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ASSESSMENT REPORT FOR PREZISTA

International Nonproprietary Name:
darunavir

Procedure No. EMEA/H/C/707/II/14

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

This submission pertains to the Specific Obligation (SO2 003.2): The data of the 48 week (primary analysis) final study report from study TMC114-C214 (A randomised, controlled, open-label trial to compare the efficacy, safety and tolerability of TMC114/RTV versus LPV/RTV in treatment-experienced HIV-1 infected patients) should be presented within a Type II variation to extend the indication to the patient population studied, as appropriate.

Prezista was granted a conditional marketing authorisation (MA), which means that the MAH has to fulfil a number of SOs prior to requesting the switching to a full MA. A conditional MA is valid for one year only and needs therefore to be renewed annually. During the first renewal the MAH already presented data of one of the specific obligations: The 48 week (primary analysis) final study report from Study TMC114-C214. The CHMP concluded then that the MAH should file a type II variation for inclusion of 'treatment experienced' patients in the indication. Up until now Prezista is only indicated for highly experienced adult patients who failed more than one regimen containing a protease inhibitor.

Study TMC114-C214 (TITAN) is a randomised, controlled, open-label multi centre trial to compare the efficacy, safety and tolerability of darunavir (DRV) administered together with the pharmacokinetic enhancer ritonavir (RTV) versus Kaletra (lopinavir; LPV co-formulated with RTV), both in combination with an optimised background regimen (OBR) in treatment-experienced HIV-1 infected patients. The duration of the trial is 96 weeks. The Week 48 primary analysis is submitted in support of the current variation. The week 96 final study report is due by March 2009.

The primary objective of this trial was to demonstrate non-inferiority in efficacy of DRV/RTV versus LPV/RTV at 48 weeks, when administered in combination with an individualised OBR.

The MAH proposed the following extension and changes in the approved indication:

"*PREZISTA, co-administered with 100 mg ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in* ***treatment-experienced*** ~~*highly pre-treated*~~ *adult patients* ~~*who failed more than one regimen containing a protease inhibitor (PI)*~~."…

The proposed posology is the same as for the presently approved indication. Consequential changes for section 5.1 of the SPC were also proposed.

2. Clinical aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.1 Methods

2.1.1 Design

This is a randomised, controlled, open-label multi-centre trial to compare the efficacy, safety and tolerability DRV/RTV versus LPV/RTV (both in combination with an OBR) in treatment-experienced HIV-1 infected patients. The duration of the trial is 96 weeks. Primary efficacy analyses for this trial were performed when all patients had reached 48 weeks of treatment or discontinued earlier (cut-off date of 17-01-2007).

Treatment-experienced (but LPV-, DRV-, tipranavir (TPV), and enfuvirtide (ENF)-naïve), HIV-1 infected patients with viral load > 1000 HIV-1 RNA copies/ml were to be randomised. Patients had to be on their current highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. At baseline, patients changed their HAART. An optimised background regimen (OBR) consisting of at

least 2 antiretrovirals (Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) with or without Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)), and the patients were randomised in a 1:1 ratio to receive a new Protease Inhibitor (PI) regimen consisting of either DRV/RTV (600/100 mg twice daily; b.i.d.) or LPV/RTV (400/100 mg b.i.d.).

The trial included a screening period of 4 weeks, a 96-week treatment period, and a 4-week follow-up period. Patients meeting the per protocol defined criteria for virological failure (DRV/RTV or LPV/RTV group), or who experienced a grade 4 adverse event (AE) or confirmed grade 4 (or specific grade 3) laboratory abnormality[1] considered at least possibly related to LPV/RTV treatment could enter a rollover phase during which all patients received DRV/RTV.

The *primary objective* of this trial was to demonstrate non-inferiority in efficacy of DRV/RTV versus LPV/RTV at 48 weeks, when administered in combination with an individualised OBR.

In addition, safety, tolerability, durability of efficacy, quality of life, pharmacokinetics, effects of covariates, and pharmacokinetic/ pharmacodynamic relationships over 96 weeks were assessed.

- **Study Participants**

Patients had to be on their current highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. Initially, patients on a structured treatment interruption (STI) of at least 4 weeks were permitted to be enrolled. When the protocol was subsequently amended, patients on a STI were excluded.

