 (0.3)	0	1 (0.3)	0
Hepatic pain	0	0	1 (0.3)	0
Hepatic steatosis	2 (0.6)	0	1 (0.3)	0
Hepatitis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Hepatitis acute	0	0	1 (0.3)	0
Hepatocellular damage	1 (0.3)	1 (0.3)	0	0
Hepatomegaly	0	0	2 (0.6)	0
Hepatorenal syndrome	0	0	1 (0.3)	0
Hepatotoxicity	0	0	1 (0.3)	0
Hyperbilirubinemia	0	0	2 (0.6)	0
Liver tenderness	1 (0.3)	0	2 (0.6)	0

Table 62: Liver-Related Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity), Cont'd

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All N = 343	Related N = 343	All N = 346	Related N = 346
Infections and Infestations	**0**	**0**	**8 (2.3)**	**1 (0.3)**
Hepatitis A	0	0	2 (0.6)	0
Hepatitis C	0	0	6 (1.7)	1 (0.3)
Investigations	**20 (5.8)**	**8 (2.3)**	**36 (10.4)**	**17 (4.9)**
ALT increased	9 (2.6)	6 (1.7)	20 (5.8)	12 (3.5)
AST increased	10 (2.9)	4 (1.2)	18 (5.2)	10 (2.9)
Blood alkaline phosphatase increased	1 (0.3)	0	6 (1.7)	2 (0.6)
Blood bilirubin increased	1 (0.3)	0	4 (1.2)	1 (0.3)
Gamma-glutamyltransferase increased	1 (0.3)	0	1 (0.3)	0
Hepatic enzyme increased	3 (0.9)	1 (0.3)	4 (1.2)	2 (0.6)
Liver function test abnormal	1 (0.3)	1 (0.3)	2 (0.6)	0
Transaminases increased	3 (0.9)	1 (0.3)	3 (0.9)	1 (0.3)

N = number of subjects; n = number of observations

Source: Display SAF.13, Display SAF.19

Table 63: Grade 3 or 4 Liver-Related Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All N = 343	Related N = 343	All N = 346	Related N = 346
Any Grade 3 or 4 Liver-Related AE	***17 (5.0)***	***8 (2.3)***	***27 (7.8)***	***11 (3.2)***
Gastrointestinal Disorders	**1 (0.3)**	**0**	**0**	**0**
Ascites	1 (0.3)	0	0	0
Hepatobiliary Disorders	**2 (0.6)**	**1 (0.3)**	**4 (1.2)**	**0**
Cholecystitis acute	1 (0.3)	0	0	0
Cholecystitis chronic	0	0	1 (0.3)	0
Cholelithiasis	1 (0.3)	0	0	0
Hepatitis	1 (0.3)	1 (0.3)	0	0
Hepatitis acute	0	0	1 (0.3)	0
Hepatorenal syndrome	0	0	1 (0.3)	0
Hepatotoxicity	0	0	1 (0.3)	0
Infections and Infestations	**0**	**0**	**4 (1.2)**	**1 (0.3)**
Hepatitis A	0	0	2 (0.6)	0
Hepatitis C	0	0	2 (0.6)	1 (0.3)
Investigations	**14 (4.1)**	**7 (2.0)**	**20 (5.8)**	**10 (2.9)**
ALT increased	5 (1.5)	4 (1.2)	9 (2.6)	6 (1.7)
AST increased	7 (2.0)	4 (1.2)	7 (2.0)	4 (1.2)
Blood alkaline phosphatase increased	0	0	1 (0.3)	0
Blood bilirubin increased	1 (0.3)	0	2 (0.6)	1 (0.3)
Gamma-glutamyltransferase increased	1 (0.3)	0	0	0
Hepatic enzyme increased	3 (0.9)	1 (0.3)	2 (0.6)	2 (0.6)
Liver function test abnormal	0	0	2 (0.6)	0
Transaminases increased	1 (0.3)	1 (0.3)	3 (0.9)	1 (0.3)

N = number of subjects; n = number of observations

Source: Display SAF.18, Display SAF.20

Table 64: Liver-Related Adverse Events Over Time

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
DRV/rtv														
Any Liver-Related AE: Clinical	***343***	***1 (0.3)***	***321***	***2 (0.6)***	***305***	***1 (0.3)***	***296***	***1 (0.3)***	***288***	***0***	***276***	***0***	***268***	***0***
Ascites	343	1 (0.3)	321	0	305	0	296	0	288	0	276	0	268	0
Cholecystitis acute	343	0	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
Cholecystitis chronic	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Cholelithiasis	343	0	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
Hepatic steatosis	343	0	321	0	305	0	296	1 (0.3)	288	0	276	0	268	0
Hepatitis	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Any Liver-Related AE: Lab	***343***	***8 (2.3)***	***321***	***4 (1.2)***	***305***	***3 (1.0)***	***296***	***2 (0.7)***	***288***	***2 (0.7)***	***276***	***2 (0.7)***	***268***	***3 (1.1)***
ALT increased	343	4 (1.2)	321	3 (0.9)	305	1 (0.3)	296	0	288	1 (0.3)	276	0	268	2 (0.7)
AST increased	343	3 (0.9)	321	4 (1.2)	305	0	296	1 (0.3)	288	1 (0.3)	276	1 (0.4)	268	2 (0.7)
Blood alkaline phosphatase increased	343	0	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
Blood bilirubin increased	343	0	321	0	305	0	296	1 (0.3)	288	0	276	0	268	0
Gamma-glutamyltransferase increased	343	0	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
Hepatic enzyme increased	343	2 (0.6)	321	0	305	0	296	1 (0.3)	288	0	276	0	268	0
Liver function test abnormal	343	0	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
Transaminases increased	343	1 (0.3)	321	0	305	0	296	0	288	1 (0.3)	276	1 (0.4)	268	0
LPV/rtv														
Any Liver-Related AE: Clinical	***346***	***6 (1.7)***	***315***	***4 (1.3)***	***302***	***0***	***286***	***2 (0.7)***	***273***	***0***	***256***	***1 (0.4)***	***251***	***2 (0.8)***
Biliary colic	346	0	315	0	302	0	286	0	273	0	256	0	251	1 (0.4)
Cholecystitis chronic	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Cholelithiasis	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Hepatic steatosis	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Hepatitis	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Hepatitis A	346	0	315	1 (0.3)	302	0	286	1 (0.3)	273	0	256	0	251	0
Hepatitis acute	346	0	315	1 (0.3)	302	0	286	0	273	0	256	0	251	0
Hepatitis C	346	3 (0.9)	315	2 (0.6)	302	0	286	0	273	0	256	0	251	0
Hepatomegaly	346	0	315	0	302	0	286	0	273	0	256	1 (0.4)	251	1 (0.4)
Hepatorenal syndrome	346	0	315	0	302	0	286	1 (0.3)	273	0	256	0	251	0

Table 64: Liver-Related Adverse Events Over Time, Cont'd

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Any Liver-Related AE: Lab	***346***	***19 (5.5)***	***315***	***7 (2.2)***	***302***	***4 (1.3)***	***286***	***3 (1.0)***	***273***	***5 (1.8)***	***256***	***5 (2.0)***	***251***	***3 (1.2)***
ALT increased	346	11 (3.2)	315	2 (0.6)	302	2 (0.7)	286	2 (0.7)	273	3 (1.1)	256	3 (1.2)	251	2 (0.8)
AST increased	346	9 (2.6)	315	1 (0.3)	302	2 (0.7)	286	2 (0.7)	273	2 (0.7)	256	4 (1.6)	251	2 (0.8)
Blood alkaline phosphatase increased	346	1 (0.3)	315	2 (0.6)	302	1 (0.3)	286	0	273	0	256	0	251	1 (0.4)
Blood bilirubin increased	346	0	315	1 (0.3)	302	0	286	0	273	0	256	1 (0.4)	251	0
Gamma-glutamyltransferase increased	346	0	315	0	302	0	286	0	273	1 (0.4)	256	0	251	0
Hepatic enzyme increased	346	2 (0.6)	315	1 (0.3)	302	1 (0.3)	286	0	273	0	256	0	251	0
Hyperbilirubinemia	346	2 (0.6)	315	1 (0.3)	302	0	286	0	273	1 (0.4)	256	0	251	0
Liver function test abnormal	346	1 (0.3)	315	1 (0.3)	302	0	286	0	273	0	256	0	251	0
Transaminases increased	346	3 (0.9)	315	0	302	0	286	0	273	0	256	0	251	0

Source: Display ADD.6

The incidence of liver-related clinical AEs during the treatment period by hepatitis B or C coinfection status at baseline is summarized in Table 65. An overview of the incidence of all liver-related AEs by hepatitis coinfection status in this trial is provided in Display SAF.14. A total of 12.5% of subjects in the DRV/rtv q.d. group and 13.9% of subjects in the DRV/rtv b.i.d. group were coinfected with hepatitis B or C virus at baseline (see Table 6).

In both treatment groups, the overall incidence of liver-related AEs was higher in subjects with hepatitis B or C coinfection (16.3% and 43.8% with DRV/rtv and LPV/rtv, respectively) than in subjects not coinfected with hepatitis B or C virus (6.3% and 9.7%). In both treatment groups, the incidence of increased ALT and increased AST was higher in subjects with coinfection than in subjects without coinfection. The incidence of ALT increased and AST increased was lower in DRV/rtv-treated subjects with coinfection than in LPV/rtv-treated subjects with coinfection (14.0% versus 27.1% for ALT; 9.3% versus 27.1% for AST). There was no relevant difference in the incidence of these events between not-coinfected subjects of both treatment groups, or between the treatment groups.

Table 65: Liver-Related Adverse Events During the Treatment Period by Hepatitis Coinfection Status (Regardless of Severity or Causality)

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	Coinfected N = 43	Not-Coinfected N = 300	Coinfected N = 48	Not-Coinfected N = 298
Any Liver-Related AE	***7 (16.3)***	***19 (6.3)***	***21 (43.8)***	***29 (9.7)***
Gastrointestinal Disorders	**1 (2.3)**	**0**	**0**	**0**
Ascites	1 (2.3)	0	0	0
Hepatobiliary Disorders	**0**	**6 (2.0)**	**4 (8.3)**	**8 (2.7)**
Biliary colic	0	0	0	1 (0.3)
Cholecystitis acute	0	1 (0.3)	0	0
Cholecystitis chronic	0	1 (0.3)	0	1 (0.3)
Cholelithiasis	0	1 (0.3)	0	1 (0.3)
Hepatic pain	0	0	1 (2.1)	0
Hepatic steatosis	0	2 (0.7)	0	1 (0.3)
Hepatitis	0	1 (0.3)	1 (2.1)	0
Hepatitis acute	0	0	0	1 (0.3)
Hepatocellular damage	0	1 (0.3)	0	0
Hepatomegaly	0	0	1 (2.1)	1 (0.3)
Hepatorenal syndrome	0	0	0	1 (0.3)
Hepatotoxicity	0	0	1 (2.1)	0
Hyperbilirubinemia	0	0	1 (2.1)	1 (0.3)
Liver tenderness	0	1 (0.3)	1 (2.1)	1 (0.3)
Infections and Infestations	**0**	**0**	**4 (8.3)**	**4 (1.3)**
Hepatitis A	0	0	0	2 (0.7)
Hepatitis C	0	0	4 (8.3)	2 (0.7)
Investigations	**6 (14.0)**	**14 (4.7)**	**17 (35.4)**	**19 (6.4)**
ALT increased	6 (14.0)	3 (1.0)	13 (27.1)	7 (2.3)
AST increased	4 (9.3)	6 (2.0)	13 (27.1)	5 (1.7)
Blood alkaline phosphatase increased	0	1 (0.3)	1 (2.1)	5 (1.7)
Blood bilirubin increased	0	1 (0.3)	1 (2.1)	3 (1.0)
Gamma-glutamyltransferase increased	0	1 (0.3)	0	1 (0.3)
Hepatic enzyme increased	0	3 (1.0)	2 (4.2)	2 (0.7)
Liver function test abnormal	0	1 (0.3)	1 (2.1)	1 (0.3)
Transaminases increased	0	3 (1.0)	3 (6.3)	0

N = number of subjects; n = number of observations

Source: Display GEN.12 (Week 96), Display SAF.14

4.6.1.3.4.6 *Lipid-Related Adverse Events of Interest*

A summary table of the lipid-related AEs in this trial is provided in Table 66. The incidence of lipid-related AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 67 (see also Display SAF.15 and Display SAF.19, respectively). The incidence of grade 3 or 4 lipid-related AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 68 (see also Display SAF.18 and Display SAF.20, respectively). An overview of the incidence of lipid-related AEs over time is provided in Table 69 and Display SAF.21. Individual subject data for lipid-related AEs are provided in Listing SAF.6 and Listing SAF.1.

Lipid-related AEs were reported less frequently in the DRV/rtv group (12.5%) than in the LPV/rtv group (19.1%). The most frequent lipid-related AEs (preferred term) were LDL increased (4.1% and 2.0%), hypercholesterolemia (3.8% and 6.6%), blood cholesterol increased

(2.6% and 2.0%), hypertriglyceridemia (2.3% and 8.4%), and hyperlipidemia (2.0% and 4.0%). All other lipid-related AEs occurred in < 1% of subjects in the DRV/rtv and/or LPV/rtv treatment groups.

The incidence of lipid-related AEs was fairly constant over time for the DRV/rtv group. For the LPV/rtv group, the incidence of lipid-related AEs was highest during the first 24 weeks of treatment and decrease beyond that time point.

Lipid-related AEs considered at least possibly related to the PI were also reported less frequently in the DRV/rtv group (9.3%) than in the LPV/rtv group (16.5%). The most frequent lipid-related AEs (preferred term) at least possibly related to the PI were LDL increased (3.2% and 2.0%), hypercholesterolemia (2.9% and 5.8%), hypertriglyceridemia (2.0% and 7.5%), blood cholesterol increased (2.0% and 1.4%), and hyperlipidemia (1.2% and 3.8%). All other lipid-related AEs occurred in < 1% of subjects in the DRV/rtv and/or LPV/rtv treatment groups.

Grade 3 or 4 lipid-related AEs were reported in 5.5% of subjects in the DRV/rtv group and 7.2% of subjects in the LPV/rtv group. These events were most frequently LDL increased (3.2% and 1.4%), and hypertriglyceridemia (1.5% and 3.5%), hypercholesterolemia (0.6% and 2.0%). In 4.7% and 6.6% of subjects, respectively, these grade 3 or 4 lipid-related events were considered at least possibly related to the PI; this occurred most frequently for the AEs LDL increased (2.3% and 1.4%), hypertriglyceridemia (1.5% and 3.2%), and hypercholesterolemia (0.6% and 1.7%).

In 3 LPV/rtv subjects, lipid-related AEs led to permanent treatment discontinuation: hypercholesterolemia (CRF ID 221-0127, grade 2, very likely related), hypercholesterolemia and hypertriglyceridemia (both in CRF ID 221-0361, grade 1 and 2, respectively, probably related; concomitant AE leading to discontinuation was diarrhea, grade 1, probably related), hyperlipidemia and hypertriglyceridemia (both in CRF ID 221-0599, grade 3, possibly related). No lipid-related AEs in the DRV/rtv group led to permanent treatment discontinuation.

No lipid-related AEs were reported as an SAE.

Table 66: Lipid-Related AEs: Summary Table

Lipid-Related AEs, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
≥ 1 AE	43 (12.5)	66 (19.1)
≥ 1 AE with a worst grade 1	7 (2.0)	13 (3.8)
≥ 1 AE with a worst grade 2	17 (5.0)	28 (8.1)
≥ 1 AE with a worst grade 3	18 (5.2)	22 (6.4)
≥ 1 AE with a worst grade 4	1 (0.3)	3 (0.9)
≥ 1 AE at least possibly related to the PI	32 (9.3)	57 (16.5)
≥ 1 AE at least possibly related to the PI and at least grade 2	27 (7.9)	47 (13.6)
≥ 1 AE at least possibly related to the PI and at least grade 3	16 (4.7)	23 (6.6)
≥ 1 SAE	0	0
≥ 1 SAE and at least possibly related	0	0
≥ 1 AE leading to permanent discontinuation	0	3 (0.9)
≥ 1 AE leading to permanent discontinuation and at least possibly related	0	3 (0.9)

N = number of subjects; n = number of observations

Source: Display SAF.1

Table 67: Lipid-Related Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity)

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All **N = 343**	**Related** **N = 343**	**All** **N = 346**	**Related** **N = 346**
Any Lipid-Related AE	***43 (12.5)***	***32 (9.3)***	***66 (19.1)***	***57 (16.5)***
Congenital, Familial and Genetic Disorders	**1 (0.3)**	**1 (0.3)**	**0**	**0**
Mixed hyperlipidemia	1 (0.3)	1 (0.3)	0	0
Investigations	**19 (5.5)**	**13 (3.8)**	**17 (4.9)**	**14 (4.0)**
Apolipoprotein α-I	0	0	1 (0.3)	0
Blood cholesterol increased	9 (2.6)	7 (2.0)	7 (2.0)	5 (1.4)
Blood triglycerides increased	2 (0.6)	1 (0.3)	3 (0.9)	3 (0.9)
Lipids increased	0	0	1 (0.3)	1 (0.3)
LDL increased	14 (4.1)	11 (3.2)	7 (2.0)	7 (2.0)
Metabolism and Nutrition Disorders	**26 (7.6)**	**19 (5.5)**	**57 (16.5)**	**51 (14.7)**
Dyslipidemia	0	0	2 (0.6)	1 (0.3)
Hypercholesterolemia	13 (3.8)	10 (2.9)	23 (6.6)	20 (5.8)
Hyperlipidemia	7 (2.0)	4 (1.2)	14 (4.0)	13 (3.8)
Hypertriglyceridemia	8 (2.3)	7 (2.0)	29 (8.4)	26 (7.5)

N = number of subjects; n = number of observations

Source: Display SAF.15, Display SAF.19

Table 68: Grade 3 or 4 Lipid-Related Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All **N = 343**	**Related** **N = 343**	**All** **N = 346**	**Related** **N = 346**
Any Grade 3 or 4 Lipid-Related AE	***19 (5.5)***	***16 (4.7)***	***25 (7.2)***	***23 (6.6)***
Investigations	**12 (3.5)**	**8 (2.3)**	**9 (2.6)**	**9 (2.6)**
Blood cholesterol increased	1 (0.3)	0	2 (0.6)	2 (0.6)
Blood triglycerides increased	0	0	2 (0.6)	2 (0.6)
LDL increased	11 (3.2)	8 (2.3)	5 (1.4)	5 (1.4)
Metabolism and Nutrition Disorders	**8 (2.3)**	**8 (2.3)**	**19 (5.5)**	**17 (4.9)**
Hypercholesterolemia	2 (0.6)	2 (0.6)	7 (2.0)	6 (1.7)
Hyperlipidemia	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Hypertriglyceridemia	5 (1.5)	5 (1.5)	12 (3.5)	11 (3.2)

N = number of subjects; n = number of observations

Source: Display SAF.18, Display SAF.20

Table 69: Lipid-Related Adverse Events Over Time

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
DRV/rtv														
Any Lipid-Related AE	***343***	***10 (2.9)***	***321***	***4 (1.2)***	***305***	***10(3.3)***	***296***	***4 (1.4)***	***288***	***7 (2.4)***	***276***	***9 (3.3)***	***268***	***6 (2.2)***
Blood cholesterol increased	343	1 (0.3)	321	0	305	1 (0.3)	296	3 (1.0)	288	1 (0.3)	276	1 (0.4)	268	2 (0.7)
Blood triglycerides increased	343	2 (0.6)	321	0	305	0	296	0	288	0	276	0	268	0
Hypercholesterolemia	343	2 (0.6)	321	2 (0.6)	305	2 (0.7)	296	0	288	1 (0.3)	276	5 (1.8)	268	2 (0.7)
Hyperlipidemia	343	3 (0.9)	321	1 (0.3)	305	1 (0.3)	296	0	288	2 (0.7)	276	1 (0.4)	268	1 (0.4)
Hypertriglyceridemia	343	1 (0.3)	321	1 (0.3)	305	3 (1.0)	296	1 (0.3)	288	1 (0.3)	276	1 (0.4)	268	0
LDL increased	343	2 (0.6)	321	1 (0.3)	305	3 (1.0)	296	1 (0.3)	288	3 (1.0)	276	2 (0.7)	268	4 (1.5)
Mixed hyperlipidemia	343	0	321	0	305	1 (0.3)	296	0	288	0	276	0	268	0
LPV/rtv														
Any Lipid-Related AE	***346***	***32 (9.2)***	***315***	***9 (2.9)***	***302***	***13 (4.3)***	***286***	***11 (3.8)***	***273***	***13 (4.8)***	***256***	***6 (2.3)***	***251***	***9 (3.6)***
Apolipoprotein α-I	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
Blood cholesterol increased	346	3 (0.9)	315	1 (0.3)	302	1 (0.3)	286	0	273	1 (0.4)	256	1 (0.4)	251	1 (0.4)
Blood triglycerides increased	346	2 (0.6)	315	0	302	0	286	1 (0.3)	273	1 (0.4)	256	0	251	0
Dyslipidemia	346	2 (0.6)	315	0	302	0	286	0	273	0	256	0	251	0
Hypercholesterolemia	346	4 (1.2)	315	2 (0.6)	302	4 (1.3)	286	5 (1.7)	273	4 (1.5)	256	2 (0.8)	251	6 (2.4)
Hyperlipidemia	346	5 (1.4)	315	4 (1.3)	302	4 (1.3)	286	0	273	2 (0.7)	256	0	251	1 (0.4)
Hypertriglyceridemia	346	17 (4.9)	315	3 (1.0)	302	4 (1.3)	286	5 (1.7)	273	5 (1.8)	256	3 (1.2)	251	1 (0.4)
Lipids increased	346	1 (0.3)	315	0	302	0	286	0	273	0	256	0	251	0
LDL increased	346	1 (0.3)	315	1 (0.3)	302	2 (0.7)	286	1 (0.3)	273	1 (0.4)	256	0	251	2 (0.8)

Source: Display ADD.6

4.6.1.3.4.7 *Glucose-Related Adverse Events of Interest*

A summary table of the glucose-related AEs in this trial is provided in Table 70. The incidence of glucose -related AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 71 (see also Display SAF.16 and Display SAF.19, respectively). The incidence of grade 3 or 4 glucose -related AEs (overall and at least possibly related to the PI) during the treatment period is summarized in Table 72 (see also Display SAF.18 and Display SAF.20, respectively). An overview of the incidence of glucose-related AEs over time is provided in Table 73 and Display SAF.21. Individual subject data for lipid-related AEs are provided in Listing SAF.6 and Listing SAF.1.