Main inclusion criteria were:

a. Male or female, aged 18 years or older.

b. Treatment with current HAART regimen for ≥ 12 weeks.

c. Pre-screening and screening plasma HIV-1 RNA > 1000 copies/ml (assayed by RNA PCR standard specimen procedure) on current HAART regimen.

Main exclusion criteria were:

a. Active AIDS-defining illness with the following exceptions: stable cutaneous Kaposi's sarcoma or wasting syndrome.

b. Previous or current use of LPV, ENF, TPV or DRV.

c. Use of any non-ARV investigational agents within 90 days prior to screening.

d. Use of disallowed concomitant therapy.

e. Pregnant or breastfeeding.

f. Patients with clinical or laboratory evidence of significantly decreased hepatic function or decompensation (i.e., liver insufficiency), irrespective of liver enzyme levels.

g. Subjects with a grade 3 or 4 laboratory abnormality as defined by DAIDS grading tables, with the following exceptions unless clinical assessment foresaw an immediate health risk to the subject:

   - Pre-existing diabetes, or asymptomatic grade 3 or 4 glucose elevations;
   - Asymptomatic grade 3 or 4 triglyceride or cholesterol elevations.

h. Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the study medication DRV, LPV or RTV.

- **Treatments**

After the screening period in which patients continued HAART regimen (4 weeks) in both groups the treatments were as follows:

[1] according to the DAIDS scale

Control Group (LPV/RTV)	**Treatment period** (96 weeks): OBR consisting of ≥ 2 ARVs (NRTIs with or without NNRTIs) and LPV/RTV 400/100 mg b.i.d. given as three 133.3/33.3-mg capsules or two 200/50mg (Meltrex) tablets per intake once Meltrex tablets became available*. In case an NNRTI such as EFV or nevirapine (NVP) was included in the OBR, to compensate for the expected decrease in plasma levels caused by the co-administration, an increased LPV/RTV dosage was required: - capsule formulation: LPV/RTV 533/133 mg (4 capsules) b.i.d.; - tablet formulation: LPV/RTV 600/150 mg (3 tablets) b.i.d.

*Once a patient had switched from the capsule to the tablet formulation, the patient had to remain on the tablet formulation for the remaining treatment period. Patients randomised to LPV/RTV subsequent to availability of the tablets, initiated therapy with the tablet formulation.

DRV/RTV ** Group	**Treatment period** (96 weeks): OBR consisting of ≥ 2 ARVs (NRTIs with or without NNRTIs) and DRV/RTV 600/100 mg b.i.d. given as: two 300-mg tablets of DRV + one 100-mg capsule of RTV per intake.

** DRV/RTV to be taken orally within 30 minutes after completion of a meal, every 12 hours.

- **Endpoints**

Efficacy

The *primary* endpoint was virological response, defined as the percentage of patients with confirmed plasma viral load < 400 copies/ml at Week 48 (using the TLOVR algorithm).

The TLOVR (time to loss of virological response) algorithm: response and loss of response had to be confirmed at 2 consecutive visits and patients who prematurely discontinued were considered as non-responders after withdrawal. Patients with intermittent missing viral load values were considered responders if the preceding and succeeding visits indicated response. In all other cases, intermittent values were imputed with non-response.

Secondary endpoints included:

- Virological response defined as a viral load < 50 copies/ml (using the TLOVR algorithm);
- Virological response defined as a decrease in viral load of ≥ 1.0 $\log_{10}$ compared with the baseline value (TLOVR);
- Immunologic parameters (CD4+ cell count (absolute and %) and CD8+ cell count (absolute and %).
- Compare the Quality of Life (QoL) questionnaire results. QoL questionnaire had to be completed by the patient if a validated translated version was available. The Functional Assessment of HIV Infection (FAHI) QoL questionnaire was used.

Safety

Safety evaluations included AEs, clinical laboratory tests, biochemistry, haematology, coagulation tests, urine analysis, hepatitis, serology/viraemia, blood pressure, ECG readings (performed by central ECG Lab.). The ECG parameters analysed were heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB (QT interval corrected for heart rate according to Bazett), and QTcF (QT interval corrected for heart rate according to Fridericia). Vital signs included pulse, systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Resistance determinations
Viral pheno- and genotype determinations were performed by Virco BVBA, by means of the Antivirogram and VircoTYPE HIV-1, respectively.