Glucose-related AEs were reported in 5.2% of subjects in the DRV/rtv group and 2.6% in the LPV/rtv group. The most frequent glucose-related AEs (preferred term) were blood glucose increased and hyperglycemia (both in 1.5% and 0.3% with DRV/rtv and LPV/rtv, respectively). All other glucose-related AEs occurred in ≤ 2 subjects in either treatment group.

There was no increase of time in the incidence of glucose-related AEs.

Glucose-related AEs considered at least possibly related to the PI reported in 1.2% of subjects in both treatment groups. All glucose-related AEs (preferred term) at least possibly related to the PI occurred in only 1 subject.

Grade 3 glucose-related AEs were reported in 3 DRV/rtv subjects and 1 LPV/rtv subject: blood glucose increased (CRF ID 211-0216, DRV/rtv, not related ; CRF ID 211-0079, LPV/rtv, doubtfully related) diabetes mellitus (CRF ID 221-0002, DRV/rtv, possibly related), and hyperglycemia (CRF ID 221-0517, DRV/rtv, not related).

There were no grade 4 glucose-related AEs in this trial.

No glucose-related AEs were reported as an SAE and none led to permanent treatment discontinuation.

Table 70: Glucose-Related AEs: Summary Table

Glucose-Related AEs, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
≥ 1 AE	18 (5.2)	9 (2.6)
≥ 1 AE with a worst grade 1	9 (2.6)	2 (0.6)
≥ 1 AE with a worst grade 2	6 (1.7)	6 (1.7)
≥ 1 AE with a worst grade 3	3 (0.9)	1 (0.3)
≥ 1 AE with a worst grade 4	0	0
≥ 1 AE at least possibly related to the PI	4 (1.2)	4 (1.2)
≥ 1 AE at least possibly related to the PI and at least grade 2	1 (0.3)	3 (0.9)
≥ 1 AE at least possibly related to the PI and at least grade 3	1 (0.3)	0
≥ 1 SAE	0	0
≥ 1 SAE and at least possibly related	0	0
≥ 1 AE leading to permanent discontinuation	0	0
≥ 1 AE leading to permanent discontinuation and at least possibly related	0	0

N = number of subjects; n = number of observations

Source: Display SAF.17

Table 71: Glucose-Related Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period (Regardless of Severity)

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All N = 343	Related N = 343	All N = 346	Related N = 346
Any Glucose-Related AE	***18 (5.2)***	***4 (1.2)***	***9 (2.6)***	***4 (1.2)***
Investigations	**7 (2.0)**	**0**	**2 (0.6)**	**0**
Blood glucose fluctuation	0	0	1 (0.3)	0
Blood glucose increased	5 (1.5)	0	1 (0.3)	0
Blood insulin increased	2 (0.6)	0	0	0
Metabolism and Nutrition Disorders	**11 (3.2)**	**4 (1.2)**	**5 (1.4)**	**3 (0.9)**
Diabetes mellitus	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
Diabetes mellitus non-insulin-dependent	2 (0.6)	1 (0.3)	0	0
Glucose tolerance impaired	0	0	1 (0.3)	1 (0.3)
Hyperglycemia	5 (1.5)	1 (0.3)	1 (0.3)	1 (0.3)
Hyperinsulinism	1 (0.3)	0	0	0
Hypoglycemia	1 (0.3)	1 (0.3)	1 (0.3)	0
Insulin-requiring type II diabetes mellitus	1 (0.3)	0	0	0
Renal and Urinary Disorders	**0**	**0**	**2 (0.6)**	**1 (0.3)**
Glycosuria	0	0	2 (0.6)	1 (0.3)

N = number of subjects; n = number of observations

Source: Display SAF.16, Display SAF.19

Table 72: Grade 3 or 4 Glucose-Related Adverse Events Overall and at Least Possibly Related to the PI During the Treatment Period

System Organ Class Preferred Term, n (%)	DRV/rtv		LPV/rtv	
	All N = 343	Related N = 343	All N = 346	Related N = 346
Any Grade 3 or 4 Glucose-Related AE	***3 (0.9)***	***1 (0.3)***	***1 (0.3)***	***0***
Investigations	**1 (0.3)**	**0**	**1 (0.3)**	**0**
Blood glucose increased	1 (0.3)	0	1 (0.3)	0
Metabolism and Nutrition Disorders	**2 (0.6)**	**1 (0.3)**	**0**	**0**
Diabetes mellitus non-insulin-dependent	1 (0.3)	1 (0.3)	0	0
Hyperglycemia	1 (0.3)	0	0	0

N = number of subjects; n = number of observations

Source: Display SAF.18, Display SAF.20

Table 73: Glucose-Related Adverse Events Over Time

Preferred Term, n (%)	0 - 24 Weeks		25 - 48 Weeks		49 - 96 Weeks		97 - 120 Weeks		121 - 144 Weeks		145 - 168 Weeks		169 - 192 Weeks	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
DRV/rtv														
Any Glucose-Related AE	***343***	***1 (0.3)***	***321***	***4 (1.2)***	***305***	***1 (0.3)***	***296***	***4 (1.4)***	***288***	***3 (1.0)***	***276***	***1 (0.4)***	***268***	***2 (0.7)***
Blood glucose increased	343	0	321	1 (0.3)	305	0	296	2 (0.7)	288	3 (1.0)	276	0	268	0
Diabetes mellitus	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Diabetes mellitus noninsulin-dependent	343	0	321	1 (0.3)	305	0	296	1 (0.3)	288	0	276	0	268	0
Hyperglycemia	343	1 (0.3)	321	0	305	1 (0.3)	296	0	288	0	276	1 (0.4)	268	2 (0.7)
Hyperinsulinism	343	0	321	1 (0.3)	305	0	296	0	288	0	276	0	268	0
Hypoglycemia	343	0	321	0	305	0	296	1 (0.3)	288	0	276	0	268	0
LPV/rtv														
Any Glucose-Related AE	***346***	***0***	***315***	***1 (0.3)***	***302***	***1 (0.3)***	***286***	***1 (0.3)***	***273***	***1 (0.4)***	***256***	***1 (0.4)***	***251***	***1 (0.4)***
Blood glucose increased	346	0	315	0	302	0	286	0	273	0	256	0	251	1 (0.4)
Diabetes mellitus	346	0	315	0	302	1 (0.3)	286	0	273	1 (0.4)	256	0	251	0
Glycosuria	346	0	315	0	302	0	286	1 (0.3)	273	0	256	1 (0.4)	251	0
Hyperglycemia	346	0	315	1 (0.3)	302	0	286	0	273	0	256	0	251	0

Source: Display ADD.6

4.6.2 Clinical Laboratory Evaluation

In this section, attention is focused on laboratory parameters that 1) are considered relevant in the DRV target population, 2) are considered class effects of ARVs, or 3) were identified as being of potential importance based on earlier clinical data. They are:

- liver-related parameters: ALT, AST, total, direct and indirect bilirubin;
- lipid- and glucose-related parameters: triglycerides, total cholesterol, LDL and LDL cholesterol, glucose (increase only);
- general biochemistry parameters: pancreatic amylase, lipase, creatinine;
- hematology parameters: PT, PTT, hematocrit, hemoglobin, and counts for RBC, WBC, platelet, lymphocytes, and neutrophils.

Descriptive statistics of the actual values of the laboratory parameters measured in this trial are provided in Display SAF.42. Descriptive statistics for the within-subject changes versus baseline are provided in Display SAF.43.

Overviews of the graded and nongraded laboratory abnormalities in this trial are provided in Display SAF.46 and Display SAF.47, respectively. Only treatment-emergent abnormalities, i.e., those abnormalities that first occurred or worsened after the start of the treatment period, are reported.

Detailed descriptions of laboratory test abnormalities reported as adverse events of interest are provided in Sections 0 through 4.6.1.3.4.6.

4.6.2.1 Liver-Related Laboratory Parameters

4.6.2.1.1 Liver-Related Laboratory Parameters Over Time

Mean changes versus baseline at Week 192 for the selected liver-related parameters of interest are summarized in Table 74. For an extensive overview of the descriptive statistics for the changes in liver-related parameters measured in this trial, see Display SAF.43.

A mean decrease versus baseline at Week 192 was observed for AST and ALT in both treatment groups; for both parameters, this decrease was slightly smaller in the DRVV/rtv group than in the LPV/rtv group. For total, direct and indirect bilirubin, there was a mean increase versus baseline in both treatment groups; these mean changes were generally small.

Table 74: Mean Changes From Baseline at Week 192 for Selected Liver-Related Parameters

	DRV/rtv				LPV/rtv			
Laboratory Parameter	N	Baseline	N	Mean Change (SE)	N	Baseline	N	Mean Change (SE)
ALT (U/L)	343	34.2	253	-2.6 (1.85)	346	35.3	228	-5.5 (2.31)
AST (U/L)	343	34.6	253	-4.9 (1.21)	346	34.9	228	-7.3 (1.65)
Total bilirubin (µmol/L)	343	7.8	253	0.6 (0.26)	346	8.0	228	2.0 (0.33)
Direct bilirubin (µmol/L)	343	2.1	252	0.1 (0.07)	346	2.1	226	0.4 (0.08)
Indirect bilirubin (µmol/L)	343	5.7	252	0.5 (0.21)	346	5.9	226	1.5 (0.26)

N = number of subjects

Source: Display SAF.42, Display SAF.43

4.6.2.1.2 Incidence of Liver-Related Laboratory Abnormalities

The incidence of graded (worst grade) and non-graded laboratory abnormalities for the selected liver-related parameters of interest are summarized in Table 75 and Table 76, respectively. For an extensive overview of the liver-related laboratory abnormalities reported in this trial, see Display SAF.46 and Display SAF.47. An overview of the incidence of liver-related laboratory abnormalities over time is provided in Display SAF.50 and Display SAF.51. Individual subject data on liver-related laboratory parameters for subjects with a grade 3 or 4 liver-related laboratory abnormality are provided in Listing SAF.10.

The majority of liver-related laboratory abnormalities were grade 1 or 2.

The most frequent liver-related laboratory abnormalities were increases in ALT and AST. Grade 2 to 4 ALT abnormalities were observed in 12.6% of DRV/rtv subjects and 15.8% of LPV/rtv subjects, and grade 2 to 4 AST abnormalities in 12.9% and 14.9% of subjects, respectively.

Grade 1 hyperbilirubinemia (increase in total bilirubin) was observed less frequently in the DRV/rtv group (2.3%) than in the LPV/rtv group (7.6%). Grade 2 or 3 hyperbilirubinemia was observed in 4 (1.2%) DRV/rtv subjects and 19 (5.5%) LPV/rtv subjects. Grade 4 hyperbilirubinemia was not observed in either treatment group. Direct bilirubin above normal was observed in 0.9% of DRV/rtv subjects and 5.8% of LPV/rtv subjects. Indirect bilirubin above normal was observed in 0.9% DRV/rtv subjects and 7.9% LPV/rtv subjects.

Table 75: Treatment-Emergent Liver-Related Laboratory Abnormalities of Interest (Worst Grade)

Laboratory Parameter Worst Grade, n (%)	DRV/rtv	LPV/rtv
ALT, N	**342**	**342**
Grade 1	57 (16.7)	44 (12.9)
Grade 2	30 (8.8)	32 (9.4)
Grade 3	10 (2.9)	12 (3.5)
Grade 4	3 (0.9)	10 (2.9)
AST, N	**342**	**342**
Grade 1	43 (12.6)	42 (12.3)
Grade 2	25 (7.3)	34 (9.9)
Grade 3	15 (4.4)	8 (2.3)
Grade 4	4 (1.2)	9 (2.6)
Hyperbilirubinemia, N	**342**	**343**
Grade 1	8 (2.3)	26 (7.6)
Grade 2	3 (0.9)	16 (4.7)
Grade 3	1 (0.3)	3 (0.9)
Grade 4	0	0

N = number of subjects; n = number of observations
Source: Display SAF.46

Table 76: Non-Graded Treatment-Emergent Liver-Related Laboratory Abnormalities of Interest

Laboratory Parameter, Abnormality, n (%)	DRV/rtv	LPV/rtv
Direct bilirubin, N	**342**	**342**
Above	3 (0.9)	20 (5.8)
Below	0	0
Indirect bilirubin, N	**342**	**342**
Above	3 (0.9)	27 (7.9)
Below	0	0

N = number of subjects; n = number of observations
Source: Display SAF.47

The incidence of liver-related laboratory abnormalities of interest during the treatment period by hepatitis B or C coinfection status is summarized in Table 77. An extensive overview of these liver-related laboratory abnormalities by hepatitis coinfection status is provided in Display SAF.49. It should be noted that, as the number of coinfected subjects was low in both treatment groups, conclusions should be drawn with caution.

In both treatment groups, the incidence of increased AST and ALT in subjects coinfected with hepatitis B or C virus was higher than in not-coinfected subjects, but lower with DRV/rtv compared to LPV/rtv. The incidence of grade 2 to 4 ALT elevations in coinfected subjects was 39.5% with DRV/rtv and 62.5% with LPV/rtv. A similar difference between the treatment groups was seen in the incidence of grade 2 to AST elevations in these subjects; 30.2% with DRV/rtv and 52.1% with LPV/rtv. Grade 4 increases in ALT and AST were not observed in DRV/rtv subjects with coinfection, but were seen in 12.5% and 10.4%, respectively, of LPV/rtv subjects with coinfection.

In both treatment groups, the incidence of hyperbilirubinemia was comparable in coinfected subjects and not-coinfected subjects. In both coinfected subjects and not-coinfected subjects, hyperbilirubinemia was less frequent with DRV/rtv than with LPV/rtv.

Table 77: Treatment-Emergent Liver-Related Laboratory Abnormalities of Interest (Worst Grade) by Hepatitis B or C Coinfection Status

Laboratory Parameter	DRV/rtv		LPV/rtv	
Worst Grade, n (%)	Coinfected N = 43	Not Coinfected N = 299	Coinfected N = 48	Not Coinfected N = 295
ALT, N	**29 (67.4)**	**71 (23.7)**	**38 (79.2)**	**60 (20.3)**
Grade 1	12 (27.9)	45 (15.1)	8 (16.7)	36 (12.2)
Grade 2	11 (25.6)	19 (6.4)	16 (33.3)	16 (5.4)
Grade 3	6 (14.0)	4 (1.3)	8 (16.7)	4 (1.4)
Grade 4	0	3 (1.0)	6 (12.5)	4 (1.4)
AST, N	**24 (55.8)**	**63 (21.1)**	**33 (68.8)**	**60 (20.3)**
Grade 1	11 (25.6)	32 (10.7)	8 (16.7)	34 (11.5)
Grade 2	7 (16.3)	18 (6.0)	16 (33.3)	18 (6.1)
Grade 3	6 (14.0)	9 (3.0)	4 (8.3)	4 (1.4)
Grade 4	0	4 (1.3)	5 (10.4)	4 (1.4)
Hyperbilirubinemia, N	**2 (4.7)**	**10 (3.3)**	**6 (12.5)**	**39 (13.2)**
Grade 1	2 (4.7)	6 (2.0)	2 (4.2)	24 (8.1)
Grade 2	0	3 (1.0)	3 (6.3)	13 (4.4)
Grade 3	0	1 (0.3)	1 (2.1)	2 (0.7)
Grade 4	0	0	0	0

N = number of subjects; n = number of observations

Source: Display SAF.49

4.6.2.2 LIPID-AND GLUCOSE-RELATED LABORATORY PARAMETERS

4.6.2.2.1 Lipid- and Glucose-Related Laboratory Parameters Over Time

Mean changes versus baseline at Week 192 for the selected lipid- and glucose-related parameters of interest are summarized in Table 78. For an extensive overview of the descriptive statistics for the changes in lipid- and glucose-related parameters measured in this trial, see Display SAF.43.

LDL was determined by the method of Friedewald et al.[33] (see Section 3.6.7.2).

A small mean increase versus baseline at Week 192 was observed for all lipid-related parameters. For triglycerides, the mean increase was less pronounced for the DRV/rtv group than for the LPV/rtv group. The mean changes for total cholesterol, HDL and LDL (calculated) cholesterol (LDLc) were comparable for both treatment groups.

The mean change in glucose was small and identical for both treatment groups.

Table 78: Mean Changes From Baseline at Week 192 for Selected Lipid-Related Parameters

Laboratory Parameter	DRV/rtv				LPV/rtv			
	N	Baseline	N	Mean Change (SE)	N	Baseline	N	Mean Change (SE)
Triglycerides (mmol/L)	343	1.5	254	0.1 (0.06)	346	1.4	228	0.8 (0.08)
Total cholesterol (mmol/L)	343	4.0	254	0.7 (0.06)	346	4.1	228	1.0 (0.06)
LDLc[a] cholesterol (mmol/L)	343	1.0	254	0.2 (0.02)	346	1.0	227	0.3 (0.02)
HDL cholesterol (mmol/L)	339	2.4	250	0.4 (0.05)	345	2.4	215	0.4 (0.05)
Glucose (mmol/L)	343	5.0	253	0.2 (0.06)	346	5.0	228	0.2 (0.08)

N = number of subjects
[a] LDL determined by the method of Friedewald et al.[33].
Source: Display SAF.42, Display SAF.43

4.6.2.2.2 Incidence of Lipid- and Glucose-Related Laboratory Abnormalities

The incidence of graded (worst grade) and non-graded laboratory abnormalities for the selected lipid- and glucose-related parameters of interest are summarized in Table 79 and Table 80, respectively. For an extensive overview of the lipid- and glucose-related laboratory abnormalities reported in this trial, see Display SAF.46 and Display SAF.47. An overview of the incidence of lipid- and glucose-related laboratory abnormalities over time is provided in Display SAF.50 and Display SAF.51. Individual subject data on lipid-and glucose-related laboratory parameters for subjects with a grade 3 or 4 lipid- and glucose-related laboratory abnormality are provided in Listing SAF.11.

Lipid-related laboratory abnormalities were commonly observed in both treatment groups. The majority of lipid-related laboratory abnormalities were grade 1 or 2.

The most frequent lipid-related laboratory abnormality was increased total cholesterol. Grade 2 and 3 increased total cholesterol was less frequent in the DRV/rtv group (24.3%) than in the LPV/rtv group (32.7%). Grade 3 increased total cholesterol was observed in 1.5% of subjects in the DRV/rtv group and 5.5% in the LPV/rtv group.

Grade 2 to 4 increases in triglycerides were also less frequent in the DRV/rtv group (5.9%) than in the LPV/rtv group (16.0%). Grade 3 or 4 increases in triglycerides were observed in 3.2% of subjects in the DRV/rtv group and 6.1% in the LPV/rtv group.

There were no relevant differences between the treatment groups with respect to LDLc or HDL,. Grade 2 or 3 increases in LDLc cholesterol were observed in 22.9% of subjects in the DRV/rtv group and 18.4% in the LPV/rtv group. Grade 3 increases in LDLc were observed in 8.8% with DRV/rtv and 6.1% with LPV/rtv. HDL cholesterol below normal was observed in 22.3% of subjects in the DRV/rtv group and 22.7% in the LPV/rtv group.

There were no relevant differences between the treatment groups with respect to glucose-metabolism-related laboratory abnormalities. Most glucose-related abnormalities were grade 1 or 2. Grade 2 or 3 hyperglycemia was observed in 12.0% of subjects in the DRV/rtv group and 9.9% in the LPV/rtv group (no grade 4 hyperglycemia was observed). Grade 3 hyperglycemia was observed in 1.2% with DRV/rtv and in 0.3% with LPV/rtv.

There was no evidence of an increased incidence over time of lipid-related laboratory abnormalities.

Table 79: Treatment-Emergent Lipid-Related Laboratory Abnormalities of Interest (Worst Grade)

Laboratory Parameter Worst Grade, n (%)	DRV/rtv	LPV/rtv
Triglycerides, N	**341**	**343**
Grade 1	NA	NA
Grade 2	9 (2.6)	34 (9.9)
Grade 3	6 (1.8)	17 (5.0)
Grade 4	5 (1.5)	4 (1.2)
Total cholesterol, N	**341**	**343**
Grade 1	103 (30.2)	98 (28.6)
Grade 2	78 (22.9)	93 (27.1)
Grade 3	5 (1.5)	19 (5.5)
Grade 4	NA	NA
LDLc, N	**341**	**342**
Grade 1	82 (24.0)	81 (23.7)
Grade 2	48 (14.1)	42 (12.3)
Grade 3	30 (8.8)	21 (6.1)
Grade 4	NA	NA
Hyperglycemia, N	**342**	**343**
Grade 1	49 (14.3)	53 (15.5)
Grade 2	37 (10.8)	33 (9.6)
Grade 3	4 (1.2)	1 (0.3)
Grade 4	0	0

N = number of subjects; n = number of observations

[a] LDL determined by the method of Friedewald et al.[33].

Source: Display SAF.46

Table 80: Non-Graded Treatment-Emergent Lipid-Related Laboratory Abnormalities of Interest

Laboratory Parameter, Abnormality, n (%)	DRV/rtv	LPV/rtv
HDL, N	**341**	**343**
Above	39 (11.4)	70 (20.4)
Below	76 (22.3)	78 (22.7)

N = number of subjects; n = number of observations

Source: Display SAF.47

4.6.2.2.3 Lipid-Related Laboratory Abnormalities According to the NCEP Criteria

The incidence of treatment-emergent abnormalities for the selected lipid-related parameters of interest according to the NCEP criteria[37] is summarized in Table 81. For an extensive overview, see Display SAF.48. An overview over time of the selected lipid-related parameters of interest according to the NCEP criteria is provided in Display SAF.52.

The incidence of abnormally high triglycerides and abnormally high total cholesterol, based on the NCEP criteria was lower in the DRV/rtv group than in the LPV/rtv group (triglycerides: 45.2% and 58.8%, respectively; total cholesterol: 46.3% and 53.8%, respectively). A similar proportion of subjects in both groups received lipid-modifying drugs: in the DRV/rtv group,

2.6% of subjects received lipid-modifying drugs at screening, and 11.7% during the trial; in the LPV/rtv group, these proportions were respectively 2.3% and 14.2% (see Display GEN.7 and Table 10).

There was no relevant difference between the treatment groups with respect to the incidence of abnormally high LDLc levels or abnormally low HDL.

Graphical presentations of the mean changes over time for the selected parameters of interest triglycerides, total cholesterol, LDLc, and HDL are provided in Figure 14 through Figure 16. Mean triglycerides levels in the DRV/rtv group remained within the normal limits at most time points throughout the trial, while in the LPV/rtv group, levels were above the limits of the normal range as early as Week 2 and remained elevated throughout. The mean levels of total cholesterol remained within the normal limits of the NCEP criteria at all time points for both treatment groups, with lower mean levels for the DRV/rtv group compared to the LPV/rtv group. The mean LDL cholesterol levels were comparable for both treatment groups and remained within the normal limits of the NCEP criteria for both treatment groups. Mean HDL levels in both treatment groups increased over the course of the trial and were above the limits of the normal range by Week 8 of the trial, remaining elevated throughout.

Table 81: NCEP Treatment-Emergent Lipid-Related Laboratory Abnormalities of Interest

Toxicity, n (%)	**DRV/rtv N = 341**	**LPV/rtv N = 342**
Triglycerides abnormally high (≥150 mg/dL)	154 (45.2)	201 (58.8)
Total cholesterol abnormally high (≥ 200 mg/dL)	158 (46.3)	184 (53.8)
LDLc[a] abnormally high (≥ 130 mg/dL)	131 (38.4)	125 (36.7)
HDL abnormally low (≤ 40 mg/dL for males, ≤ 50 mg/dL for females)	74 (21.7)	70 (20.5)

N = number of subjects

[a] LDL determined by the method of Friedewald et al.[33].

Source: Display SAF.48

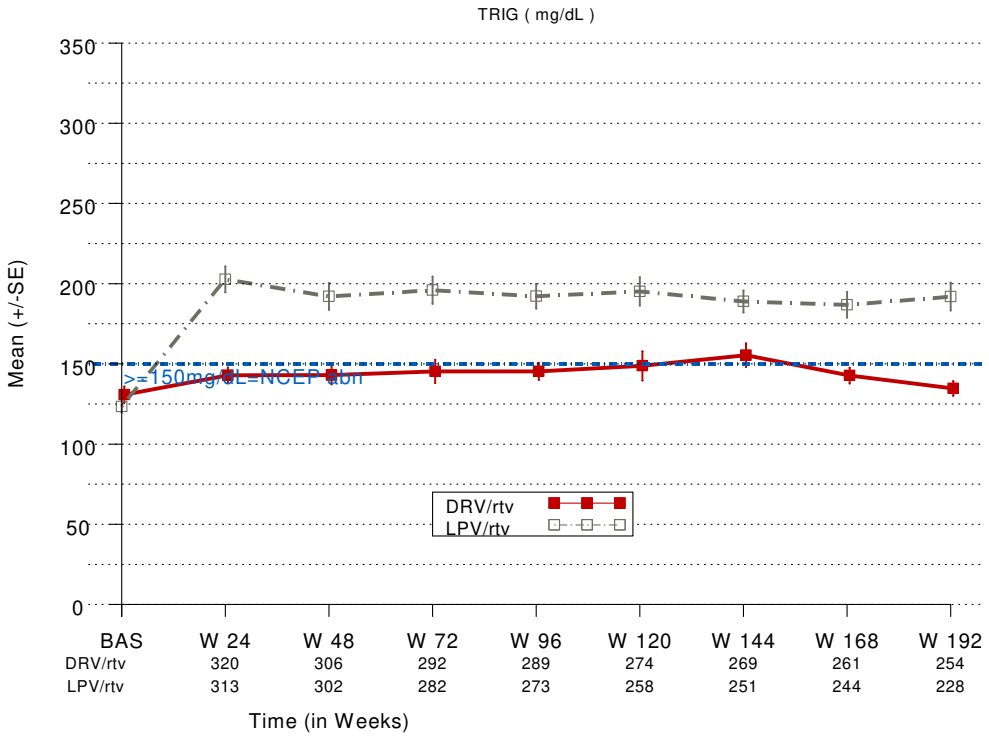


Figure 13: Mean Triglycerides (mg/dL) Over Time

Source: Display SAF.42

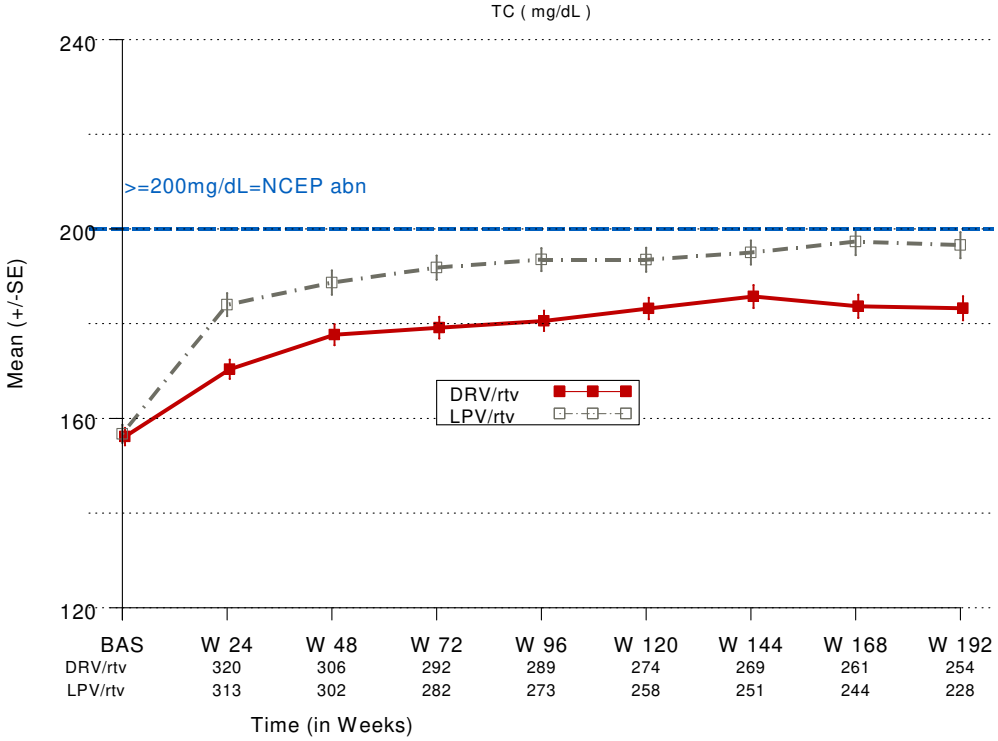


Figure 14: Mean Total Cholesterol (mg/dL) Over Time

Source: Display SAF.42

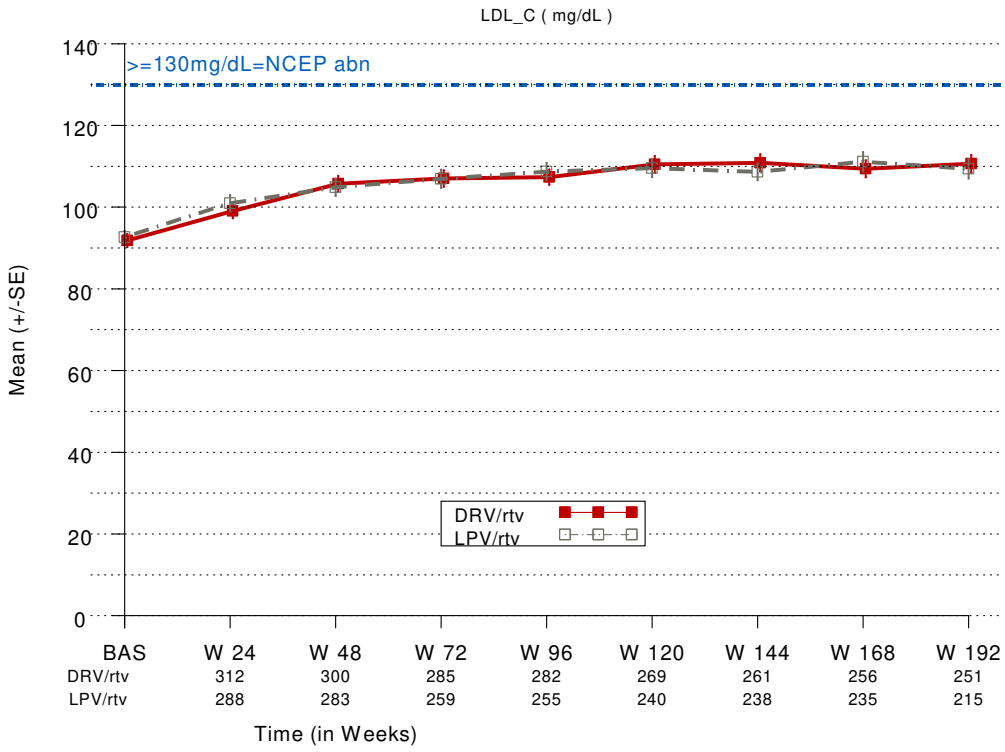


Figure 15: Mean LDLc (mg/dL) Over Time

Source: Display SAF.42

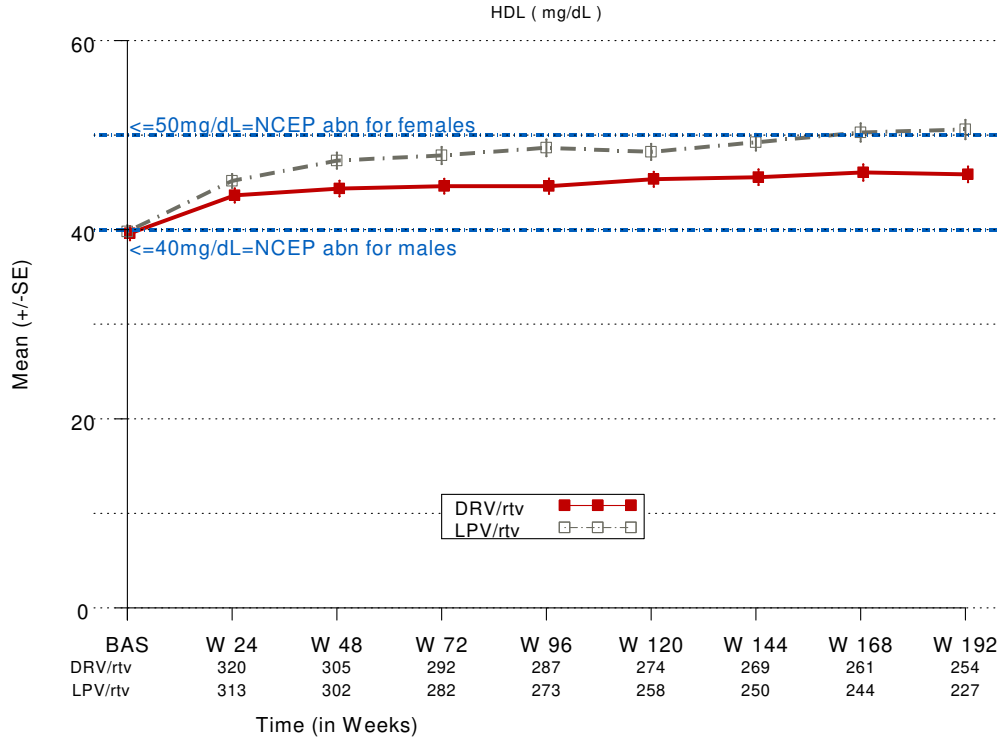


Figure 16: Mean HDL (mg/dL) Over Time

Source: Display SAF.42

4.6.2.3 GENERAL BIOCHEMISTRY LABORATORY PARAMETERS

4.6.2.3.1 General Biochemistry Laboratory Parameters Over Time

Mean changes versus baseline at Week 192 for the selected general biochemistry parameters of interest are summarized in Table 82. For an extensive overview of the descriptive statistics for the changes in the general biochemistry parameters measured in this trial, see Display SAF.43.

A mean decrease versus baseline at Week 192 was observed for amylase in both treatment groups. For lipase and creatinine, a small mean increase versus baseline was observed in both treatment groups.

Table 82: Mean Changes From Baseline at Week 192 for Selected General Biochemistry Parameters

	DRV/rtv				LPV/rtv			
Laboratory Parameter	**N**	**Baseline**	**N**	**Mean Change (SE)**	**N**	**Baseline**	**N**	**Mean Change (SE)**
Pancreatic amylase (U/L)	343	33.0	254	-1.3 (0.84)	346	33.6	228	-3.1 (0.72)
Lipase (U/L)	343	34.7	254	2.6 (1.22)	346	35.0	229	0.6 (0.93)
Creatinine (umol/L)	343	74.7	254	7.0 (0.78)	346	76.2	228	5.8 (0.80)

N = number of subjects

Source: Display SAF.42, Display SAF.43

4.6.2.3.2 Incidence of General Biochemistry Laboratory Abnormalities

The incidence of graded (worst grade) laboratory abnormalities for the selected general biochemistry parameters of interest are summarized in Table 83. For an extensive overview of the general biochemistry laboratory abnormalities reported in this trial, see Display SAF.46. An overview of the incidence of biochemistry abnormalities over time is provided in Display SAF.50 and Display SAF.51. Individual subject data on general biochemistry laboratory parameters for subjects with a grade 3 or 4 general biochemistry laboratory abnormality are provided in Listing SAF.13.

The incidence of increased amylase, increased lipase and creatinine was comparable for both treatment groups. There were no relevant differences between the treatment groups in the incidence of grade 2 to 4 abnormalities for amylase (9.4% versus 7.3%), lipase (3.2% versus 3.8%), or creatinine (1.2% versus 0.6%).

Table 83: Treatment-Emergent General Biochemistry Laboratory Abnormalities of Interest (Worst Grade)

Laboratory Parameter, Worst Grade, n (%)	DRV/rtv	LPV/rtv
Amylase, N	**341**	**343**
Grade 1	53 (15.5)	42 (12.2)
Grade 2	16 (4.7)	8 (2.3)
Grade 3	16 (4.7)	14 (4.1)
Grade 4	0	3 (0.9)
Creatinine, N	**342**	**343**
Grade 1	22 (6.4)	17 (5.0)
Grade 2	2 (0.6)	1 (0.3)
Grade 3	2 (0.6)	1 (0.3)
Grade 4	0	0
Lipase, N	**341**	**343**
Grade 1	14 (4.1)	10 (2.9)
Grade 2	9 (2.6)	6 (1.7)
Grade 3	2 (0.6)	4 (1.2)
Grade 4	0	3 (0.9)

N = number of subjects; n = number of observations
Source: Display SAF.46

4.6.2.4 COAGULATION AND HEMATOLOGY LABORATORY PARAMETERS

4.6.2.4.1 Coagulation and Hematology Laboratory Parameters Over Time

Mean changes versus baseline at Week 192 for the selected hematology parameters of interest are summarized in Table 84. The coagulation parameters of interest, PT and PTT, are not included in this table as these parameters were not routinely tested at Week 192. For an extensive overview of the descriptive statistics for the mean changes in hematology parameters measured in this trial, see Display SAF.43.

The mean changes for hematocrit (increase), and counts for RBC (zero with DRV/rtv and decrease with LPV/rtv), WBC (increase), lymphocyte (increase), and neutrophil (increase) were small and comparable for the DRV/rtv and LPV/rtv treatment groups. For hemoglobin, a mean increase was observed for both treatment groups, which was slightly greater with DRV/rtv than with LPV/rtv. For platelet count, a mean increase was observed for both treatment groups, which was smaller with DRV/rtv than with LPV/rtv.

Table 84: Mean Changes From Baseline at Week 192 for Selected Hematology Parameters[a]

	DRV/rtv 800/100 mg q.d.				DRV/rtv 600/100 mg b.i.d.			
Laboratory Parameter	N	Baseline	N	Mean Change (SE)	N	Baseline	N	Mean Change (SE)
Hematocrit (%)	343	41.2	242	1.7 (0.28)	346	41.7	222	0.9 (0.28)
Hemoglobin (g/L)	343	135.2	243	8.0 (0.94)	346	136.9	223	5.4 (0.97)
Platelet count (giga/L)	338	220.0	235	35.2 (4.08)	344	219.9	217	48.2 (4.67)
RBC count (tera/L)	343	4.7	243	0.0 (0.03)	346	4.8	223	-0.1 (0.03)
WBC count (giga/L)	343	4.6	243	1.0 (0.12)	346	4.5	223	1.2 (0.13)
Lymphocytes (giga/L)	342	1.6	243	0.3 (0.04)	346	1.5	223	0.5 (0.04)
Neutrophils (giga/L)	342	2.6	243	0.7 (0.10)	346	2.5	223	0.7 (0.11)

N = number of subjects

[a] Coagulation parameters are not included in this table as these parameters were not routinely tested at Week 192.
Source: Display SAF.42, Display SAF.43

4.6.2.4.2 Incidence of Coagulation and Hematology Laboratory Abnormalities

The incidence of graded (worst grade) and non-graded laboratory abnormalities for the selected coagulation and hematology parameters of interest are summarized in Table 85 and Table 86, respectively. For an extensive overview of the coagulation and hematology laboratory abnormalities reported in this trial, see Display SAF.46 and Display SAF.47. An overview of the incidence of coagulation and hematology laboratory abnormalities over time is provided in Display SAF.50 and Display SAF.51. Individual subject data for subjects with a grade 3 or 4 hematology laboratory abnormality and coagulation results for subjects with a ≥ grade 1 abnormality are provided in Listing SAF.12 and Listing SAF.4, respectively.

The incidences of coagulation and hematology abnormalities showed a few numerical differences between treatment groups. None of the observed differences were considered clinically relevant. The majority of coagulation and hematology abnormalities in this trial were grade 1 or 2.

The incidence of PT and PTT abnormalities was low. Grade 4 increased PT was not observed in DRV/rtv subjects and in 1 LPV/rtv subject (0.3%); grade 4 increased PTT was observed in 3 DRV/rtv subjects (0.9%) and 5 LPV/rtv subjects (1.6%). There were no grade 4 decreases in hemoglobin or platelet count. Grade 4 decreases in WBC were observed in 1 subject (0.3%) each in both treatment groups. Grade 4 decreases in neutrophil count were less frequent with DRV/rtv (1.2%) than with LPV/rtv (10.2%).

Hematocrit, RBC and lymphocyte counts below normal were observed in both treatment groups, with a lower incidence in the DRV/rtv group than in the LPV/rtv group for hematocrit and RBC count (hematocrit: 15.9% versus 26.2%; RBC: 28.8% versus 36.2%) and no relevant difference between the groups in the incidence of low lymphocyte count abnormalities (7.6% versus 10.6%).

Table 85: Treatment-Emergent Coagulation and Hematology Laboratory Abnormalities of Interest (Worst Grade)

Laboratory Parameter, Worst Grade, n (%)	DRV/rtv	LPV/rtv
PT, N	**322**	**322**
Grade 1	5 (1.6)	4 (1.2)
Grade 2	1 (0.3)	3 (0.9)
Grade 3	1 (0.3)	5 (1.6)
Grade 4	0	1 (0.3)
PTT, N	**322**	**322**
Grade 1	16 (5.0)	8 (2.5)
Grade 2	5 (1.6)	3 (0.9)
Grade 3	0	2 (0.6)
Grade 4	3 (0.9)	5 (1.6)
Hemoglobin, N	**340**	**343**
Grade 1	15 (4.4)	14 (4.1)
Grade 2	5 (1.5)	3 (0.9)
Grade 3	2 (0.6)	1 (0.3)
Grade 4	0	0
WBC, N	**340**	**343**
Grade 1	15 (4.4)	8 (2.3)
Grade 2	6 (1.8)	3 (0.9)
Grade 3	1 (0.3)	1 (0.3)
Grade 4	1 (0.3)	1 (0.3)
Platelet count, N	**340**	**342**
Grade 1	9 (2.6)	7 (2.0)
Grade 2	4 (1.2)	5 (1.5)
Grade 3	1 (0.3)	0
Grade 4	0	0
Neutrophil count, N	**340**	**343**
Grade 1	29 (8.5)	1 (0.3)
Grade 2	21 (6.2)	7 (2.0)
Grade 3	8 (2.4)	8 (2.3)
Grade 4	4 (1.2)	35 (10.2)

N = number of subjects
Source: Display SAF.46

Table 86: Nongraded Treatment-Emergent Hematology Laboratory Abnormalities of Interest

Laboratory Parameter, Abnormality, n (%)	DRV/rtv	LPV/rtv
Hematocrit, N	**340**	**343**
Above	15 (4.4)	10 (2.9)
Below	54 (15.9)	90 (26.2)
RBC, N	**340**	**343**
Above	8 (2.4)	2 (0.6)
Below	98 (28.8)	124 (36.2)
Lymphocite count, N	**340**	**343**
Above	16 (4.7)	12 (3.5)
Below	26 (7.6)	36 (10.6)

N = number of subjects; n = number of observations
Source: Display SAF.47

4.6.2.5 RESULTS OF URINALYSIS

An overview of the urinalysis results is provided Display SAF.55. Individual subjects data for urinalysis are provided in Listing SAF.15.