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 guidelines, and PI mutations as defined by FDA [FDA-defined PI RAMs]), and number of all reverse transcriptase (RT) mutations (NRTI RAMs and NNRTI RAMs as defined by the IAS-USA guidelines, and extended NNRTI RAMs) were tabulated per treatment group. The incidence of all individual protease and RT mutations was also tabulated.

The FC measured by Antivirogram was analysed, and categorised into 'susceptible' or 'resistant' based on cut-off values. A drug was considered susceptible if the FC was below or equal to the clinical cut-off when this was available (i.e., LPV, TDF, abacavir [ABC], TPV, and DRV), or below or equal to the biological cut-off otherwise.

The FC measured by VircoTYPE was also analysed. For each drug, FC was categorised into 'susceptible/maximal response', 'reduced response' and 'resistant/minimal response' based on cut-off values. To get an idea of the overall sensitivity to a class of drugs (NRTIs, PIs, NNRTIs, all ARV), a total sensitivity score was calculated as the sum of continuous phenotypic sensitivity scores (CPSS) of the individual drugs in the corresponding class.

- **Sample size**

Assuming a virological response (confirmed viral load < 400 copies/ml) rate of 70% at 48 weeks in both treatment arms, 229 patients were required per treatment arm to establish non-inferiority of DRV/RTV versus LPV/RTV with a maximum allowable difference (delta) of 12%, with a 1-sided significance level of $\alpha = 0.025$ and 80% power. To account for an approximate 10% of patients expected to be excluded for the on-protocol analysis, a total of 500 HIV-1 positive patients were needed in the trial, 250 per treatment group. However, 95 supplementary patients were recruited compared to what was planned per protocol. This was due to the high rate of enrolment in particular during the last month of recruitment for the trial.

A delta of 12 % was considered appropriate, as it was small relative to observed differences between LPV/RTV and other active regimen or between other ARTs in a similar patient population.

- **Randomisation**

Patients were randomised in a 1:1 ratio to treatment with DRV/RTV or LPV/RTV and according to stratification for:

- use of an NNRTI in the OBR (yes/no) (due to potential interaction that impacts on PI plasma levels)
- screening plasma viral load (< 50,000 or ≥ 50,000 copies/ml)

A central randomisation system was used. Randomisation was done by a predefined randomisation list, constructed via random permuted blocks to ensure balance across treatments groups in each stratum of the 2 stratification factors.

- **Blinding**

No blinding took place (open-label). The MAH justified this by referring to a very high pill burden for patients.

- **Statistical methods**

The present primary efficacy analysis was performed when all patients in this trial reached Week 48 or discontinued earlier. All statistical tests were interpreted at the 1-sided 2.5% or equivalently at the 95% 2-sided significance level, unless specified differently.

The primary objective analysis was to demonstrate non-inferiority in virological response defined as a confirmed plasma viral load of < 400 copies/ml with DRV/RTV 600/100 mg b.i.d. versus LPV/RTV

400/100 mg b.i.d. at Week 48 with a delta/ non-inferiority margin of 12%. Secondary objectives were to evaluate other virological and immunologic parameters, to compare the QoL, and to evaluate pharmacokinetics, effects of covariates, and pharmacokinetic/ pharmacodynamic relationships, as well as safety and tolerability over time.

In case non-inferiority was concluded, superiority in virological response defined as a confirmed plasma viral load of < 400 copies/ml with DRV/RTV 600/100 mg b.i.d. versus LPV/RTV 400/100 mg b.i.d. at Week 48 was assessed.

Two populations were defined for analysis:

- Intent-to-treat (ITT) population: all patients who where randomised and who received trial medication, regardless of their compliance with the Protocol.
- On-protocol (OP) population: all randomised patients who received trial medication, and who did not take any disallowed ARV medication as described in the Protocol for > 1 week; in addition, patients who were not compliant for the trial medication for > 4 weeks were excluded.

The primary population for testing the primary efficacy parameter was the OP population.

A logistic regression model, including baseline $\log_{10}$ plasma viral load as covariate and use of an NNRTI in OBR ('as used', not 'as stratified') as factor, was applied to estimate the difference in virological response rate (defined as a confirmed plasma viral load < 400 copies/ml [TLOVR]) 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 48: if the lower limit of the 95% 2-sided CI of the difference between DRV/RTV and LPV/RTV did not exceed -12% (for the OP population), non-inferiority of DRV/RTV versus LPV/RTV was concluded. In case non-inferiority was concluded and the lower limit of the 95% 2-sided CI of the difference between DRV/RTV and LPV/RTV exceeded 0 (for the ITT population), superiority of DRV/RTV versus LPV/RTV could be 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.