Abnormal urinalysis test results were reported in 16.2% of subjects in the DRV/rtv group and 16.4% in the LPV/rtv group.

The incidence of AEs related to urinalysis reported during the treatment period is included in Display SAF.2 (all grades) and Display SAF.25 (grade 3 or 4 AEs). Individual subject data for AEs are provided in Listing SAF.1.

The incidence of AEs related to urinalysis was low and comparable for the DRV/rtv and LPV/rtv treatment groups. The most frequent AEs related to urinalysis was hematuria, reported in 2.0% of DRV/rtv subjects and 3.5% of LPV/rtv subjects. All other AEs related to urinalysis were reported in < 1 % of subjects in either treatment group. One subject in the DRV/rtv group had a grade 3 AE related to urinalysis (hematuria); there were no grade 4 AEs related to urinalysis.

No AEs related to urinalysis were reported as SAEs, and none led to permanent discontinuation of the trial medication.

4.6.3 Cardiovascular Safety

4.6.3.1 VITAL SIGNS

Descriptive statistics on the vital signs parameters measured in this trial are provided in Display SAF.63. Descriptive statistics on orthostatic vital signs values (standing - supine) are provided in Display SAF.65. Individual subject data on vital signs parameters are provided in Listing SAF.20.

In both the DRV/rtv and LPV/rtv treatment group, within-group comparison for the changes from baseline in vital signs parameters revealed a number of statistically significant differences for all parameters. None of the observed mean changes in vital signs parameters were considered clinically relevant.

Between-group comparisons showed statistically significant differences between the DRV/rtv and LPV/rtv treatment groups at several time points for all vital signs parameters except supine SBP. None of the between-group differences were considered clinically relevant.

There were no relevant differences between the mean orthostatic vital signs values at baseline and those observed during the treatment period.

4.6.3.2 INDIVIDUAL ABNORMALITIES IN VITAL SIGNS

The incidence of vital signs abnormalities is summarized in Table 87. A complete overview of the vital signs abnormalities in this trial is provided in Display SAF.66 and Display SAF.68 (orthostatic values). Only treatment-emergent abnormalities, i.e., those abnormalities that first occurred or worsened after the start of the treatment period, are reported. For a definition of the vital signs abnormalities, see Section 3.6.7.3.

Vital signs abnormalities were commonly observed in both treatment groups. The incidence of vital signs abnormalities was generally comparable for the DRV/rtv and LPV/rtv treatment groups.

The most frequent abnormalities (> 10% of subjects in any treatment group) were high blood pressure values: standing SBP (29.0% and 26.2% with DRV/rtv and LPV/rtv, respectively), supine SBP (26.6% and 25.4%), standing DBP (36.4% and 30.3%), supine DBP (27.8% and 20.7%).

Grade 3 elevated standing SBP occurred in 0.3% of DRV/rtv subjects and 0.9% of LPV/rtv subjects, and grade 3 elevated supine SBP occurred in 1.5% and 1.2% subjects, respectively. Grade 3 elevated standing DBP occurred in 3.5% of subjects in both treatment groups, and grade 3 elevated supine DBP occurred in 2.9% of subjects in both treatment groups.

Abnormalities related to orthostatic vital signs values were observed frequently: 43.7% and 43.3% of subjects in the DRV/rtv and LPV/rtv groups, respectively, experienced an abnormal increase in orthostatic pulse, 19.9% and 19.5% of subjects in the respective treatment groups experienced an abnormal decrease in orthostatic SBP, and 32.8% and 35.3% of subjects experienced an abnormal decrease in orthostatic DBP.

The proportion of subjects in each treatment group receiving blood-pressure-lowering drugs (agents acting on the renin-angiotensin system, antihypertensives, beta blocking agents, calcium channel blockers, and diuretics), during screening and during treatment, respectively were 6.4% and 13.1% in the DRV/rtv group, versus 4.6% and 13.3% in the LPV/rtv group (see Display ADD.5).

Table 87: Treatment-Emergent Vital Signs Abnormalities (Worst Grade)

Vital Signs Parameter, Worst Grade/Abnormality, n (%)	DRV/rtv	LPV/rtv
Measured Values		
Standing pulse (bpm), N	**341**	**343**
Abnormally high	14 (4.1)	7 (2.0)
Abnormally low	10 (2.9)	10 (2.9)
Supine pulse (bpm), N	**341**	**343**
Abnormally high	6 (1.8)	2 (0.6)
Abnormally low	34 (9.9)	37 (10.8)
Standing SBP (mmHg), N	**341**	**343**
Grade 1	75 (22.0)	72 (21.0)
Grade 2	23 (6.7)	15 (4.4)
Grade 3	1 (0.3)	3 (0.9)
Abnormally low	25 (7.3)	30 (8.7)
Supine SBP (mmHg), N	**342**	**343**
Grade 1	73 (21.3)	68 (19.8)
Grade 2	13 (3.8)	15 (4.4)
Grade 3	5 (1.5)	4 (1.2)
Abnormally low	30 (8.8)	40 (11.7)
Standing DBP (mmHg), N	**341**	**343**
Grade 1	74 (21.7)	69 (20.1)
Grade 2	38 (11.1)	23 (6.7)
Grade 3	12 (3.5)	12 (3.5)
Abnormally low	11 (3.2)	25 (7.3)
Supine DBP (mmHg), N	**342**	**343**
Grade 1	64 (18.7)	46 (13.4)
Grade 2	21 (6.1)	15 (4.4)
Grade 3	10 (2.9)	10 (2.9)
Abnormally low	18 (5.3)	23 (6.7)
Orthostatic Values		
Pulse (bpm), N	**341**	**343**
Abnormal increase	149 (43.7)	149 (43.4)
SBP (mmHg), N	**341**	**343**
Abnormal decrease	68 (19.9)	67 (19.5)
DBP (mmHg), N	**341**	**343**
Abnormal decrease	112 (32.8)	121 (35.3)

N = number of subjects; n = number of observations
[a] For the definition of the vital signs abnormalities, refer to Section 3.6.7.3.
Source: Display SAF.66, Display SAF.68

The incidence of AEs related to vital signs abnormalities reported during the treatment period is summarized in Table 88 (see also Display SAF.2). The incidence of grade 3 or 4 AEs related to vital signs abnormalities reported during the treatment period is summarized in Table 89 (see also Display SAF.25). Individual subject data for AEs are provided in Listing SAF.1.

The incidence of AEs related to vital signs abnormalities was low. The most frequent AE related to vital signs was hypertension (7.0% and 4.9% in the DRV/rtv and LPV/rtv treatment groups, respectively); tachycardia occurred in 0.3% and 1.2% of subjects in the respective treatment groups. All other AEs related to vital signs occurred in < 1% of subjects in either treatment group. Grade 3 AEs related to vital signs abnormalities were observed in 3 DRV/rtv subjects and 3 LPV/rtv subjects; there were no grade 4 AEs related to vital signs abnormalities in this trial.

Table 88: Adverse Events Related to Vital Signs Abnormalities Reported During the Treatment Period (Regardless of Severity or Causality)

Preferred Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Blood pressure increased	2 (0.6)	3 (0.9)
Blood pressure orthostatic decreased	1 (0.3)	0
Bradycardia	2 (0.6)	3 (0.9)
Diastolic hypertension	0	1 (0.3)
Essential hypertension	0	1 (0.3)
Hypertension	24 (7.0)	17 (4.9)
Hypertensive crisis	0	1 (0.3)
Hypotension	1 (0.3)	1 (0.3)
Orthostatic hypotension	0	1 (0.3)
Palpitations	2 (0.6)	2 (0.6)
Sinus bradycardia	1 (0.3)	1 (0.3)
Sinus tachycardia	1 (0.3)	0
Tachycardia	1 (0.3)	4 (1.2)

N = number of subjects; n = number of observations

Source: Display SAF.2

Table 89: Grade 3[a] Adverse Events Related to Vital Signs Abnormalities Reported During the Treatment Period (Regardless of Causality)

Preferred Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Hypertension	3 (0.9)	2 (0.6)
Hypertensive crisis	0	1 (0.3)

N = number of subjects; n = number of observations

[a] There were no grade 4 AEs related to vital signs.

Source: Display SAF.25

4.6.3.3 ELECTROCARDIOGRAM

Descriptive statistics on the ECG parameters measured in this trial are provided in Display SAF.57. Individual subject data on ECG parameters are provided in Listing SAF.18 (measured intervals) and Listing SAF.19 (abnormalities). A graphical presentation of the mean change over time for QTcF is provided in Figure 17.

ECG assessments were routinely performed at several time points up to Week 96. After Week 96, an ECG was only performed locally at Week 192, if deemed necessary by the investigator. Therefore, no Week-192 data are described in this section.

For both the DRV/rtv and LPV/rtv group, comparison of the change versus baseline in ECG parameters at Week 96 revealed small mean changes. None of the observed within-group mean changes versus baseline were considered clinically relevant.

For QTcF, a mean change versus baseline of -0.3, -0.8, and 0.9 ms at Weeks 4, 48, and 96, respectively, was observed for the DRV/rtv group, and a mean change versus baseline of -1.4, 0.6, and 2.2 ms at these respective time points was observed for the LPV/rtv group. For QTcB, a

mean decrease of -0.3, -4.9, and -4.0 ms was observed for the DRV/rtv group, versus a mean decrease of -1.7, -4.6, and -3.6 ms for the LPV/rtv group. There were no statistically significant differences between the treatment groups with respect to these parameters.

For PR interval, a mean change versus baseline of 1.8, 1.7, and 2.3 ms at Weeks 4, 48, and 96 respectively, was observed for the DRV/rtv group, whereas for the LPV/rtv group, a mean change versus baseline of 6.1, 5.2, and 6.3 ms was observed. This resulted in a significant difference between the treatment groups at all time points.

For QRS width, a mean change versus baseline of 0.3, 0.6, and 0.7 ms was observed for the DRV/rtv group, versus a mean change versus baseline of 2.0, 2.8, and 2.6 ms for the LPV/rtv group. This resulted in a significant difference between the treatment groups at all time points.

For heart rate, a mean decrease was observed in both treatment groups (up to -5.5 bpm for the DRV/rtv group, and up to -6.3 bpm for the LPV/rtv group), with no statistically significant differences between the treatment groups.

None of the between-group differences were considered clinically relevant.

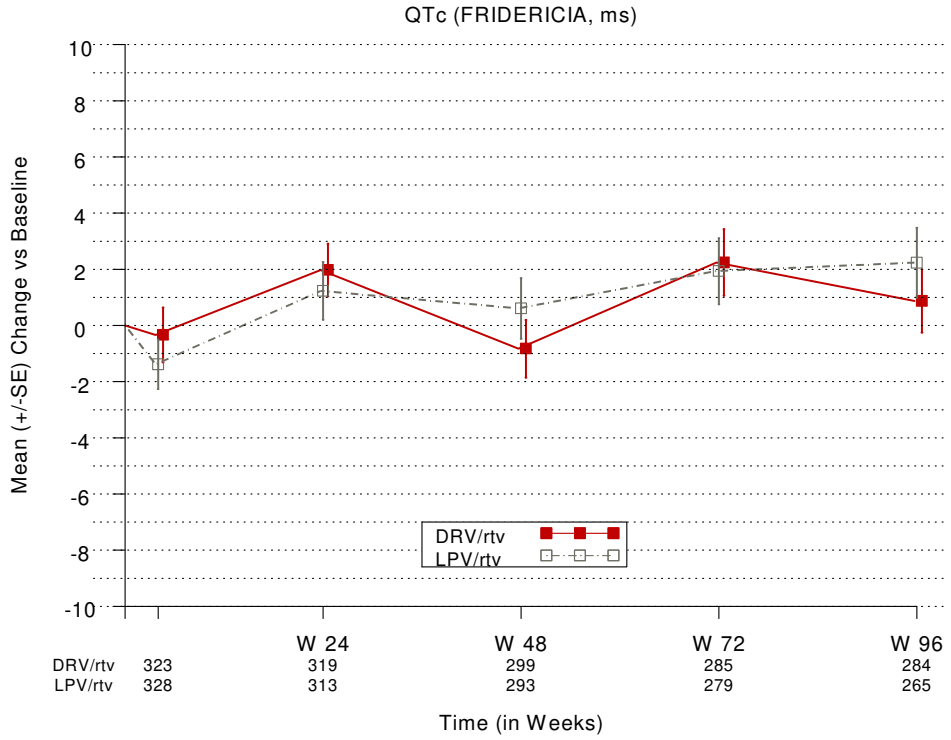


Figure 17: Mean Change in QTcF (ms) Over Time
Source: Display SAF.57

4.6.3.4 INDIVIDUAL ABNORMALITIES IN ECG

The incidence of ECG abnormalities is summarized in Table 90. A complete overview of the ECG abnormalities in this trial is provided in Display SAF.59 (actual values) and Display SAF.60 (QTc change). Only treatment-emergent abnormalities, i.e., those abnormalities that first occurred or worsened after the start of the treatment period, are reported. For a definition of the ECG abnormalities, see Section 3.6.7.3.

ECG abnormalities were commonly observed in both treatment groups, and their incidence was generally comparable between the DRV/rtv and LPV/rtv treatment groups.

QTcF and QTcB values of > 500 ms were not observed. Isolated increases in QTcF of > 60 ms were observed in 1.5% and 1.8% of subjects receiving DRV/rtv or LPV/rtv, respectively. Increases in QTcB of > 60 ms were observed in 1.8% and 1.5% of subjects, respectively. No subjects presented any clinical events related to QTc prolongation.

Only 1 subject (CRF ID C211-0611) had a QTcF ≥ 480 ms. This patient had an increased QTcF of 473 ms at baseline. In addition, the clinical event syncope or loss of consciousness occurred in 5 subjects. QTc interval values were within the normal range for 4 subjects. The fifth subject (CRF ID C211-0336; QTc interval was 508 ms in the emergency room) took illicit drugs during the trial (methamphetamine and GHB). This event was reported as an SAE (for details, refer to TMC114-C211-W192-narratives).

Abnormally low heart rate values were observed in 8.3% and 10.9% of subjects in the DRV/rtv and LPV/rtv groups, respectively.

Abnormally high values were observed for PR interval in 3.3% and 5.3%, and for QRS width in 0.6% and 0.3% of subjects in the DRV/rtv and LPV/rtv groups, respectively.

All treatment-emergent ECG abnormalities were transient in nature and no consistent pattern in the incidence of these abnormalities was observed. None of the abnormalities required treatment interruption and/or medical intervention.

Table 90: Treatment-Emergent ECG Abnormalities (Worst Abnormality)

ECG Parameter, Abnormality, n (%)	DRV/rtv	LPV/rtv
Heart rate (bpm), N	**336**	**340**
Abnormally high	1 (0.3)	1 (0.3)
Abnormally low	28 (8.3)	37 (10.9)
PR interval (ms), N	**336**	**340**
Abnormally high	11 (3.3)	18 (5.3)
QRS width (ms), N	**336**	**340**
Abnormally high	2 (0.6)	1 (0.3)
QTcF (ms), N	**336**	**340**
> 450 - ≤ 480 ms	6 (1.8)	5 (1.5)
> 480 - ≤ 500 ms	1 (0.3)	0
> 500 ms	0	0
QTcB (ms), N	**336**	**340**
> 450 - ≤ 480 ms	14 (4.2)	8 (2.4)
> 480 - ≤ 500 ms	1 (0.3)	1 (0.3)
> 500 ms	0	0
QTcF (ms), N	**336**	**340**
Increase by 30 - 60 ms	50 (14.9)	55 (16.2)
Increase by > 60 ms	5 (1.5)	6 (1.8)
QTcB (ms), N	**336**	**340**
Increase by 30 - 60 ms	59 (17.6)	60 (17.6)
Increase by > 60 ms	6 (1.8)	5 (1.5)

N = number of subjects; n = number of observations
[a] For the definition of the ECG abnormalities, refer to Section 3.6.7.3.
Source: Display SAF.59, Display SAF.60

For information on the incidence AEs related to ECG abnormalities, see Section 4.6.1.3.4.2.

4.6.4 Other Safety Evaluations

4.6.4.1 Physical Examination

A physical examination was performed at screening, baseline, and several visits throughout the trial. Clinically relevant changes occurring between screening and the last trial visit had to be reported as AEs and are as such included in the AE reporting in Section 4.6.1. Individual subject data on physical examination abnormalities are provided in Listing SAF.22.

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

4.6.4.2 Anthropometric Measurements

The mean change from baseline at Week 192 for the anthropometric parameters is summarized in Table 91. Extensive descriptive statistics for the anthropometric parameters in this trial are provided in Display SAF.71. Individual subject data on the anthropometric parameters are provided in Listing SAF.21.

A graphical presentation of the mean change in weight in the 2 treatment groups over time is shown in Figure 18. The mean weight increase versus baseline at Week 192 was 4.2 kg in the DRV/rtv group and 3.5 kg in the LPV/rtv group.

Within-group comparison for the changes from baseline at Week 192 in anthropometric parameters revealed statistically significant differences for the DRV/rtv group and LPV/rtv group with respect to BMI, breast circumference, hip circumference, midwaist circumference, minimal waist circumference, umbilical waist circumference, and weight. For midwaist/hip ratio, there was a statistically significant difference for the DRV/rtv group only. For neck circumference, there was no statistically difference for either treatment group.

Between-group comparisons at Week 192 showed statistically significant differences between the DRV/rtv and LPV/rtv treatment groups for umbilical waist circumference only. This difference was considered not clinically relevant.

Table 91: **Mean Change from Baseline in Anthropometric Parameters at Week 192**

	DRV/rtv				LPV/rtv				
Parameter	**N**	**Baseline (Mean)**	**N**	**Mean Change From Baseline (SE)**	**N**	**Baseline (Mean)**	**N**	**Mean Change From Baseline (SE)**	**p-Value[a]**
Weight	343	69.6	255	4.2 (0.42)	346	71.2	227	3.5 (0.51)	0.2938
BMI	341	24.1	253	1.5 (0.15)	344	24.3	227	1.2 (0.18)	0.2932
Neck circumference	338	36.4	236	0.2 (0.13)	333	36.4	205	-0.0 (0.14)	0.1618
Breast circumference	336	93.1	235	2.8 (0.33)	336	94.4	204	2.7 (0.47)	0.4720
Hip circumference	341	95.9	240	3.0 (0.38)	340	96.9	207	2.5 (0.47)	0.2092
Midwaist circumference	289	86.5	201	3.7 (0.47)	282	87.1	178	2.7 (0.54)	0.0668
Minimum waist circumference	327	82.4	226	3.3 (0.45)	329	83.1	198	2.5 (0.57)	0.1451
Umbilical waist circumference	298	85.1	210	4.3 (0.47)	295	86.4	186	2.8 (0.61)	0.0410
Midwaist/hip ratio	289	0.9	201	0.0 (0.00)	281	0.9	177	0.0 (0.00)	0.1874

N = number of subjects
[a] Weight in kg, circumferences in cm
[b] Mann-Whitney-U test for between-group comparison
Source: Display SAF.71

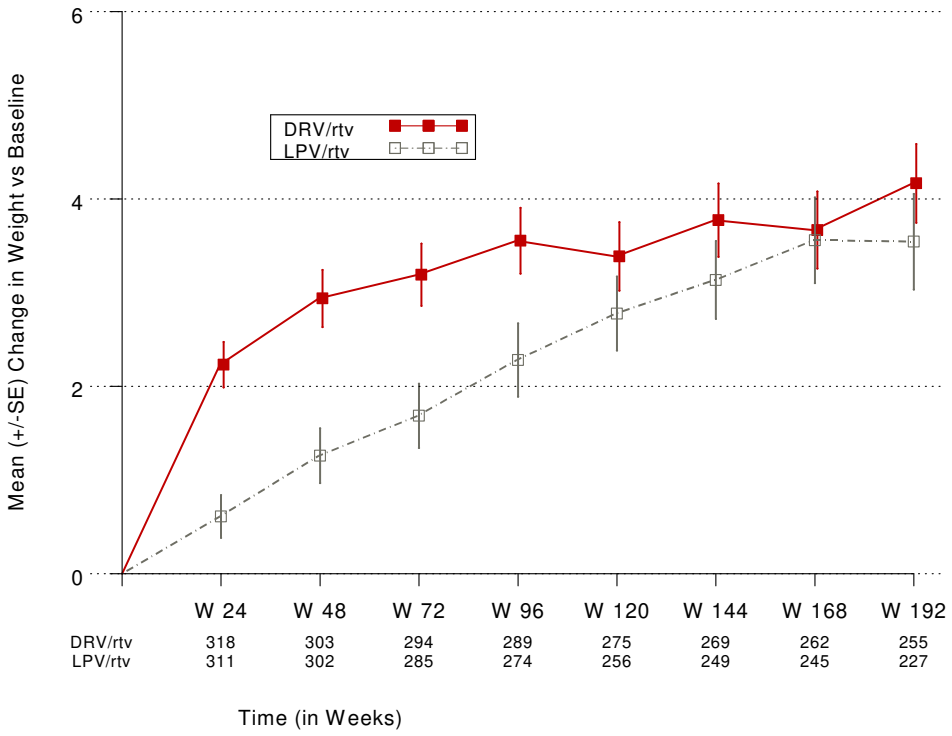


Figure 18: Mean Change in Weight (kg) Over time

Source: Display SAF.71

The incidence of AEs related to anthropometric measurements reported during the treatment period is summarized in Table 92. For the incidence of AEs related to anthropometric measurements during the entire trial, refer to Display SAF.2 (all grades) and Display SAF.25 (grade 3 or 4 AEs).