In addition, several sensitivity analyses were performed e.g. observed response defined as a viral load < 400 copies/ml (without requiring confirmation of response or loss of response), and NC = F (non-completer is failure analysis). In addition, the impact on the conclusions of discontinuation due to patient wish (DCPW; non compliance, withdrawal of consent, or lost to follow-up) was assessed by a last observation carried forward (LOCF) analysis, i.e., the last observed virological response was carried forward to Week 48 for patients discontinuing due to patient wish.

2.1.2 Outcomes

- **Patient disposition**

Trial TMC114-C214 enrolled 595 patients, 148 (25%) patients prematurely discontinued. For disposition of the patients see the following table.

Table 1 Patient Disposition – ITT and OP Populations

	DRV/RTV	LPV/RTV	All Patients
Intent-to-Treat Population			
N screened	302	302	785
N not randomised - not treated	0	0	180
N not randomised - treated	0	0	1[a]
N randomised - not treated	4	5	9
N randomised - treated	298	297	595
Discontinuations - Reason, n (%)			
Any reason	***62 (20.8)***	***86 (29.0)***	***148 (24.9)***
Adverse event/HIV related event	20 (6.7)	21 (7.1)[b]	41 (6.9)
Patient reached a virologic endpoint	4 (1.3)	34 (11.4)	38 (6.4)
Patient lost to follow-up	10 (3.4)	10 (3.4)	20 (3.4)
Patient withdrew consent	9 (3.0)	10 (3.4)	19 (3.2)
Patient noncompliant	11 (3.7)	4 (1.3)	15 (2.5)
Other	2 (0.7)	4 (1.3)	6 (1.0)
Patient ineligible to continue the trial	4 (1.3)	1 (0.3)	5 (0.8)
Sponsor's decision	1 (0.3)	2 (0.7)	3 (0.5)
Patient did not fulfil all inclusion/exclusion criteria	1 (0.3)	0	1 (0.2)
On-Protocol Population			
N randomised - treated	274	280	554
Discontinuations - Reason, n (%)			
Any reason	***53 (19.3)***	***79 (28.2)***	***132 (23.8)***
Adverse event/HIV related event	19 (6.9)	19 (6.8)[b]	38 (6.9)
Patient reached a virologic endpoint	4 (1.5)	31 (11.1)	35 (6.3)
Patient lost to follow-up	8 (2.9)	9 (3.2)	17 (3.1)
Patient withdrew consent	8 (2.9)	9 (3.2)	17 (3.1)
Patient noncompliant	10 (3.6)	4 (1.4)	14 (2.5)
Other	1 (0.4)	4 (1.4)	5 (0.9)
Sponsor's decision	0	2 (0.7)	2 (0.4)
Patient ineligible to continue the trial	2 (0.7)	1 (0.4)	3 (0.5)
Patient did not fulfil all inclusion/exclusion criteria	1 (0.4)	0	1 (0.2)

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

[a] One patient received both DRV/RTV and LPV/RTV.

[b] Additionally taking into account one patient who discontinued due to an AE (diarrhoea) after 17 January 2007, the cut-off date for the current analysis.

The overall discontinuation rate (for any reason) was lower in the DRV/RTV group (21%) than in the LPV/RTV group (29%). The majority of discontinuations was due to AE/HIV related events (7%), or virological failure (6%). Discontinuation due to AE/HIV-related events occurred with similar frequency in both treatment groups (7%); discontinuations due to virological failure occurred less frequently in the DRV/RTV group (1%) than in the LPV-RTV group (11%).

Up to Week 24, the number of patients in the trial was similar for both treatment groups; at Week 24, this was 91% for both treatment groups. At Weeks 36 and 48, the number of patients remaining in the trial was higher in the DRV/RTV group than in the LPV/RTV group: 87% versus 83%, and 85% versus 77%, respectively. This was mainly due to a higher rate of discontinuations due to virological failure in the LPV/RTV group compared to the DRV/RTV Group.

At the time of database cut-off, 79.2% of DRV/RTV-treated patients and 71.0% of LPV/RTV-treated control patients were still in the trial. The mean duration of exposure for the respective treatment groups was 53.5 and 51.5 weeks.