The incidence of AEs related to anthropometric measurements was low. In both the DRV/rtv and LPV/rtv treatment groups, anorexia (3.8% and 4.9%, respectively) and weight decreased (3.2% and 2.3%) were observed most frequently. The incidence of lipodystrophy-related AEs was comparable for both treatment groups. One DRV/rtv subject (weight increased) and 2 LPV/rtv subjects had an AE related to anthropometric measurements (anorexia and weight decreased) were grade 3 in severity. No AEs related to anthropometric measurements were grade 4 in severity.

No anthropometric AEs during the treatment period were reported as SAEs. Two AEs related to an anthropometric measurement led to permanent discontinuation of the trial medication: anorexia (CRF ID 211-0504, DRV/rtv, grade 2, probably related), and weight increased (211-0190, LPV/rtv, grade 2, possibly related) (for the subject narratives, refer to TMC114-C211-W192-narratives).

Table 92: Adverse Events Related to Anthropometric Measurement Reported During the Treatment Period (Regardless of Severity and Causality)

Preferred Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Anorexia	13 (3.8)	17 (4.9)
Facial wasting	1 (0.3)	2 (0.6)
Fat tissue increased	0	1 (0.3)
Lipoatrophy	1 (0.3)	3 (0.9)
Lipodystrophy acquired	5 (1.5)	2 (0.6)
Lipohypertrophy	1 (0.3)	3 (0.9)
Obesity	2 (0.6)	2 (0.6)
Underweight	0	1 (0.3)
Weight decreased	11 (3.2)	8 (2.3)
Weight increased	7 (2.0)	3 (0.9)

N = number of subjects; n = number of observations
Source: Display SAF.2

4.6.5 Safety Conclusions

The safety data from trial TMC114-C211 up to 4 years (192 weeks, cut-off data 29 March 2010) demonstrated that DRV/rtv 800/100 mg q.d. was generally safe and well tolerated in treatment-naïve subjects. DRV/rtv 800/100 mg q.d. was associated with a lower incidence of diarrhea, nausea and vomiting compared with LPV/rtv 800/200 mg total daily dose. Furthermore, the incidence of increased triglycerides and increased total cholesterol was lower with DRV/rtv than with LPV/rtv in this population. The incidence of rash-related AEs was higher with DRV/rtv compared to LPV/rtv.

The most frequent (≥ 10%) AEs were diarrhea (39.4% and 54.9% with DRV/rtv and LPV/rtv, respectively), upper respiratory tract infection (24.5% and 23.1%), headache (22.4% and 17.6%), nausea (18.4% and 30.3%), nasopharyngitis (17.2% and 14.5%), abdominal pain (12.8% and 14.5%), cough (12.2% and 14.7%), bronchitis (11.1% and 11.8%), back pain (11.1% and 8.1%), rash (10.2% and 8.7%), influenza (8.7% and 12.7%), fatigue (8.7% and 10.7%), and vomiting (8.2% and 13.3%). Diarrhea, nausea and vomiting were reported less frequently with DRV/rtv than with LPV/rtv.

AEs considered at least possibly related to the PI were less frequent with DRV/rtv (56.6%) than with LPV/rtv (74.9%). The most frequent (≥ 5%) AEs considered at least possibly related to DRV/rtv or LPV/rtv, respectively, were diarrhea (24.5% and 48.6%), nausea (14.0% and 25.7%), headache (6.4% and 8.1%), abdominal pain (3.5% and 6.9%), vomiting (3.2% and 8.1%), hypercholesterolemia (2.9% and 5.8%), and hypertriglyceridemia (2.0% and 7.5%).

AEs ≥ grade 2 and considered by the investigator at least possibly related to the PI were also less frequent with DRV/rtv (28.0%) than with LPV/rtv (35.8%). The most frequent (≥ 3%) AEs ≥ grade 2 and considered at least possibly related to DRV/rtv or LP/rtv, respectively, were diarrhea (5.0% and 11.3%), LDL increased (3.2% and 1.7%), hypercholesterolemia (2.3% and 4.9%), hypertriglyceridemia (2.0% and 5.8%), ALT increased (1.5% and 3.2%), and hyperlipidemia (0.6% and 3.2%).

Grade 3 or 4 AEs were reported with comparable frequency in the DRV/rtv and LPV/rtv treatment groups (30.0% and 31.8%, respectively). The most frequent (≥ 1%) grade 3 or 4 AEs

were LDL increased (3.2% and 1.4% with DRV/rtv and LPV/rtv, respectively), AST increased (2.0% and 2.0%), blood amylase increased (2.0% and 2.0%), hypertriglyceridemia (1.5% and 3.5%), and ALT increased (1.5% and 2.6%), hypercholesterolemia (0.6% and 2.0%), and abdominal pain (0.6% and 1.2%).

Four subjects in the DRV/rtv treatment group and 7 subjects in the LPV/rtv treatment group died during the treatment period. None of the deaths were considered related to trial treatment by the investigator.

SAEs were less frequent with DRV/rtv (16.0%) than with LPV/rtv (20.8%). The majority of SAEs occurred in ≤ 2 subjects in any treatment group. Three subjects (0.9%) in the DRV/rtv group and 10 subjects (2.9%) in the LPV/rtv group had an SAE considered at least possibly related to the PI. Except ALT increased (which occurred in 2 LPV/rtv subjects), all SAEs considered at least possibly related to the PI occurred in only 1 subject in any treatment group. Related SAEs with DRV/rtv were QT prolonged, arrhythmia, drug interaction (same subject who took illicit drugs), nausea, headache (same subject) and Stevens-Johnson syndrome. Related SAEs in the LPV/rtv group were vomiting and diarrhea (same subject), transaminases increased and hepatitis (same subject), hepatic enzyme increased and blood bilirubin increased (same subject), ALT increased and AST increased (same subject), ALT increased, rash, immune reconstitution syndrome, pancreatitis acute, intracranial aneurysm, and neutrophil count decreased.

Permanent discontinuation of treatment due to an AEs was less frequent with DRV/rtv (7.6%) than with LPV/rtv (14.5%). AEs leading to permanent discontinuation were most commonly due to pregnancy (2.6% and 1.4%, respectively). Gastrointestinal Disorders leading to discontinuation were reported in 0.3% of DRV/rtv subjects and 2.9% of LPV/rtv subjects, of which diarrhea (0% and 2.0%, respectively) was reported most frequently. In total 1.7% of subjects in the DRV/rtv group and 6.6% of subjects in the LPV/rtv group experienced an AE leading to permanent discontinuation that was considered at least possibly related to treatment. No DRV/rtv subjects permanently discontinued treatment for the same related AE; AEs occurring in > 1 subject in the LPV/rtv group were diarrhea (2.0%), ALT increased (0.9%), and hypertriglyceridemia, hypercholesterolemia, and rash (all 3 in 0.6%).

Special attention was given to rash-, and cardiac-related, GI, pancreatic, liver-, lipid-, and glucose-related AEs.

Rash-related AEs occurred mostly within the first 24 weeks of treatment and their incidence was higher with DRV/rtv (21.6%) compared to LPV/rtv (15.5%). The incidence of grade 3 or 4 rash-related events was low in both groups and rash only occasionally led to treatment discontinuation.

A comparable incidence for the DRV/rtv and LPV/rtv groups was observed for cardiac AEs (5.8% versus 6.1%).

The overall incidence of GI-related AEs was lower during treatment with DRV/rtv (54.8%) than with LPV/rtv (69.4%), with diarrhea (39.4% and 54.9% with DRV/rtv and LPV/rtv, respectively), nausea (18.4% and 30.3%), abdominal pain (12.8% and 14.5%), and vomiting (8.2% and 13.3%) as the most frequent AEs. The incidence of GI-related events considered by the investigator to be at least possibly related to treatment was also lower in the DRV/rtv group (35.9%) than in the LPV/rtv group (59.2%). During the trial, fewer subjects in the DRV/rtv

group compared to the LPV/rtv group used concomitant antidiarrheal agents and drugs for GI disorders (27.7% versus 38.7%).

The incidence of laboratory abnormalities was low and generally comparable for the DRV/rtv q.d. and DRV/rtv b.i.d. treatment groups, but with some notable differences.

Liver-related laboratory abnormalities for AST and ALT were observed with a similar incidence in the DRV/rtv and LPV/rtv group. Hyperbilirubinemia was less frequent with DRV/rtv than with LPV/rtv. There was a clear difference between the treatment groups in the incidence of elevated liver enzymes in subjects coinfected with hepatitis B or C virus: grade 2 to 4 ALT elevations in coinfected subjects was 39.5% with DRV/rtv versus 62.5% with LPV/rtv, and grade 2 to 4 AST elevations were seen in 30.2% with DRV/rtv versus 52.1% with LPV/rtv. The overall incidence of liver-related AEs was lower with DRV/rtv than with LPV/rtv (7.6% versus 14.5%). The most frequent liver-related AEs were AST increased (2.9% and 5.2%), and ALT increased (2.6% and 5.8%). In both treatment groups, the overall incidence of liver-related AEs was higher in subjects with hepatitis B or C coinfection (16.3% and 43.8% with DRV/rtv and LPV/rtv, respectively) than in not-coinfected subjects (6.3% and 9.7%).

With respect to lipid-related laboratory abnormalities, grade 2 to 4 increases in triglycerides were observed less frequently in the DRV/rtv group (5.9%) than in the LPV/rtv group (16.0%). Also grade 2 to 3 increases in total cholesterol were observed less frequently with DRV/rtv (24.3%) than with LPV/rtv (32.7%). Grade 2 or 3 increases in LDLc cholesterol were observed in 22.9% of subjects in the DRV/rtv group and 18.4% in the LPV/rtv group. The overall incidence of lipid-related AEs was lower with DRV/rtv (12.5%) than with LPV/rtv (19.2%). The most frequent lipid-related AEs were LDL increased (4.1% and 2.0%), hypercholesterolemia (3.8% and 6.6%), blood cholesterol increased (2.6% and 2.0%), hypertriglyceridemia (2.3% and 8.4%), and hyperlipidemia (2.0% and 4.0%). A similar proportion of subjects in both groups received lipid-modifying drugs: in the DRV/rtv group, 2.6% of subjects received lipid-modifying drugs at screening, and 11.7% during the trial; in the LPV/rtv group, these proportions were respectively 2.3% and 14.2%.

There were no relevant differences between the treatment groups with respect glucose-related laboratory abnormalities. Grade 2 or 3 hyperglycemia was observed in 12.0% of subjects in the DRV/rtv group and 9.9% in the LPV/rtv group (no grade 4 hyperglycemia was observed). The overall incidence of glucose-related AEs was 5.2% with DRV/rtv and 2.6% with LPV/rtv. The most frequent glucose-related AEs were blood glucose increased and hyperglycemia (both in 1.5% and 0.3%, respectively).

There were no relevant differences between the treatment groups in the incidence of grade 2 to 4 abnormalities for amylase (9.4% versus 7.3%), lipase (3.2% versus 3.8%). The overall incidence of pancreatic AEs was comparable between both treatment groups (3.2% and 3.8%, respectively).

The incidences of coagulation and hematology abnormalities showed a few numerical differences between treatment groups. None of the observed differences were considered clinically relevant. The majority of coagulation and hematology abnormalities in this trial were grade 1 or 2. Grade 4 increased PT was not observed in DRV/rtv subjects and in 0.3% of LPV/rtv subjects; grade 4 increased PTT was observed in 0.9% of DRV/rtv subjects and 1.6% of LPV/rtv subjects. There were no grade 4 decreases in hemoglobin or platelet count. Grade 4 decreases in WBC were observed in 0.3% of subjects in both treatment groups. Grade 4

decreases in neutrophil count were less frequent with DRV/rtv (1.2%) than with LPV/rtv (10.2%).

The incidence of AEs related to urinalysis was low and similar for both treatment groups.

Small median changes from baseline were observed for vital signs parameters. None of the observed mean changes from baseline and no between-group differences for any of the vital signs parameters were considered clinically relevant. Vital signs abnormalities were commonly observed in both the DRV/rtv and LPV/rtv treatment groups and their incidence was generally comparable; the most frequent abnormalities were elevated blood pressure values. The incidence of AEs related to vital signs was low; hypertension was the most frequent AE related to vital signs, reported in 7.0% and 4.9% of subjects in the DRV/rtv and LPV/rtv groups, respectively. The proportion of subjects in each treatment group receiving blood-pressure-lowering drugs during screening and during treatment, respectively, were 6.4% and 13.1% in the DRV/rtv group, versus 4.6% and 13.3% in the LPV/rtv group.

For both treatment groups, QTc abnormalities were generally transient occurrences in the absence of clinical symptoms, which resolved with continued dosing. QTcF values of > 500 ms were not observed; increases in QTcF of > 60 ms were observed in 1.5% and 1.8% of subjects in the DRV/rtv and LPV/rtv treatment groups. No subjects presented with any clinically relevant events related to QTc prolongation.

There were no clinically relevant changes over time in physical examination findings. A mean increase in 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. In both the DRV/rtv and LPV/rtv treatment groups, anorexia (3.8% and 4.9%, respectively) and weight decreased (3.2% and 2.3%) were observed most frequently. The incidence of lipodystrophy-related AEs was comparable for both treatment groups.

4.7 PHARMACOKINETIC RESULTS

No updated pharmacokinetic analysis was performed at Week 192.

4.8 PHARMACOKINETIC/PHARMACODYNAMIC RESULTS

No updated pharmacokinetic/pharmacodynamic analyses were performed at Week 192.

4.9 SUMMARY OF RESULTS FOR THE ROLLOVER PHASE

In the original Protocol, subjects from both the DRV/rtv or LPV/rtv treatment groups meeting the per protocol defined criteria for 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 the rollover phase. After Protocol Amendment TMC114-C211-CTPA-GEN-III, this rollover phase was no longer available (for details, see Section 3.1.1.2).

On 29 March 2010, only a limited number of subjects (16, see Section 4.9.1) had permanently discontinued trial medication during the treatment period (main phase) and continued in the

rollover phase. Compared to the Week-96 analysis, there was 1 additional rollover subject (see Sections 4.9.1 and 4.9.1.2). The duration of treatment during the rollover phase was limited (mean duration of 48.8 weeks, see Section 4.9.1.1).

The results from the rollover phase are presented descriptively in this section. The in-text table column headings reflect the treatment actually received during the rollover phase and are structured as follows:

- **DRV/rtv - LPV/rtv**: all subjects who were randomized to and received DRV/rtv during the treatment period (main phase) and who switched to LPV/rtv in the rollover phase; further referred to as **LPV/rtv-rollover subjects**;
- **LPV/rtv - DRV/rtv**: all subjects who were randomized to and received LPV/rtv during the treatment period (main phase), and who switched to DRV/rtv in the rollover phase; further referred to as **DRV/rtv-rollover subjects**.

4.9.1 Subject and Treatment Information

The subject disposition and trial termination reasons during the rollover phase are summarized in Table 93 (see also Display GEN.1 and Display GEN.2). On 29 March 2010, 5 subjects treated with DRV/rtv and 11 subjects treated with LPV/rtv in the main phase of the trial had continued in the rollover phase following permanent discontinuation of the trial medication during the treatment period. Compared to the Week-96 analysis, there was 1 additional rollover subject (CRF ID 211-0653), who rolled over from DRV/rtv to LPV/rtv treatment in the rollover phase. One LPV/rtv subject (CRF ID 211-0596) was planned to continue with DRV/rtv in the rollover phase but withdrew consent before taking any drug in the rollover phase.

Of the 16 subjects who rolled over, 9 (56.3%) subjects prematurely discontinued treatment during the rollover phase, 5 (31.3%) subjects continued treatment in the extension phase of the trial when the rollover phase was ended, and 2 (12.5%) subjects completed the trial.

Table 93: Subject Disposition - Rollover Phase

N (%)	DRV/rtv-rollover N = 11	LPV/rtv-rollover N = 5	All Subjects N = 16
Rollover - Reason (%)			
Adverse Event/HIV-related event	5 (1.4)	3 (0.9)	8 (1.2)
Subject Reached a virologic Endpoint	7 (2.0)[a]	2 (0.6)	9 (1.3)[a]
Discontinuations - Reason, n (%)			
Any reason	***6 (54.5)***	***3 (60.0)***	***9 (56.3)***
Adverse event/HIV-related event	3 (27.3)	1 (20.0)	4 (25.0)
Subject withdrew consent	2 (18.2)	2 (40.0)	4 (25.0)
Subject reached a virologic endpoint	1 (9.1)	0	1 (6.3)
Switch to extension	5 (45.5)	0	5 (31.3)

N = number of subjects; n = number of observations
a Including Subject CRF ID 211-0519 who withdrew consent before taking any drug during the rollover phase.
Source: Display GEN.2

4.9.1.1 EXTENT OF EXPOSURE

Treatment duration during the rollover phase is provided in Table 94 (see also Display GEN.8).

Table 94: Extent of Exposure - Rollover Phase

Total Duration (Weeks)	DRV/rtv-rollover N = 11	LPV/rtv-rollover N = 5	All Subjects N = 16
Mean (SE)	45.7 (13.51)	55.6 (17.37)	48.8 (10.50)
Median (range)	36.3 (1.0; 107.7)	44.7 (16.0; 97.0)	40.5 (1.0; 107.7)
Patient years of exposure	9.7	5.3	15.0

N = number of subjects; n = number of observations
[a] Patient years exposure = mean number of weeks treated x N / 52 weeks
Source: Display GEN.8

4.9.1.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The main demographic and disease characteristics of the subjects participating in the rollover phase are summarized in Table 95 and Table 96, respectively (see also Display GEN.8 [Week 96] and Display GEN.10 [Week 96]). These tables reflect the demographic and disease characteristics at trial entry of the subjects who where in the rollover phase in the Week-96 analysis (N = 15). Selected demographic and disease characteristics of the additional rolled-over subject in the Week-192 analysis (CRF ID 211-0653) are described separately. Individual subject data on demographics and disease characteristics are provided in Listing GEN.6 (Week 96), and Listing GEN.7 (Week 96), Listing EFF.1, and Listing EFF.3, respectively.

Table 95: Demographic Data - Rollover Phase

Demographic Parameter	DRV/rtv-rollover	LPV/rtv-rollover	All Subjects
Sex, n (%), N	**11**	**4**	**15**
Female	5 (45.5)	0	5 (33.3)
Male	6 (54.5)	4 (100.0)	10 (66.7)
Age (years), N	**11**	**4**	**15**
Mean (SD)	29.5 (8.72)	32.3 (9.60)	30.2 (8.70)
Median (Range)	26.0 (19; 46)	29.5 (24; 46)	28.0 (19; 46)
Age, n (%), N	**11**	**4**	**15**
≤ 30	6 (54.5)	2 (50.0)	8 (53.3)
31 - ≤ 45	4 (36.4)	1 (25.0)	5 (33.3)
46 - ≤ 55	1 (9.1)	1 (25.0)	2 (13.3)
Height (cm), N	**11**	**4**	**15**
Mean (SD)	164.6 (10.65)	178.3 (4.99)	168.3 (11.20)
Median (Range)	167.5 (138; 179)	176.9 (174; 185)	168.0 (138; 185)
Weight (kg), N	**11**	**4**	**15**
Mean (SD)	64.0 (13.54)	66.1 (7.59)	64.5 (12.01)
Median (Range)	66.0 (34; 78)	66.7 (58; 73)	66.0 (34; 78)
Body mass index (kg/m²), N	**11**	**4**	**15**
Mean (SD)	23.4 (4.25)	20.8 (2.04)	22.7 (3.91)
Median (Range)	23.2 (18; 31)	20.7 (18; 23)	21.2 (18; 31)
Race, n (%), N	**11**	**4**	**15**
Black	2 (18.2)	2 (50.0)	4 (26.7)
Caucasian/White	2 (18.2)	2 (50.0)	4 (26.7)
Hispanic	4 (36.4)	0	4 (26.7)
Oriental/Asian	2 (18.2)	0	2 (13.3)
Other	1 (9.1)	0	1 (6.7)

N = number of subjects; n = number of observations

Source: Display GEN.8 (Week 96)

Table 96: Baseline Disease Characteristics - Rollover Phase

Disease Characteristic	Treatment Phase[a]		Rollover Phase[b]	
	LPV/rtv	DRV/rtv	DRV/rtv-rollover	LPV/rtv-rollover
Log_{10} viral load (Copies/mL), N	**11**	**4**	**11**	**4**
Mean (SD)	4.92 (0.612)	5.47 (0.236)	3.73 (1.472)	4.03 (2.739)
Median (Range)	4.78 (4.13; 5.97)	5.42 (5.27; 5.79)	4.28 (1.69; 5.82)	3.73 (1.69; 6.95)
Viral load, n (%), N	**11**	**4**	**11**	**4**
< 20,000 copies/mL	2 (18.2)	0	6 (54.5)	2 (50.0)
20,000 - < 50,000 copies/mL	2 (18.2)	0	1 (9.1)	0
50,000 - < 100,000 copies/mL	3 (27.3)	0	1 (9.1)	0
≥ 100,000 copies/mL	4 (36.4)	4 (100.0)	3 (27.3)	2 (50.0)
CD4+ cell count (x10^6 /L), N	**11**	**4**	**11**	**3**
Mean (SD)	238 (123.4)	171 (159.6)	362 (191.0)	284 (217.8)
Median (Range)	219 (58; 421)	142 (11; 389)	329 (186; 907)	167 (149; 535)
CD4+ cell count, n (%), N	**11**	**4**	**11**	**3**
< 50 x 10^6 cells/L	0	1 (25.0)	0	0
50 - < 100 x 10^6 cells/L	2 (18.2)	0	0	0
100 - < 200 x 10^6 cells/L	3 (27.3)	2 (50.0)	1 (9.1)	2 (66.7)
200 - < 350 x 10^6 cells/L	3 (27.3)	0	7 (63.6)	0
≥ 350 x 10^6 cells/L	3 (27.3)	1 (25.0)	3 (27.3)	1 (33.3)
Duration HIV infection (years), N	**11**	**4**	-	-
Mean (SD)	1.3 (1.36)	1.2 (1.41)	-	-
Median (Range)	0.3 (0; 4)	0.8 (0; 3)	-	-
Clinical stage of HIV infection, n (%), N	**11**	**4**	-	-
A	7 (63.6)	2 (50.0)	-	-
B	3 (27.3)	1 (25.0)	-	-
C	1 (9.1)	1 (25.0)	-	-
Clade, n (%), N	**11**	**4**	**11**	**4**
B	8 (72.7)	4 (100.0)	8 (72.7)	4 (100.0)
C	2 (18.2)	0	2 (18.2)	0
CRF01_AE	1 (9.1)	0	1 (9.1)	0

N = number of subjects; n = number of observations

[a] Information available at baseline of treatment phase.

[b] Information available at baseline of rollover phase.

Source: Display GEN.10 (Week 96)

The additional rollover subject in the Week-192 analysis (CRF ID 211-0653) was a 27-year-old, Caucasian/White female, with height 1.53 m, weight 46 kg, and BMI 19.6 kg/m^2. At baseline of the treatment phase, this subject had a log_{10} viral load of 5.00 copies/mL, CD4+ cell count of 32, clinical stage of HIV infection B, and the known duration of HIV infection was 8.8 years. At baseline of the rollover phase, this subject had a log_{10} viral load of 5.00 copies/mL, and CD4+ cell count of 174.

4.9.2 Efficacy Results

4.9.2.1 VIROLOGIC EFFICACY

The observed virologic response defined as the percentages of subjects with viral load < 50 and < 400 copies/mL (Observed Case) during the rollover phase is summarized in Table 97 (see also Display EFF.17). The observed mean change in $\log_{10}$ viral load from baseline (Observed Case) during the rollover phase is summarized in Table 98 (see also Display EFF.4). Individual subject data for virologic efficacy are provided in Listing EFF.1.

At the time of the data cut-off, 6 DRV/rtv-rollover subjects and 4 LPV/rtv-rollover subjects had reached the Week-24 time point. Virologic response (plasma viral load < 50 copies/mL) was observed for 5 DRV/rtv-rollover subjects and 2 LPV/rtv-rollover subjects. The mean change in $\log_{10}$ viral load from baseline was -0.89 and -3.21 $\log_{10}$ copies/mL, respectively.

Two subjects in both treatment groups had reached the Week-96 time point, and all these subjects achieved a plasma viral load < 50 copies/mL. The mean change in $\log_{10}$ viral load from baseline was -0.39 and -2.63 $\log_{10}$ copies/mL for the DRV/rtv-rollover and LPV/rtv-rollover subjects, respectively.

Table 97: Observed Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 and < 400 Copies/mL per Time Point - Rollover Phase

	DRV/rtv-rollover		LPV/rtv-rollover	
Time Point	**N**	**Number of Responders, n (%)**	**N**	**Number of Responders, n (%)**
Viral Load < 50 Copies/mL				
Week 2	9	5 (55.6)	5	1 (20.0)
Week 4	8	3 (37.5)	4	1 (25.0)
Week 8	7	4 (57.1)	4	1 (25.0)
Week 12	7	5 (71.4)	3	1 (33.3)
Week 16	6	6 (100)	4	1 (25.0)
Week 24	6	5 (83.3)	4	2 (50.0)
Week 36	6	3 (50.0)	3	2 (66.7)
Week 48	4	4 (100)	3	1 (33.3)
Week 60	4	3 (75.0)	2	2 (100)
Week 72	4	4 (100)	2	2 (100)
Week 84	3	3 (100)	2	2 (100)
Week 96	2	2 (100)	2	2 (100)
Viral Load < 400 Copies/mL				
Week 2	9	7 (77.8)	5	2 (40.0)
Week 4	8	6 (75.0)	4	1 (25.0)
Week 8	7	6 (85.7)	4	2 (50.0)
Week 12	7	6 (85.7)	3	1 (33.3)
Week 16	6	6 (100)	4	3 (75.0)
Week 24	6	5 (83.3)	4	4 (100)
Week 36	6	5 (83.3)	3	2 (66.7)
Week 48	4	4 (100)	3	2 (66.7)
Week 60	4	4 (100)	2	2 (100)
Week 72	4	4 (100)	2	2 (100)
Week 84	3	3 (100)	2	2 (100)
Week 96	2	2 (100)	2	2 (100)

N = number of subjects; n = number of observations

Source: Display EFF.17

Table 98: Observed Mean and Median Change in log_{10} Plasma Viral Load From Baseline - Rollover Phase

Time Point	DRV/rtv-rollover N	DRV/rtv-rollover Mean (SE) Median (Range)	LPV/rtv-rollover N	LPV/rtv-rollover Mean (SE) Median (Range)
Baseline Log_{10} Viral Load (Copies/mL)				
Baseline	11	3.73 (0.444) 4.28 (1.7; 5.8)	5	4.38 (1.118) 5.78 (1.7; 6.9)
Change Versus Baseline in Log_{10} Viral Load (Copies/mL)				
Week 2	9	-1.14 (0.276) -1.11 (-2.6; 0.0)	5	-0.86 (0.556) -0.06 (-2.3; 0.2)
Week 4	8	-1.06 (0.358) -0.62 (-2.4; 0.0)	4	-1.95 (0.668) -2.47 (-2.8; 0.0)
Week 8	7	-1.20 (0.464) -0.94 (-3.1; 0.0)	4	-2.37 (0.841) -2.87 (-3.8; 0.0)
Week 12	7	-1.02 (0.482) -0.52 (-3.1; 0.1)	3	-2.35 (1.207) -3.05 (-4.0; 0.0)
Week 16	6	-1.24 (0.531) -0.73 (-3.1; 0.0)	4	-2.80 (1.004) -3.24 (-4.7; 0.0)
Week 24	6	-0.89 (0.463) -0.52 (-3.1; 0.0)	4	-3.21 (1.127) -3.81 (-5.2; 0.0)
Week 36	6	-0.82 (0.476) -0.48 (-3.1; 0.0)	3	-1.79 (1.735) -0.10 (-5.3; 0.0)
Week 48	4	-0.43 (0.201) -0.39 (-0.9; 0.0)	3	-1.54 (1.434) -0.22 (-4.4; 0.0)
Week 60	4	-0.37 (0.153) -0.39 (-0.7; 0.0)	2	-2.63 (2.628) -2.63 (-5.3; 0.0)
Week 72	4	-0.43 (0.201) -0.39 (-0.9; 0.0)	2	-2.63 (2.628) -2.63 (-5.3; 0.0)
Week 84	3	-0.57 (0.198) -0.52 (-0.9; -0.3)	2	-2.63 (2.628) -2.63 (-5.3; 0.0)
Week 96	2	-0.39 (0.133) -0.39 (-0.5; -0.3)	2	-2.63 (2.628) -2.63 (-5.3; 0.0)

N = number of subjects; n = number of observations
Source: Display EFF.2, Display EFF.4

4.9.2.2 IMMUNOLOGIC CHANGE

The observed mean change in CD4+ cell count from baseline during the rollover phase is summarized in Table 99 (see also Display EFF.42). Individual subject data for the change in CD4+ cell count from baseline are provided in Listing EFF.3.

At Week 24 of the rollover phase, 6 DRV/rtv-rollover subjects and 3 LPV/rtv-rollover subjects had paired immunology data. The change in CD4+ cell count from baseline was 112 x 10^6/L for the DRV/rtv-rollover subjects and 125 x 10^6/L for the LPV/rtv-rollover subjects. The median change in CD4+ cell count was 133 and 117 x 10^6/L, respectively.

Table 99: Observed Mean and Median Change in CD4+ Cell Count From Baseline - Rollover Phase

Time Point	DRV/rtv-rollover N	DRV/rtv-rollover Mean (SE) Median (Range)	LPV/rtv-rollover N	LPV/rtv-rollover Mean (SE) Median (Range)
Baseline CD4+ Cell Count (x 10^6/L)				
Baseline	11	362 (57.6) 329 (186; 907)	4	256 (93.1) 171 (149; 535)
Change Versus Baseline in Cell Count (x 10^6/L)				
Week 2	9	19 (31.3) 20 (-115; 170)	3	120 (50.2) 159 (20; 180)
Week 4	8	-8 (15.4) 9 (-80; 46)	3	123 (27.7) 115 (80; 175)
Week 8	7	-4 (26.1) -29 (-100; 75)	3	111 (49.8) 128 (18; 188)
Week 12	7	45 (51.6) -9 (-77; 265)	3	207 (57.6) 199 (111; 310)
Week 16	6	-9 (31.9) 12 (-128; 84)	3	175 (32.3) 151 (135; 239)
Week 24	6	112 (42.4) 133 (-40; 269)	3	125 (11.7) 117 (110; 148)
Week 36	6	67 (48.2) 101 (-89; 200)	2	107 (131.0) 107 (-24; 238)
Week 48	4	21 (41.2) -4 (-46; 138)	1	143 (-) 143 (143; 143)
Week 60	4	143 (42.7) 119 (69; 263)	1	66 (-) 66 (66; 66)
Week 72	4	105 (65.0) 88 (-30; 273)	1	178 (-) 178 (178; 178)
Week 84	3	213 (61.0) 186 (124; 330)	1	182 (-) 182 (182; 182)
Week 96	2	6 (113.0) 6 (-107; 119)	0	-

N = number of subjects; n = number of observations
Source: Display EFF.40, Display EFF.42

4.9.3 Safety

4.9.3.1 ADVERSE EVENTS

4.9.3.1.1 Summary of All Adverse Events.

A summary of the AEs reported during the rollover phase in this trial is provided in Table 100 (see also Display SAF.1). The incidence of AEs reported in > 1 subject in any treatment group during the rollover phase is summarized in Table 101. For an overview of all AEs during the rollover phase, see Display SAF.2. Individual subject data for AEs are provided in Listing SAF.1.

Ten of the DRV/rtv-rollover subjects and 4 of the LPV/rtv-rollover subjects experienced ≥ 1 AE during the rollover phase. The most frequent AEs (by preferred term, observed in ≥ 2 subjects in any treatment group) were headache (2 and 1 in DRV/rtv- and LPV/rtv-rollover subjects, respectively), upper respiratory tract infection (1 and 2 subjects), nausea and vomiting (each

in 0 and 2 subjects), and bronchitis (2 and 0 subjects). All other AEs during the rollover phase occurred in at most 1 subject in either treatment group.

Table 100: Adverse Events: Summary Table - Rollover Phase

n (%)	DRV/rtv-rollover N = 11	LPV/rtv-rollover N = 5
≥ 1 AE	10 (90.9)	4 (80.0)
≥ 1 SAE	1 (9.1)	0
≥ 1 grade 3 or 4 AE	3 (27.3)	2 (40.0)
≥ 1 AE at least possibly related to the PI[a]	5 (45.5)	3 (60.0)
≥ AE leading to permanent discontinuation	3 (27.3)	1 (20.0)

N = number of subjects; n = number of observations
[a] DRV/rtv or LPV/rtv
Source: Display SAF.1

Table 101: Adverse Events Reported in > 1 Subject of any Treatment Group (Regardless of Severity and Causality) - Rollover Phase

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv-rollover N = 11	LPV/rtv-rollover N = 5
Any AE	***10 (90.9)***	***4 (80.0)***
Gastrointestinal Disorders	**1 (9.1)**	**3 (60.0)**
Nausea	0	2 (40.0)
Vomiting	0	2 (40.0)
Infections and Infestations	**6 (54.5)**	**3 (60.0)**
Bronchitis	2 (18.2)	0
Upper respiratory tract infection	1 (9.1)	2 (40.0)
Metabolism and Nutrition Disorders	**4 (36.4)**	**1 (20.0)**
Musculoskeletal and Connective Tissue Disorders	**0**	**2 (40.0)**
Nervous System Disorders	**2 (18.2)**	**2 (40.0)**
Headache	2 (18.2)	1 (20.0)
Respiratory, Thoracic and Mediastinal Disorders	**1 (9.1)**	**2 (40.0)**
Skin and Subcutaneous Tissue Disorders	**2 (18.2)**	**3 (60.0)**

N = number of subjects; n = number of observations
Source: Display SAF.2

The incidence of grade 3 or 4 AEs during the rollover phase is provided in Table 102 (see also Display SAF.25). Grade 3 or 4 AEs were reported in 3 DRV/rtv-rollover subjects and 2 LPV/rtv-rollover subjects. All grade 3 or 4 AEs occurred in only 1 subject each.

Table 102: Grade 3 or 4 Adverse Events (Regardless of Causality) - Rollover Phase

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv-rollover N = 11	LPV/rtv-rollover N = 5
Any Grade 3 or 4 AE	**3 (27.3)**	**2 (40.0)**
Blood and Lymphatic System Disorders	**1 (9.1)**	**0**
Neutropenia	1 (9.1)	0
General Disorders and Administration Site Conditions	**0**	**1 (20.0)**
Pyrexia	0	1 (20.0)
Investigations	**1 (9.1)**	**0**
Transaminases increased	1 (9.1)	0
Metabolism and Nutrition Disorders	**1 (9.1)**	**0**
Hyperlipidemia	0	1 (20.0)
Nervous System Disorders		
Headache	1 (9.1)	0

N = number of subjects; n = number of observations
Source: Display SAF.25

4.9.3.1.2 Deaths, Other Serious Adverse Events, and Adverse Events Leading to Permanent Treatment Discontinuation

No subjects died during the rollover phase.

The incidence of SAEs and AEs leading to permanent discontinuation of the trial medication during the rollover phase is presented in Display SAF.23 and Display SAF.28, respectively. Narratives on SAEs (if considered at least probably drug related) and AEs leading to discontinuation are provided in TMC114-C211-W192-narratives.

One SAE was reported during the rollover phase: transaminases increased (CRF ID 211-0318, DRV/rtv-rollover, grade 4, probably related). This event led to permanent discontinuation of trial treatment.

Three additional AEs reported during the rollover phase led to permanent discontinuation of the trial medication: rash macular (CRF ID 211-0114, DRV/rtv-rollover, grade 2, doubtfully related), headache (CRF ID 211-0266, DRV/rtv-rollover, grade 4, probably related), and stomach discomfort (CRF ID 211-0344, LPV/rtv-rollover, grade 2, very likely related).

4.9.3.2 Clinical Laboratory Evaluation

In this section, laboratory abnormalities during the rollover phase that were treatment-emergent, i.e., those abnormalities that first occurred or worsened after the start of the rollover phase, are presented.

The incidence of selected parameters of interest for liver, lipid and glucose, and hematology laboratory tests (see Section 1.1.1) is provided in Table 103, Table 104, and Table 105, respectively (see also Display SAF.46 and Display SAF.47). Individual subject data on laboratory abnormalities for subjects with grade 3 or 4 laboratory abnormalities are provided in Listing SAF.10, Listing SAF.11, and Listing SAF.12.

Laboratory abnormalities were infrequent during the rollover phase.

One DRV/rtv-rollover subject (CRF ID 211-0255) had both grade 4 ALT and grade 4 AST abnormalities.

Two subjects (CRF ID 211-0226, DRV/rtv-rollover; 211-0653, 1 LPV-rtv-rollover) had both grade 3 increased total cholesterol and grade 3 increased high LDL.

Two DRV/rtv-rollover subjects (CRF ID 211-0318, 211-0683) and 1 LPV/rtv subject-rollover (CRF ID 211-0344) had grade 4 neutrophil count.

There were no abnormalities for general biochemistry laboratory parameters of interest during the rollover phase.

Table 103: Treatment-Emergent Liver-Related Laboratory Abnormalities of Interest - Rollover Phase

Laboratory Parameter Worst Grade, n (%)	DRV/rtv	LPV/rtv
ALT, N	**9**	**4**
Grade 1	2 (22.2)	1 (20.0)
Grade 2	0	1 (20.0)
Grade 3	0	0
Grade 4	1 (11.1)	0
AST, N	**9**	**4**
Grade 1	0	1 (20.0)
Grade 2	0	0
Grade 3	0	0
Grade 4	1 (11.1)	0

N = number of subjects; n = number of observations

Source: Display SAF.46, Display SAF.47

Table 104: Treatment-Emergent Lipid-and Glucose-Related Laboratory Abnormalities of Interest - Rollover Phase

Laboratory Parameter Worst Grade/Abnormality, n (%)	DRV/rtv	LPV/rtv
Triglycerides, N	**9**	**4**
Grade 1	0	0
Grade 2	1 (11.1)	0
Grade 3	0	0
Grade 4	0	0
Total cholesterol, N	**9**	**4**
Grade 1	1 (11.1)	3 (60.0)
Grade 2	1 (11.1)	0
Grade 3	1 (11.1)	1 (20.0)
Grade 4	0	0
LDLc, N	**9**	**4**
Grade 1	2 (22.2)	1 (20.0)
Grade 2	1 (11.1)	0
Grade 3	1 (11.1)	1 (20.0)
Grade 4	0	0
HDL, N	**9**	**4**
Above	1 (11.1)	1 (20.0)
Below	2 (22.2)	0
Hyperglycemia, N	**9**	**4**
Grade 1	0	0
Grade 2	1 (11.1)	0
Grade 3	0	0
Grade 4	0	0

N = number of subjects; n = number of observations
Source: Display SAF.46, Display SAF.47

Table 105: Treatment-Emergent Hematology Laboratory Abnormalities of Interest - Rollover Phase

Laboratory Parameter Worst Grade/Abnormality, n (%)	DRV/rtv	LPV/rtv
WBC count, N	**9**	**4**
Grade 1	2 (22.2)	0
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
Neutrophil count, N	**9**	**4**
Grade 1	0	0
Grade 2	0	0
Grade 3	0	0
Grade 4	2 (22.2)	1 (25.0)
Hematocrit, N	**9**	**4**
Above	1 (11.1)	0
Below	0	2 (50.0)
RBC count, N	**9**	**4**
Above	1 (11.1)	0
Below	2 (22.2)	1 (25.0)

N = number of subjects; n = number of observations
Source: Display SAF.46, Display SAF.47

For the incidence of AEs related to liver, and lipid and glucose laboratory abnormalities, refer to Display SAF.2 (all grades) and Display SAF.25 (grade 3 or 4 AEs).

All AEs related to laboratory abnormalities during the rollover phase occurred in 6 subjects and all AEs occurred in only 1 subject.

Three AEs related to laboratory abnormalities during the rollover phase were grade 3 or 4 in severity: neutropenia (grade 4, possibly related, leading to temporary treatment interruption for 1 day) in 1 DRV-rollover subject (CRF ID 211-0683), transaminases increased (grade 4, probably related) in 1 DRV-rtv-rollover subject (CRF ID 211-0318, this AE was reported as an SAE and led to treatment discontinuation, see Section 4.9.3.1.2), hyperlipidemia (grade 3, possibly related) in 1 LPV-rtv-rollover subject (CRF ID 211-0653).

No other AEs related to laboratory abnormalities during the rollover phase were reported as an SAE or led to permanent discontinuation of the trial medication.

4.9.3.3 CARDIOVASCULAR SAFETY

In this section, vital signs and ECG abnormalities during the rollover phase that were treatment-emergent, i.e., those abnormalities that first occurred or worsened after the start of the rollover phase, are presented.

The incidence of vital signs and ECG abnormalities during the rollover phase is provided in Table 106 (see also Display 66, Display 68, Display SAF.59, and Display SAF.60). Individual subject data on vital signs and ECG are provided in Listing SAF.20, Listing SAF.18, and Listing SAF.19, respectively.

Vital signs abnormalities were mostly blood-pressure-related abnormalities. No grade 3 vital signs abnormalities were observed.

Two DRV/rtv-rollover subjects had an ECG abnormality during the rollover phase: abnormally low heart rate in 1 subject, and QtcF and QtcB increases between 30 and 60 ms in 1 subject.

There was 1 AE related to a vital signs abnormality (supraventricular extrasystoles, grade 1, not related).

Table 106: Treatment-Emergent Vital Signs and ECG Abnormalities (Worst Grade) - Rollover Phase

Parameter, Worst Grade/Abnormality, n (%)	DRV/rtv-rollover	LPV/rtv-rollover
Vital Signs		
Standing pulse (bpm), N	**9**	**5**
Abnormally high	0	0
Abnormally low	1 (11.1)	0
Standing SBP (mmHg), N	**9**	**5**
Grade 1	0	1 (20.0)
Grade 2	0	0
Grade 3	0	0
Abnormally low	0	0
Supine SBP (mmHg), N	**9**	**5**
Grade 1	0	1 (20.0)
Grade 2	0	0
Grade 3	0	0
Abnormally low	2 (22.2)	0
Standing DBP (mmHg), N	**9**	**5**
Grade 1	0	1 (20.0)
Grade 2	0	1 (20.0)
Grade 3	0	0
Abnormally low	2 (22.2)	0
Supine DBP (mmHg), N	**9**	**5**
Grade 1	1 (11.1)	0
Grade 2	0	0
Grade 3	0	0
Abnormally low	1 (11.1)	0
ECG		
Heart rate (bpm), N	**7**	**4**
Abnormally high	0	0
Abnormally low	1 (12.5)	0
QTcF (ms), N	**7**	**4**
Increase by 30 - 60 ms	1 (12.5)	0
Increase by > 60 ms	0	0
QTcB (ms), N	**7**	**4**
Increase by 30 - 60 ms	1 (12.5)	0
Increase by > 60 ms	0	0

N = number of subjects; n = number of observations

[a] For the definition of the vital signs abnormalities, refer to Addendum 11 of the Protocol in Appendix 8.1.1 and the Statistical Analysis Plan (SAP) in Appendix 8.1.8.