Compliance

Compliance was generally high in both treatment groups. The proportion of patients with DRV plasma concentrations below the detection limit was ≤ 5%, and the proportion of patients with LPV plasma concentrations below the detection limit was ≤ 6% at all time points.

- **Baseline data**

The demographic characteristics of the patients in the two arms are displayed in the following table.

Table 2 Demographic Data

Demographic Parameter	DRV/RTV	LPV/RTV	All Subjects
Sex, n (%), N	298	297	595
Female	69 (23.2)	56 (18.9)	125 (21.0)
Male	229 (76.8)	241 (81.1)	470 (79.0)
Age (years), N	298	297	595
Mean (SD)	40.9 (9.049)	40.8 (8.615)	40.9 (8.828)
Median (Range)	40.0 (18.0; 68.0)	41.0 (22.0; 76.0)	40.0 (18.0; 76.0)
Height (cm), N	293	295	588
Mean (SD)	171.2 (9.415)	172.6 (9.760)	171.9 (9.606)
Median (Range)	172.0 (146.0; 193.0)	172.7 (146.1; 197.0)	172.4 (146.0; 197.0)
Weight (kg), N	297	295	592
Mean (SD)	71.5 (15.379)	71.3 (13.501)	71.4 (14.462)
Median (Range)	71.2 (37.5; 146.1)	70.0 (40.0; 110.7)	70.8 (37.5; 146.1)
Body mass index (kg/m²), N	293	293	586
Mean (SD)	24.3 (4.795)	23.9 (3.883)	24.1 (4.363)
Median (Range)	23.8 (15.5; 56.1)	23.7 (16.5; 44.4)	23.7 (15.5; 56.1)
Race, n (%), N	298	296	594
Black	54 (18.1)	51 (17.2)	105 (17.7)
Caucasian/White	161 (54.0)	168 (56.8)	329 (55.4)
Hispanic	44 (14.8)	43 (14.5)	87 (14.6)
Oriental/Asian	28 (9.4)	28 (9.5)	56 (9.4)
Other	11 (3.7)	6 (2.0)	17 (2.9)
Hepatitis B or C coinfection status, n (%), N	297	295	592
Coinfected	52 (17.5)	37 (12.5)	89 (15.0)
Not Coinfected	245 (82.5)	258 (87.5)	503 (85.0)

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

The study groups were generally well balanced with regard to demographic characteristics. The same holds for baseline disease characteristics as displayed in the following table. Approximately 15 % of the patients were co-infected with hepatitis B or C.

Table 3 Baseline Disease Characteristics

Baseline Characteristic	DRV/RTV	LPV/RTV	All Subjects
Log_{10} viral load (copies/ml), N	298	297	595
Mean (SD)	4.33 (0.785)	4.28 (0.808)	4.30 (0.796)
Median (Range)	4.35 (2.33; 6.31)	4.30 (1.69; 6.66)	4.31 (1.69; 6.66)
CD4+ cell count (x 10^6/L), N	294	295	589
Mean (SD)	264 (175.16)	267 (182.30)	266 (178.63)
Median (Range)	235 (3; 831)	230 (2; 1096)	232 (2; 1096)
Log_{10} viral load, n (%), N	298	297	595
< 20,000 copies/ml	144 (48.3)	149 (50.2)	293 (49.2)
[20,000 - 50,000[copies/ml	50 (16.8)	53 (17.8)	103 (17.3)
[50,000 - 100,000[copies/ml	48 (16.1)	45 (15.2)	93 (15.6)
≥ 100,000 copies/ml	56 (18.8)	50 (16.8)	106 (17.8)
CD4+ cell count, n (%), N	294	295	589
< 50 x 10^6/L	27 (9.2)	24 (8.1)	51 (8.7)
[50 - 100[x 10^6/L	28 (9.5)	30 (10.2)	58 (9.8)
[100 - 200[x 10^6/L	61 (20.7)	65 (22.0)	126 (21.4)
[200 - 350[x 10^6/L	97 (33.0)	88 (29.8)	185 (31.4)
≥ 350 x 10^6/L	81 (27.6)	88 (29.8)	169 (28.7)
Known duration of HIV infection (years) , N	297	296	593
Mean (SD)	9.7 (5.47)	9.8 (5.79)	9.8 (5.63)
Median (Range)	9.1 (0.68; 22.61)	9.1 (0.23; 23.48)	9.1 (0.23; 23.48)
Structured treatment interruption at screening, n (%), N	298	297	595
No	234 (78.5)	226 (76.1)	460 (77.3)
Yes	64 (21.5)	71 (23.9)	135 (22.7)
DRV FC, N	292	290	582
Geometric Mean	0.64	0.63	0.63
Median (Range)	0.60 (0.10; 37.40)	0.60 (0.10; 43.80)	0.60 (0.10; 43.80)
LPV FC, N	292	290	582
Geometric Mean	1.18	1.27	1.22
Median (Range)	0.70 (0.40; 74.40)	0.80 (0.30; 74.50)	0.75 (0.30; 74.50)
DRV FC, n (%), N	292	290	582
[0, 4]	282 (96.6)	280 (96.6)	562 (96.6)
]4, 10]	5 (1.7)	6 (2.1)	11 (1.9)
]10, 40]	5 (1.7)	3 (1.0)	8 (1.4)
]40, 100]	0	1 (0.3)	1 (0.2)
LPV FC, n (%), N	292	290	582
[0, 4]	254 (87.0)	243 (83.8)	497 (85.4)
]4, 10]	9 (3.1)	18 (6.2)	27 (4.6)
]10, 40]	24 (8.2)	21 (7.2)	45 (7.7)
]40, 100]	5 (1.7)	8 (2.8)	13 (2.2)
Clinical stage of HIV infection, n (%), N	298	297	595
A	142 (47.7)	137 (46.1)	279 (46.9)
B	55 (18.5)	66 (22.2)	121 (20.3)
C	101 (33.9)	94 (31.6)	195 (32.8)