Source: Display 66, Display 68, Display SAF.59, Display SAF.60

4.9.4 Conclusions on the Rollover Phase

On 29 March 2010, 5 DRV/rtv-treated subjects and 11 LPV/rtv-treated subjects had permanently discontinued trial medication during the treatment period (main phase) and continued in the rollover phase of the trial. Of these, 9 subjects (6 DRV/rtv-rollover subjects and 3 LPV/rtv-rollover subjects) prematurely discontinued treatment during the rollover phase. The mean duration of treatment was 45.7 weeks for the DRV/rtv subjects and 55.6 weeks for the LPV/rtv subjects.

At the time the rollover phase ended, 6 DRV/rtv-rollover subjects and 4 LPV/rtv-rollover subjects had reached the Week-24 time point. Virologic response (plasma viral load < 50 copies/mL) was observed for 5 DRV/rtv-rollover subjects and 2 LPV/rtv-rollover subjects The change in $\log_{10}$ viral load from baseline was at Week 24 -0.89 and -3.21 $\log_{10}$ copies/mL for the DRV/rtv-rollover and LPV/rtv-rollover subjects, respectively. The mean change in CD4+ cell count from baseline at Week 24 was 112 x 10^6/L for the DRV/rtv-rollover subjects and the mean change from baseline was 125 x 10^6/L for the LPV/rtv-rollover subjects. The median change in CD4+ cell count was 133 and 117 x 10^6/L, respectively.

Ten (90.9%) DRV/rtv subjects and 4 (80.0%) LPV/rtv subjects experienced ≥ 1 AE during the rollover phase. The most frequent AEs were headache, upper respiratory tract infection, nausea, vomiting and bronchitis. All other AEs occurred in ≤ 1 subject in either treatment group. Grade 3 or 4 AEs were reported in 3 DRV/rtv-rollover subjects and 2 LPV/rtv-rollover subjects. All grade 3 or 4 AEs occurred in only 1 subject each. No subjects died during the rollover phase. One SAE was reported in a DRV/rtv subject (transaminases increased). This event led to permanent discontinuation of trial treatment. Three additional AEs (rash macular, headache, and stomach discomfort) led to permanent discontinuation of trial medication.

Laboratory abnormalities were infrequent during the rollover phase. One DRV/rtv-rollover subject had grade 4 liver-related abnormalities (ALT and AST increased). Two subjects (1 DRV/rtv-rollover and 1 LPV/rtv-rollover subject) had grade 3 lipid-related laboratory abnormalities (both total cholesterol as well as LDLc increased). Two DRV/rtv-rollover subjects and 1 LPV/rtv-rollover subject experienced grade 4 neutrophil counts. There were no abnormalities for general biochemistry laboratory parameters of interest.

Vital signs abnormalities (all grade 1 or 2) were mostly blood-pressure-related abnormalities, and 2 subjects had an ECG abnormality (abnormally low heart rate; QtcF and QtcB increase between 30 and 60 ms) during the rollover phase.

4.10 DISCUSSION AND OVERALL CONCLUSIONS

Trial TMC114-C211 enrolled a population of ART-naïve, HIV-1 infected subjects that included a majority of subjects with early stage of HIV disease. The mean time since HIV-1 infection diagnosis was 2.5 years. The trial population included a high percentage of female subjects (approximately 30%) and was enrolled in a variety of geographic regions with subjects of differing ethnic backgrounds; 42% of subjects were Caucasian, 22% were Black, 22% were Hispanic and 12% were Asian. A similar percentage of subjects in the DRV/rtv and LPV/rtv treatment groups were coinfected with hepatitis B or C virus at baseline.

At baseline, the mean $\log_{10}$ viral load for all subjects was 4.85 $\log_{10}$ copies/mL; 18.7% of subjects had a baseline viral load < 20,000 copies/mL and 34.4% had a baseline viral load ≥ 100,000 copies/mL. The median baseline CD4+ cell count for all subjects was 225 x 10^6/L; 58.1% of subjects had a baseline CD4+ cell count ≥ 200 x 10^6/L and 16.2% had a baseline CD4+ cell count < 100 x 10^6/L. The majority of subjects (64.3%) had CDC category A HIV infection at time of entry into the trial; 8.7% had CDC category C. The mean time since HIV-1 infection diagnosis was 2.5 years.

There was a high diversity of clades in the trial population, with 39.2% of subjects harboring non-clade B viruses. The occurrence of natural polymorphisms in the different clades is reflected in the median number of PI RAMs (4; range: 0 - 11) observed at baseline. The prevalence of PI RAMs in this trial is in agreement with the reported prevalence in PI-naïve infected subjects[34]. The median number of primary PI mutations at baseline was 0 (range: 0 - 3), the median number of DRV RAMs and LPV RAMs was 0 (range: 0 - 2) and 1 (range: 0 - 6), respectively.

4.10.1 Efficacy

The Week-192 efficacy results of this trial in treatment-naïve subjects demonstrated statistically significant noninferiority in confirmed virologic response (plasma viral load < 50 copies/mL) at Week 192 with DRV/rtv 800/100 mg q.d. compared to LPV/rtv 800/200 mg total daily dose, both in combination with a fixed background regimen of TDF/FTC, in view of the predefined delta of 12%. At Week 192, virologic response defined as the percentage of subjects with confirmed plasma viral load < 50 copies/mL (ITT - TLOVR) was 68.8% for the DRV/rtv group and 57.2% for the LPV/rtv group. The lower limit of the 95% CI of the difference between the treatment groups was > -12% (i.e., delta, the maximum allowable difference). The estimated difference [95% CI] between the treatment groups was 11.6 [4.4; 18.8] and was statistically significant, thereby demonstrating noninferiority (p-value < 0.001). The lower limit of the 95% CI for the difference in virologic response was above 0, and the secondary objective to test for superiority of DRV/rtv over LPV/rtv showed a statistically significant difference between the treatments, thus superiority of DRV/rtv over LPV/rtv in this patient population could be concluded (p = 0.002).

The results for virologic response (plasma viral load < 50 copies/mL) were robust and consistent as confirmed by different sensitivity analyses.

Subgroup analyses consistently showed a higher virologic response with DRV/rtv compared to LPV/rtv at Week 192 across subgroups by baseline viral load, gender, region, age, and clade. In both subgroups for the stratification factor viral load subjects receiving DRV/rtv had a statistically superior virologic response compared with subjects receiving LPV/rtv (< 100,000

copies/mL, p = 0.038; ≥ 100,000 copies/mL, p = 0.012). In addition, subjects with CD4+ cell counts ≥ 200 x 10^6 cells/L at baseline receiving DRV/rtv demonstrated statistical superiority in virologic responses compared with LPV/rtv (p = 0.014). In subjects with baseline CD4+ cell counts < 200 x 10^6 cells/L, DRV/rtv was shown to be noninferior compared to LPV/rtv (p < 0.001).

Virologic response was well sustained in both treatment groups. Of the DRV/rtv subjects with a confirmed virologic response of < 50 copies/mL (undetectable) at Week 48, 81.3% remained undetectable at Week 192 versus 68.5% with LPV/rtv. When comparing the Weeks-96 and -192 results, 87.7% of DRV/rtv subjects and 80.0% of LPV/rtv subjects remained undetectable at Week 192 if they were undetectable at Week 96.

The results for virologic response defined as the percentage of subjects with confirmed plasma viral load < 400 copies/mL were in line with those for the primary virologic response parameter. At Week 192, virologic response (ITT - TLOVR) was 75.2% and 65.0% for the DRV/rtv and LPV/rtv groups, respectively (estimated difference [95% CI]: 10.2 [3.4; 17.0]; lower limit of the 95% CI > -12%). The between-group difference was statistically significant, demonstrating noninferiority (p < 0.001). The lower limit of the 95% CI for the difference in virologic response was also above 0, and thus superiority of DRV/rtv over LPV/rtv for this parameter could be concluded (p = 0.002).

The results for the other secondary efficacy parameters were also supportive of those for the primary virologic response parameter.

The mean change in $\log_{10}$ viral load from baseline (ITT - NC = F) at Week 192 was -2.35 and -2.03 $\log_{10}$ copies/mL for the DRV/rtv and LPV/rtv groups, respectively (difference [95% CI]: -0.32 [-0.55; 0.09]. The between-group difference was statistically significant (ANCOVA, p = 0.007).

There was no statistically significant difference between the treatment groups with respect to the time to virologic response (viral load < 50 copies/mL) (p = 0. 5197). In contrast, statistical analysis of the time to loss of virologic response showed a between-group difference that was statistically significant for < 50 copies/mL (TLOVR) (p = 0.0034), with a smaller probability of failing under DRV/rtv treatment compared to LPV/rtv treatment (hazard ratio [95% CI]: 0.69 [0.54; 0.88]).

Immunologic response was similar in the DRV/rtv and LPV/rtv treatment groups. The median change in CD4+ cell count from baseline (ITT - NC = F) at Week 192 was 258 and 263 x 10^6/L for the DRV/rtv and LPV/rtv groups, respectively. Mean change at Week 192 was 266 x 10^6 cells/L and 269 x 10^6 cells/L, respectively. Also when considering immunologic results by CD4+ cell count category, there were no relevant differences between the DRV/rtv and LPV/rtv groups both at baseline and at Week 192.

The percentage of adherent subjects determined by the M-MASRI questionnaire for DRV/rtv subjects ranged from 82.0% to 89.4% and for LPV/rtv subjects ranged from 78.3% to 86.1% at the successive time points. There was no statistically significant difference between the treatment groups with respect to the percentage of adherent subjects during the trial.

Overall, the efficacy responses observed in subjects receiving DRV/rtv 800/100 mg q.d., the consistently higher response rates compared with LPV/rtv 800/200 mg (total daily dose) and

low number of virologic failures provide further evidence of the durable potency of a DRV/rtv-containing regimen in the treatment-naïve HIV-1 infected patient population.

4.10.2 Resistance

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 (viral load > 50 copies/mL) 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.

In general there was almost no development of PI resistance and a low level of NRTI resistance observed in the virologic failures of both treatment groups. The absence of genotypic or phenotypic resistance in virologic failures is not uncommon and has been described for other boosted PIs in treatment-naïve patients[16]. Failure of a first-line boosted PI-based regimen virtually always occurs in the presence of a wildtype HIV-1 protease (complete lack of major protease mutations at virologic failure)[38,39] and initial therapy with boosted PI regimens results in less resistance within and across drug classes[40].

4.10.3 Safety

The 4-year safety data from trial TMC114-C211 (192 weeks, cut-off data 29 March 2010) demonstrated that DRV/rtv 800/100 mg q.d. was generally safe and well tolerated in the studied population. This regimen was associated with a lower incidence of diarrhea, nausea and vomiting compared with LPV/rtv 800/200 mg total daily dose. Furthermore, the incidence of increased triglycerides and increased total cholesterol was lower with DRV/rtv than with LPV/rtv in this population. The incidence of rash-related AEs was higher with DRV/rtv than with LPV/rtv.

The most frequent (≥ 10%) AEs were diarrhea (39.4% and 54.9% with DRV/rtv and LPV/rtv, respectively), upper respiratory tract infection (24.5% and 23.1%), headache (22.4% and 17.6%), nausea (18.4% and 30.3%), nasopharyngitis (17.2% and 14.5%), abdominal pain (12.8% and 14.5%), cough (12.2% and 14.7%), bronchitis (11.1% and 11.8%), back pain (11.1% and 8.1%), rash (10.2% and 8.7%), influenza (8.7% and 12.7%), fatigue (8.7% and 10.7%), and vomiting (8.2% and 13.3%). Diarrhea, nausea and vomiting were reported less frequently with DRV/rtv than with LPV/rtv.

AEs considered at least possibly related to the PI were less frequent with DRV/rtv (56.6%) than with LPV/rtv (74.9%). The most frequent (≥ 5%) AEs considered at least possibly related to DRV/rtv or LPV/rtv, respectively, were diarrhea (24.5% and 48.6%), nausea (14.0% and 25.7%),

headache (6.4% and 8.1%), abdominal pain (3.5% and 6.9%), vomiting (3.2% and 8.1%), hypercholesterolemia (2.9% and 5.8%), and hypertriglyceridemia (2.0% and 7.5%).

AEs ≥ grade 2 and considered by the investigator at least possibly related to the PI were also less frequent with DRV/rtv (28.0%) than with LPV/rtv (35.8%). The most frequent (≥ 3%) AEs ≥ grade 2 and considered at least possibly related to DRV/rtv or LP/rtv, respectively, were diarrhea (5.0% and 11.3%), LDL increased (3.2% and 1.7%), hypercholesterolemia (2.3% and 4.9%), hypertriglyceridemia (2.0% and 5.8%), ALT increased (1.5% and 3.2%), and hyperlipidemia (0.6% and 3.2%).

Grade 3 or 4 AEs were reported with comparable frequency in the DRV/rtv and LPV/rtv treatment groups (30.0% and 31.8%, respectively). The most frequent (≥ 1%) grade 3 or 4 AEs were LDL increased (3.2% and 1.4% with DRV/rtv and LPV/rtv, respectively), AST increased (2.0% and 2.0%), blood amylase increased (2.0% and 2.0%), hypertriglyceridemia (1.5% and 3.5%), and ALT increased (1.5% and 2.6%), hypercholesterolemia (0.6% and 2.0%), and abdominal pain (0.6% and 1.2%).

Four subjects in the DRV/rtv treatment group and 7 subjects in the LPV/rtv treatment group died during the treatment period. None of the deaths were considered related to trial treatment by the investigator.

SAEs were less frequent with DRV/rtv (16.0%) than with LPV/rtv (20.8%). The majority of SAEs occurred in ≤ 2 subjects in any treatment group. Three subjects (0.9%) in the DRV/rtv group and 10 subjects (2.9%) in the LPV/rtv group had an SAE considered at least possibly related to the PI. Except ALT increased (which occurred in 2 LPV/rtv subjects), all SAEs considered at least possibly related to the PI occurred in only 1 subject in any treatment group. Related SAEs with DRV/rtv were QT prolonged, arrhythmia, drug interaction (same subject who took illicit drugs), nausea, headache (same subject) and Stevens-Johnson syndrome. Related SAEs in the LPV/rtv group were vomiting and diarrhea (same subject), transaminases increased and hepatitis (same subject), hepatic enzyme increased and blood bilirubin increased (same subject), ALT increased and AST increased (same subject), ALT increased, rash, immune reconstitution syndrome, pancreatitis acute, intracranial aneurysm, and neutrophil count decreased.

Permanent discontinuation of treatment due to an AEs was less frequent with DRV/rtv (7.6%) than with LPV/rtv (14.5%). AEs leading to permanent discontinuation were most frequently due to pregnancy (2.6% and 1.4%, respectively). GI disorders leading to discontinuation were reported in 0.3% of DRV/rtv subjects and 2.9% of LPV/rtv subjects, of which diarrhea (0% and 2.0%, respectively) was reported most frequently. In total 1.7% of DRV/rtv subjects and 6.6% of LPV/rtv subjects experienced an AE leading to permanent discontinuation that was considered at least possibly related to treatment. No DRV/rtv subjects permanently discontinued treatment for the same related AE; AEs occurring in > 1 subject in the LPV/rtv group were diarrhea (2.0%), ALT increased (0.9%), and hypertriglyceridemia, hypercholesterolemia, and rash (all 3 in 0.6%).

Special attention was given to rash-, and cardiac-related, GI, pancreatic, liver-, lipid-, and glucose-related AEs.

Rash-related AEs occurred mostly within the first 24 weeks of treatment and their incidence was higher with DRV/rtv (21.6%) compared to LPV/rtv (15.5%). The incidence of grade 3 or 4 rash-

related events was low in both groups and rash only occasionally led to treatment discontinuation. Rash-related AEs occurred mostly early during treatment.

A comparable incidence for the DRV/rtv and LPV/rtv groups was observed for cardiac AEs (5.8% versus 6.1%).

The overall incidence of GI-related AEs was lower during treatment with DRV/rtv (54.8%) than with LPV/rtv (69.4%), with diarrhea (39.4% and 54.9% with DRV/rtv and LPV/rtv, respectively), nausea (18.4% and 30.3%), abdominal pain (12.8% and 14.5%), and vomiting (8.2% and 13.3%) as the most frequent AEs. The incidence of GI-related events considered by the investigator to be at least possibly related to treatment was also lower in the DRV/rtv group (35.9%) than in the LPV/rtv group (59.2%). During the trial, fewer subjects in the DRV/rtv group compared to the LPV/rtv group used concomitant antidiarrheal agents and drugs for GI disorders (27.7% versus 38.7%).

The incidence of laboratory abnormalities was low and generally comparable for the DRV/rtv q.d. and DRV/rtv b.i.d. treatment groups, but with some notable differences.

Liver-related laboratory abnormalities for AST and ALT were observed with a similar incidence in the DRV/rtv and LPV/rtv group. Hyperbilirubinemia was less frequent with DRV/rtv than with LPV/rtv. There was a clear difference between the treatment groups in the incidence of elevated liver enzymes in subjects coinfected with hepatitis B or C virus: grade 2 to 4 ALT elevations in coinfected subjects was 39.5% with DRV/rtv versus 62.5% with LPV/rtv, and grade 2 to 4 AST elevations were seen in 30.2% with DRV/rtv versus 52.1% with LPV/rtv. The overall incidence of liver-related AEs was lower with DRV/rtv than with LPV/rtv (7.6% versus 14.5%). The most frequent liver-related AEs were AST increased (2.9% and 5.2%), and ALT increased (2.6% and 5.8%). In both treatment groups, the overall incidence of liver-related AEs was higher in subjects with hepatitis B or C coinfection (16.3% and 43.8% with DRV/rtv and LPV/rtv, respectively) than in not-coinfected subjects (6.3% and 9.7%).

With respect to lipid-related laboratory abnormalities, grade 2 to 4 increases in triglycerides were observed less frequently in the DRV/rtv group (5.9%) than in the LPV/rtv group (16.0%). Also grade 2 to 3 increases in total cholesterol were observed less frequently with DRV/rtv (24.3%) than with LPV/rtv (32.7%). Grade 2 or 3 increases in LDLc cholesterol were observed in 22.9% of subjects in the DRV/rtv group and 18.4% in the LPV/rtv group. The overall incidence of lipid-related AEs was lower with DRV/rtv (12.5%) than with LPV/rtv (19.2%). The most frequent lipid-related AEs were LDL increased (4.1% and 2.0%), hypercholesterolemia (3.8% and 6.6%), blood cholesterol increased (2.6% and 2.0%), hypertriglyceridemia (2.3% and 8.4%), and hyperlipidemia (2.0% and 4.0%). A similar proportion of subjects in both groups received lipid-modifying drugs: in the DRV/rtv group, 2.6% of subjects received lipid-modifying drugs at screening, and 11.7% during the trial; in the LPV/rtv group, these proportions were respectively 2.3% and 14.2%.

There were no relevant differences between the treatment groups with respect glucose-related laboratory abnormalities. Grade 2 or 3 hyperglycemia was observed in 12.0% of subjects in the DRV/rtv group and 9.9% in the LPV/rtv group (no grade 4 hyperglycemia was observed). The overall incidence of glucose-related AEs was 5.2% with DRV/rtv and 2.6% with LPV/rtv. The most frequent glucose-related AEs were blood glucose increased and hyperglycemia (both in 1.5% and 0.3%, respectively).

There were no relevant differences between the treatment groups in the incidence of grade 2 to 4 abnormalities for amylase (9.4% versus 7.3%), lipase (3.2% versus 3.8%). The overall incidence of pancreatic AEs was comparable between both treatment groups (3.2% and 3.8%, respectively).

The incidence of grade 2 to 4 hematology-related abnormalities was generally low. Grade 4 increased PT was not observed in DRV/rtv subjects and in 0.3% of LPV/rtv subjects; grade 4 increased PTT was observed in 0.9% of DRV/rtv subjects and 1.6% of LPV/rtv subjects. There were no grade 4 decreases in hemoglobin or platelet count. Grade 4 decreases in WBC were observed in 0.3% of subjects in both treatment groups. Grade 4 decreases in neutrophil count were less frequent with DRV/rtv (1.2%) than with LPV/rtv (10.2%).

The incidence of AEs related to urinalysis was low and similar for both treatment groups.

Small median changes from baseline were observed for vital signs parameters. None of the observed mean changes from baseline and no between-group differences for any of the vital signs parameters were considered clinically relevant. Vital signs abnormalities were commonly observed in both the DRV/rtv and LPV/rtv treatment groups and their incidence was generally comparable; the most frequent abnormalities were elevated blood pressure values. The incidence of AEs related to vital signs was low; hypertension was the most frequent AE related to vital signs, reported in 7.0% and 4.9% of subjects in the DRV/rtv and LPV/rtv groups, respectively. The proportion of subjects in each treatment group receiving blood-pressure-lowering drugs during screening and during treatment, respectively, were 6.4% and 13.1% in the DRV/rtv group, versus 4.6% and 13.3% in the LPV/rtv group.

For both treatment groups, QTc abnormalities were generally transient occurrences in the absence of clinical symptoms, which resolved with continued dosing. QTcF values of > 500 ms were not observed; increases in QTcF of > 60 ms were observed in 1.5% and 1.8% of subjects in the DRV/rtv and LPV/rtv treatment groups. No subjects presented with any clinically relevant events related to QTc prolongation.

There were no clinically relevant changes over time in physical examination findings. A mean increase in 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. In both the DRV/rtv and LPV/rtv treatment groups, anorexia (3.8% and 4.9%, respectively) and weight decreased (3.2% and 2.3%) were observed most frequently. The incidence of lipodystrophy-related AEs was comparable for both treatment groups.