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

The trial included patients who were not highly ART-experienced. This ranged from patients who were NNRTI (23.7%) or PI naïve (31.4%) to those who had been experienced to ≥ 2 PIs (31.1%). Approximately half of the patients had received ≥ 4 previous NRTIs. The median FC (fold change in EC_{50}) for DRV and LPV was 0.6 and 0.7, demonstrating a relatively low overall PI resistance. At baseline 32.0% of the patients in trial TMC114-C214 had ≥ 1 primary PI mutation and 9.4% had 1 DRV resistance-associated mutation (RAM). The median number of primary PI mutations was 0 (range: 0 - 6); the median number of PI RAMs was 4 (range: 0 - 17). The median number of DRV RAMs and LPV RAMs was 0 (range: 0 - 5) and 1 (range: 0 - 11), respectively.

There were no notable differences between the treatment groups with respect to susceptibility to PIs, NRTIs and NNRTIs at baseline, or with respect to the number of susceptible PIs, NRTIs, or NNRTIs used in the screening ART, or underlying OBR. Most patients (87.5%) were able to use ≥ 1 NRTIs in the OBR to which the virus was susceptible.

There were no relevant differences between the DRV/RTV and LPV/RTV treatment groups with respect to the ARV therapies used in the initial OBR. The overwhelming majority of patients (90%) used only NRTIs in the OBR. The majority of patients used 2 or 3 NRTIs (69% and 25%, respectively); the three combinations emtricitabine (FTC) and tenofovir (TDF) (11%), lamivudine (3TC) and zidovudine (AZT) (10%) and 3TC, TDF and AZT (12%) were most frequently used.

Concomitant disease

In addition to the cases of co-infection with hepatitis B or C, the incidence of other concomitant diseases at screening was high in both treatment groups. The most common were dermatologic conditions (29%) and conditions related to the gastrointestinal (GI) system (29%). These conditions were noted more frequently in the DRV/RTV group than in the LPV/RTV group (34% versus 23%, and 34% versus 24%, respectively). There were no other relevant differences between the DRV/RTV and LPV/RTV treatment groups with respect to the concomitant diseases reported at screening. Eleven percent of all patients (10% and 13% of patients in the DRV/RTV and LPV/RTV groups, respectively) had a history of sulfonamide allergy.

2.2 Efficacy

Primary endpoint

The percentage of patients with confirmed plasma viral load < 400 copies/ml at Week 48 in the OP population was 77% for the DRV/RTV group and 68% for the LPV/RTV group. The difference in virological response [95% CI] between the treatment groups was 9.5 [2.1; 16.9]; the lower limit of the 95% CI of the difference between the treatment groups was > -12%, therefore, non-inferiority of DRV/RTV versus LPV/RTV was concluded. The lower limit of the 95% CI of the difference between the treatment groups was also > 0 (in support of the pre-defined superiority rationale). Statistical comparison using the logistic regression model showed an estimated difference [95% CI] in virological response at Week 48 between the DRV/RTV and LPV/RTV treatment groups of 9.1 [1.9; 16.4], with a p-value confirming non-inferiority of < 0.001. See the following table.