4.10.4 Overall Conclusions

Consistent with the results of the analyses at 48 and 96 weeks, the Week-192 analysis demonstrated noninferiority in confirmed virologic response (plasma viral load < 50 copies/mL, ITT - TLOVR) for DRV/rtv 800/100 mg q.d. (68.8%) when compared to LPV/rtv 800/200 mg total daily dose (57.2%). Superiority for DRV/rtv over LPV/rtv in virologic response rates for the efficacy parameter viral load < 50 copies/mL at Week 192 was demonstrated. Virologic response over 192 weeks was sustained to a greater degree in the DRV/rtv group than in the LPV/rtv group. The efficacy response observed in subjects receiving DRV/rtv 800/100 mg q.d. provides further evidence of the durable potency of a DRV/rtv-containing regimen in the treatment-naïve population. The results of this trial are robust in view of the low discontinuation rates and the

high overall response rates in both groups. The virologic failure rate was lower in the DRV/rtv group (16.0%) than in the LPV/rtv group (20.5%). There were no developing primary PI mutations identified in the virologic failures of both treatment groups. All virologic failures remained susceptible to DRV, LPV, amprenavir, atazanavir, indinavir, saquinavir, and tipranavir.

The safety data confirmed that treatment with DRV/rtv 800/100 mg q.d. was generally safe and well tolerated with no new clinically relevant safety findings compared with the currently known safety profile of DRV. The incidence of gastrointestinal disorders (diarrhea, nausea, vomiting) and lipid abnormalities (triglycerides and total cholesterol) was lower with DRV/rtv than with LPV/rtv. Rash was more frequent with DRV/rtv than with LPV/rtv.

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6 SUPPORTING DATA DISPLAYS

Supporting Data Display 1: Grade 3 Adverse Events During the Treatment Period (Regardless of Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any Grade 3 AE	***93 (27.1)***	***98 (28.3)***
Blood and Lymphatic System Disorders	**3 (0.9)**	**3 (0.9)**
Agranulocytosis	1 (0.3)	0
Anemia	1 (0.3)	1 (0.3)
Febrile neutropenia	1 (0.3)	1 (0.3)
Neutropenia	0	1 (0.3)
Thrombocytopenia	0	1 (0.3)
Cardiac Disorders	**3 (0.9)**	**3 (0.9)**
Angina pectoris	1 (0.3)	0
Brugada syndrome	1 (0.3)	0
Cardiopulmonary failure	0	1 (0.3)
Myocardial infarction	0	1 (0.3)
Pericardial effusion	1 (0.3)	0
Right ventricular failure	0	1 (0.3)
Congenital, Familial and Genetic Disorders	**0**	**1 (0.3)**
Dermoid cyst of ovary	0	1 (0.3)
Endocrine Disorders	**1 (0.3)**	**0**
Hypopituitarism	1 (0.3)	0
Gastrointestinal Disorders	**12 (3.5)**	**12 (3.5)**
Abdominal pain	2 (0.6)	4 (1.2)
Ascites	1 (0.3)	0
Constipation	0	1 (0.3)
Diarrhea	2 (0.6)	0
Diverticulum intestinal hemorrhagic	0	1 (0.3)
Dysphagia	0	1 (0.3)
Gastritis	1 (0.3)	0
Gastroesophageal reflux disease	1 (0.3)	0
Hemorrhoids	1 (0.3)	0
Intestinal perforation	0	1 (0.3)
Irritable bowel syndrome	0	1 (0.3)
Melena	0	1 (0.3)
Nausea	3 (0.9)	1 (0.3)
Pancreatitis	1 (0.3)	0
Proctalgia	0	1 (0.3)
Rectal fissure	0	1 (0.3)
Rectal hemorrhage	1 (0.3)	0
Toothache	1 (0.3)	1 (0.3)
Umbilical hernia, obstructive	1 (0.3)	0
Vomiting	2 (0.6)	1 (0.3)
General Disorders and Administration Site Conditions	**4 (1.2)**	**4 (1.2)**
Chest pain	1 (0.3)	1 (0.3)
Chills	1 (0.3)	0
Noncardiac chest pain	1 (0.3)	3 (0.9)
Pyrexia	2 (0.6)	0
Hepatobiliary Disorders	**2 (0.6)**	**4 (1.2)**
Cholecystitis acute	1 (0.3)	0

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Cholecystitis chronic	0	1 (0.3)
Cholelithiasis	1 (0.3)	0
Hepatitis	1 (0.3)	0
Hepatorenal syndrome	0	1 (0.3)
Hepatotoxicity	0	1 (0.3)
Jaundice	0	1 (0.3)
Immune System Disorders	**1 (0.3)**	**0**
Immune reconstitution syndrome	1 (0.3)	0
Infections and Infestations	**15 (4.4)**	**24 (6.9)**
Appendicitis	0	1 (0.3)
Bronchitis	1 (0.3)	3 (0.9)
Carbuncle	1 (0.3)	0
Cerebral toxoplasmosis	0	1 (0.3)
Condyloma acuminatum	0	1 (0.3)
Cytomegalovirus chorioretinitis	1 (0.3)	0
Dental caries	0	1 (0.3)
Empyema	0	1 (0.3)
Escherichia urinary tract infection	0	1 (0.3)
Furuncle	1 (0.3)	0
Gastroenteritis	3 (0.9)	0
Gastrointestinal infection	0	1 (0.3)
Hepatitis A	0	1 (0.3)
Hepatitis C	0	2 (0.6)
Herpes zoster	3 (0.9)	3 (0.9)
Lower respiratory tract infection	1 (0.3)	0
Mycobacterium avium complex infection	1 (0.3)	0
Neurosyphilis	0	1 (0.3)
Otitis media	1 (0.3)	0
Periorbital cellulitis	0	1 (0.3)
Pharyngitis	1 (0.3)	0
Pneumonia	2 (0.6)	2 (0.6)
Progressive multifocal leukoencephalopathy	1 (0.3)	0
Pulmonary tuberculosis	2 (0.6)	1 (0.3)
Pyelonephritis	0	1 (0.3)
Sinusitis	1 (0.3)	1 (0.3)
Superinfection lung	0	1 (0.3)
Syphilis	0	1 (0.3)
Wound infection	1 (0.3)	0
Injury, Poisoning and Procedural Complications	**3 (0.9)**	**4 (1.2)**
Burns second degree	0	1 (0.3)
Chest injury	0	1 (0.3)
Joint sprain	1 (0.3)	0
Laceration	1 (0.3)	0
Road traffic accident	1 (0.3)	0
Snake bite	0	1 (0.3)
Wound	0	1 (0.3)
Investigations	**34 (9.9)**	**37 (10.7)**
Alanine aminotransferase increased	5 (1.5)	6 (1.7)
Aspartate aminotransferase increased	5 (1.5)	4 (1.2)
Blood alkaline phosphatase increased	0	1 (0.3)
Blood amylase increased	7 (2.0)	7 (2.0)
Blood bilirubin increased	0	2 (0.6)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Blood cholesterol increased	1 (0.3)	2 (0.6)
Blood creatine phosphokinase increased	1 (0.3)	0
Blood creatinine increased	1 (0.3)	1 (0.3)
Blood glucose increased	1 (0.3)	1 (0.3)
Blood HIV RNA increased	2 (0.6)	0
Blood triglycerides increased	0	2 (0.6)
Electrocardiogram QT corrected interval Prolonged	0	1 (0.3)
Hepatic enzyme increased	2 (0.6)	1 (0.3)
Lipase increased	1 (0.3)	3 (0.9)
Liver function test abnormal	0	2 (0.6)
Low density lipoprotein increased	11 (3.2)	5 (1.4)
Neutrophil count decreased	1 (0.3)	1 (0.3)
Prothrombin time prolonged	0	1 (0.3)
Transaminases increased	1 (0.3)	2 (0.6)
Weight decreased	0	1 (0.3)
Weight decreased	1 (0.3)	0
Metabolism and Nutrition Disorders	**11 (3.2)**	**22 (6.4)**
Anorexia	0	1 (0.3)
Diabetes mellitus noninsulin-dependent	1 (0.3)	0
Hyperamylasemia	0	1 (0.3)
Hypercholesterolemia	2 (0.6)	7 (2.0)
Hyperglycemia	1 (0.3)	0
Hyperlipidemia	1 (0.3)	2 (0.6)
Hypernatremia	0	1 (0.3)
Hypertriglyceridemia	5 (1.5)	12 (3.5)
Hyperuricemia	0	1 (0.3)
Hyponatremia	1 (0.3)	0
Musculoskeletal and Connective Tissue Disorders	**5 (1.5)**	**5 (1.4)**
Back Pain	1 (0.3)	0
Bursitis	0	1 (0.3)
Flank pain	0	1 (0.3)
Intervertebral disc protrusion	2 (0.6)	1 (0.3)
Muscle contracture	0	1 (0.3)
Osteoporosis	1 (0.3)	0
Periarthritis	1 (0.3)	0
Spinal osteoarthritis	0	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**3 (0.9)**	**2 (0.6)**
Anal neoplasm	0	1 (0.3)
Hodgkin's disease	1 (0.3)	0
Lung neoplasm malignant	1 (0.3)	0
Plasmablastic lymphoma	1 (0.3)	0
Squamous cell carcinoma	0	1 (0.3)
Nervous System Disorders	**9 (2.6)**	**4 (1.2)**
Cerebrovascular accident	0	1 (0.3)
Encephalitis	1 (0.3)	0
Extrapyramidal disorder	1 (0.3)	0
Facial palsy	1 (0.3)	0
Headache	1 (0.3)	2 (0.6)
Hypoesthesia	1 (0.3)	0
Loss of consciousness	1 (0.3)	0
Spinal cord compression	0	1 (0.3)

System Organ Class **Dictionary-Derived Term, n (%)**	**DRV/rtv** **N = 343**	**LPV/rtv** **N = 346**
Status epilepticus	1 (0.3)	0
Syncope	2 (0.6)	0
Syncope vasovagal	0	1 (0.3)
Transient ischemic attack	0	1 (0.3)
Pregnancy, Puerperium and Perinatal Conditions	**0**	**1 (0.3)**
Abortion spontaneous	0	1 (0.3)
Psychiatric Disorders	**1 (0.3)**	**2 (0.6)**
Depression	1 (0.3)	1 (0.3)
Mental status changes	0	1 (0.3)
Renal and Urinary Disorders	**1 (0.3)**	**2 (0.6)**
Hematuria	1 (0.3)	0
Nephropathy	0	1 (0.3)
Renal impairment	0	1 (0.3)
Reproductive System and Breast Disorders	**3 (0.9)**	**0**
Epididymitis	1 (0.3)	0
Erectile dysfunction	1 (0.3)	0
Menorrhagia	1 (0.3)	0
Respiratory, Thoracic and Mediastinal Disorders	**2 (0.6)**	**3 (0.9)**
Allergic bronchitis	1 (0.3)	0
Asthma	0	1 (0.3)
Bronchopneumopathy	0	1 (0.3)
Dyspnea	0	1 (0.3)
Pneumothorax	1 (0.3)	0
Respiratory failure	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	**4 (1.2)**	**0**
Dermatitis allergic	1 (0.3)	0
Lipodystrophy acquired	1 (0.3)	0
Rash	2 (0.6)	0
Surgical and Medical Procedures	**1 (0.3)**	**1 (0.3)**
Colostomy closure	0	1 (0.3)
Surgery	1 (0.3)	0
Vascular Disorders	**5 (1.5)**	**3 (0.9)**
Arterial occlusive disease	1 (0.3)	0
Arteriosclerosis	1 (0.3)	0
Circulatory collapse	0	1 (0.3)
Hypertension	3 (0.9)	2 (0.6)
Hypertensive crisis	0	1 (0.3)
Leriche syndrome	1 (0.3)	0
Thrombosis	1 (0.3)	0
Vascular pseudoaneurysm	1 (0.3)	0

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

Source: Display SAF.26

Supporting Data Display 2: Grade 4 Adverse Events During the Treatment Period (Regardless of Causality)

System Organ Class Dictionary-Derived Term, n (%)	DRV/rtv N = 343	LPV/rtv N = 346
Any Grade 4 AE	***23 (6.7)***	***33 (9.5)***
Blood and Lymphatic System Disorders	**3 (0.9)**	**2 (0.6)**
Anemia	1 (0.3)	0
Febrile neutropenia	1 (0.3)	0
Neutropenia	1 (0.3)	2 (0.6)
Cardiac Disorders	**1 (0.3)**	**2 (0.6)**
Angina unstable	0	1 (0.3)
Cardio-respiratory arrest	0	1 (0.3)
Coronary artery disease	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Gastrointestinal Disorders	**0**	**3 (0.9)**
Diarrhea	0	1 (0.3)
Pancreatic duct obstruction	0	1 (0.3)
Rectal hemorrhage	0	1 (0.3)
Vomiting	0	1 (0.3)
General Disorders and Administration Site Conditions	**0**	**2 (0.6)**
Death	0	1 (0.3)
Multi-organ failure	0	1 (0.3)
Hepatobiliary Disorders	**0**	**2 (0.6)**
Hepatitis acute	0	1 (0.3)
Hepatotoxicity	0	1 (0.3)
Immune System Disorders	**0**	**1 (0.3)**
Immune reconstitution syndrome	0	1 (0.3)
Infections and Infestations	**2 (0.6)**	**5 (1.4)**
Disseminated tuberculosis	0	1 (0.3)
Hepatitis A	0	1 (0.3)
Meningitis cryptococcal	0	2 (0.6)
Meningitis meningococcal	1 (0.3)	0
Secondary syphilis	1 (0.3)	0
Septic shock	0	1 (0.3)
Injury, Poisoning and Procedural Complications	**3 (0.9)**	**3 (0.9)**
Carbon monoxide poisoning	0	1 (0.3)
Contusion	0	1 (0.3)
Drug toxicity	1 (0.3)	0
Intentional overdose	1 (0.3)	0
Multiple drug overdose	1 (0.3)	0
Road traffic accident	0	1 (0.3)
Whiplash injury	0	1 (0.3)
Investigations	**5 (1.5)**	**13 (3.8)**
Alanine aminotransferase increased	0	5 (1.4)
Aspartate aminotransferase increased	2 (0.6)	4 (1.2)
Blood bilirubin increased	1 (0.3)	0
Blood triglycerides increased	0	1 (0.3)
Blood uric acid increased	1 (0.3)	0
Gamma-glutamyltransferase increased	1 (0.3)	0
Hepatic enzyme increased	1 (0.3)	1 (0.3)
Lipase increased	0	1 (0.3)
Neutrophil count decreased	0	1 (0.3)
Transaminases increased	0	3 (0.9)

System Organ Class **Dictionary-Derived Term, n (%)**	**DRV/rtv** **N = 343**	**LPV/rtv** **N = 346**
Metabolism and Nutrition Disorders	**1 (0.3)**	**4 (1.2)**
Dehydration	0	1 (0.3)
Hypercalcemia	0	1 (0.3)
Hypertriglyceridemia	1 (0.3)	2 (0.6)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**2 (0.6)**	**4 (1.2)**
Abdominal neoplasm	0	1 (0.3)
Diffuse large B-cell lymphoma	1 (0.3)	0
Hodgkin's Disease	0	2 (0.6)
Leukoerythroblastosis	0	1 (0.3)
Lymphoma	1 (0.3)	0
Nervous System Disorders	**0**	**4 (1.2)**
Cerebrovascular accident	0	1 (0.3)
Headache	0	1 (0.3)
Intracranial Aneurysm	0	1 (0.3)
Myelitis	0	1 (0.3)
Psychiatric Disorders	**5 (1.5)**	**1 (0.3)**
Depression	1 (0.3)	1 (0.3)
Paranoia	0	1 (0.3)
Psychotic disorder	1 (0.3)	0
Suicidal ideation	1 (0.3)	0
Suicide attempt	2 (0.6)	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	**3 (0.9)**	**0**
Chronic obstructive pulmonary disease	1 (0.3)	0
Dyspnea	1 (0.3)	0
Respiratory failure	1 (0.3)	0
Skin and Subcutaneous Tissue Disorders	**1 (0.3)**	**0**
Stevens-Johnson syndrome	1 (0.3)	0

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

Source: Display SAF.27

7 SIGNATURES

SIGNATURE OF COORDINATING INVESTIGATOR

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. This trial is referred to as ARTEMIS.
Author(s):	S. Spinosa-Guzman, T. Van De Casteele, E. Lathouwers

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

Name:	R. Ortiz
Affiliation:	Orlando Immunology Center, 1701 N Mills Ave, Orlando FL, 32803 US

Signature
& Date:

SIGNATURE OF TIBOTEC RESPONSIBLE MEDICAL OFFICER

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. This trial is referred to as ARTEMIS.
Author(s):	S. Spinosa-Guzman, T. Van De Casteele, E. Lathouwers

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

Name:	S. Spinosa-Guzman
Affiliation:	Tibotec

See Appended Electronic Signature Page

8 APPENDICES

8.1 STUDY INFORMATION

8.1.1 Protocol and Protocol Amendments
8.1.2 Sample Case Report Form
8.1.3 List of IECs/IRBs - Representative Written Information for Subject and Sample Consent Form
8.1.4 List of Investigators and Subinvestigators, and CVs
8.1.5 Batch Numbers and Corresponding Subjects if More than 1 Batch of Study Drug was Used
8.1.6 Randomization Scheme
Listing in TMC114-C211-W192-Anal-GEN
8.1.7 Audit Certificates
Not applicable
8.1.8 Documentation on Statistical Methods
8.1.9 Interlaboratory Standardization Methods and Quality Assurance Procedures
8.1.10 Publications Based on the Study
Not applicable
8.1.11 Important Documents Referred to in the Report
8.1.12 Signatures of Sponsor's Responsible Medical Officer, and Coordinating Investigator

8.2 SUMMARY DISPLAYS AND SUBJECT DATA LISTINGS

8.2.1 Study Completion/Withdrawal Information
Listings and displays in TMC114-C211-W192-Anal-GEN
8.2.2 Protocol Deviations
Listings and displays in TMC114-C211-W192-Anal-GEN
8.2.3 Demographic and Other Baseline Information
Listings and displays in TMC114-C211-W192-W96-Anal-GEN
8.2.4 Concomitant Therapies
Display in TMC114-C211-W192-W96-Anal-GEN;
display in TMC114-C211-W192-Anal-GEN
8.2.5 Compliance and/or Drug Concentration Data
Listing in TMC114-C211-W192-Anal-GEN;
Listing in TMC114-C211-W192-W48-Anal-PK
8.2.6 Pharmacokinetic Data
Listings and displays in TMC114-C211-W192-W48-Anal-PK
8.2.7 Subjects Excluded From the Efficacy Analysis
Not applicable
8.2.8 Efficacy Response Data
Listings and displays in TMC114-C211-W192-Anal-EFF
8.2.9 Resistance Determination Data
Listings and displays in TMC114-C211-W192-Anal-VIR
8.2.10 Pharmacokinetic/Pharmacodynamic Data

Listings and displays in TMC114-C211-W192-W48-Anal-PK

8.2.11 Adverse Events

Listings and displays in TMC114-C211-W192-Anal-Saf-AE

8.2.12 Clinical Laboratory Data

Listings and displays in TMC114-C211-W192-Anal-Saf-LAB

8.2.13 Cardiovascular Safety

8.2.13.1 Vital Signs

Listings and displays in TMC114-C211-W192-Anal-Saf-CV

8.2.13.2 ECG

Listings and displays in TMC114-C211-W192-Anal-Saf-CV

8.2.14 Other Safety Evaluations

8.2.14.1 Physical Examination Data

Listings and displays in TMC114-C211-W192-Anal-Saf-OTH

8.2.14.2 Other Evaluations

Listings and displays in TMC114-C211-W192-Anal-Saf-OTH

8.3 CASE REPORT FORMS

8.3.1 Case Report Forms for Deaths, Other Serious Adverse Events and Withdrawal for Adverse Events

211-0005, 211-0013, 211-0017, 211-0080, 211-0099, 211-0114, 211-0117, 211-0127, 211-0142, 211-0154, 211-0159, 211-0167, 211-0176, 211-0182, 211-0183, 211-0190, 211-0201, 211-0207, 211-0208, 211-0212, 211-0219, 211-0234, 211-0237, 211-0249, 211-0254, 211-0255, 211-0266, 211-0275, 211-0278, 211-0286, 211-0295, 211-0300, 211-0309, 211-0311, 211-0318, 211-0336, 211-0339, 211-0340, 211-0344, 211-0346 211-0361, 211-0369, 211-0371, 211-0390, 211-0448, 211-0454, 211-0458, 211-0462, 211-0263, 211-0503, 211-0504, 211-0510, 211-0517, 211-0527, 211-0539, 211-0548, 211-0571, 211-0574, 211-0580, 211-0584, 211-0585, 211-0599, 211-0600, 211-0610, 211-0611, 211-0627, 211-0628, 211-0633, 211-0635, 211-0636, 211-0645, 211-0683, 211-0685, 211-0697, 211-0702, 211-0714, 211-0723, 211-0746, 211-0760, 211-0764, 211-0800, 211-0819, 211-0820, 211-0837, 211-0845

8.3.2 Other Case Report Forms

211-0002, 211-0008, 211-0009, 211-0012, 211-0018, 211-0027, 211-0031, 211-0040, 211-0048, 211-0061, 211-0079, 211-0083, 211-0129, 211-0137, 211-0140, 211-0158, 211-0216, 211-0218, 211-0224, 211-0229, 211-0248, 211-0252, 211-0259, 211-0273, 211-0299, 211-0327, 211-0330, 211-0334, 211-0337, 211-0363, 211-0366, 211-0391, 211-0393, 211-0409, 211-0418, 211-0422, 211-0424, 211-0426, 211-0466, 211-0494, 211-0498, 211-0499, 211-0507, 211-0521, 211-0528, 211-0554, 211-0595, 211-0653, 211-0655, 211-0674, 211-0696, 211-0699, 211-0717, 211-0729, 211-0743, 211-0749, 211-0752, 211-0757, 211-0794, 211-0818