Table 4 Virological Response: Percentage of Patients with Viral Load < 400 copies/ml at Week 48 (OP & ITT – TLOVR)

Population	Treatment Group	Estimated[a] % Response	Estimated Difference in % Response	95% CI of Difference in % Response[b]	p-Value of Noninferiority	p-Value of Superiority
OP	DRV/RTV LPV/RTV	79.7 70.5	9.1	[1.9, 16.4]	< 0.001	0.011
ITT	DRV/RTV LPV/RTV	78.2 68.6	9.6	[2.4, 16.7]	< 0.001	0.008

a Percent response estimated from a logistic regression model including use of an NNRTI in the OBR as factor and baseline $\log_{10}$ plasma viral load as covariate.

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

The percentages of patients with confirmed plasma viral load < 400 copies/ml per time point (OP – TLOVR) is summarised in the following table.

Table 5 Percentage of Patients with Viral Load< 400 copies/ml (OP – TLOVR) per Time Point

Time Point	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]
On-Protocol Population						
Week 4	274	155 (56.6)	280	156 (55.7)	0.9	[-7.4; 9.1]
Week 8	274	212 (77.4)	280	201 (71.8)	5.6	[-1.7; 12.8]
Week 12	274	231 (84.3)	280	221 (78.9)	5.4	[-1.1; 11.8]
Week 16	274	236 (86.1)	280	227 (81.1)	5.1	[-1.1; 11.2]
Week 24	274	226 (82.5)	280	213 (76.1)	6.4	[-0.3; 13.2]
Week 36	274	216 (78.8)	280	197 (70.4)	8.5	[1.2; 15.7]
Week 48	274	211 (77.0)	280	189 (67.5)	9.5	[2.1; 16.9]

N = number of patients; n = of observations.
a Observed proportion of responders.
b Based on a normal approximation to the difference in % response.

The results obtained for the ITT population were consistent with those of the OP population.

The favourable results of DRV/RTV were also reflected in the following display of the virological response (% patients with confirmed plasma viral load < 400 copies/ml at Week 48) according to the TLOVR algorithm. Of the 298 DRV/RTV patients, 31 (10.7%) experienced virological failure versus 65 of 297 (21.2%) LPV/RTV patients. There were less patients with an initial lack of response (7% versus 14% of patients) and less rebounders (3% versus 6% of patients) in the DRV/RTV group compared to the LPV/RTV group.

Table 6 Virological Response: Percentage of Patients With Viral Load < 400 copies/ml at Week 48 TLOVR algorithm as per FDA Algorithm[2]

Number of Responders, n (%)	DRV/RTV N = 298	LPV/RTV N = 297
Confirmed virological response	227 (76.2)	193 (65.0)
Virological failures	32 (10.7)	63 (21.2)
Initial lack of response	22 (7.4)	41 (13.8)
Rebounder	9 (3.0)	17 (5.7)
Discontinued due virological failure: rebounder	1 (0.3)	4 (1.3)
Discontinued due virological failure: never suppressed	0	1 (0.3)
Death	2 (0.7)	2 (0.7)
Discontinuation due to AE	15 (5.0)	13 (4.4)
Discontinuation due to other reasons	22 (7.4)	26 (8.8)

The different sensitivity analyses indicated that the results for virological response defined as the percentage of patients with confirmed viral load < 400 copies/ml were robust and consistent across the different populations and imputation methods used. See the following display.

[2] FDA Guidance for industry, antiretroviral drugs using plasma HIV RNA Measurements - Clinical considerations for accelerated and traditional approval, prepared by the Division of Antiviral Drug Products: Office of Drug Evaluation IV in the Centre for Drug Evaluation and Research (CDER), Appendix B, October 2002

Table 7 Sensitivity Analyses for Virologic Response Defined as the Percentage of Subjects with Viral Load < 400 copies/ml at Week 48

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]
OP - TLOVR	274	211 (77.0)	280	189 (67.5)	9.5	[2.1; 16.9]
ITT - TLOVR	298	228 (76.5)	297	199 (67.0)	9.5	[2.3; 16.7]
OP as specified per protocol - TLOVR	286	220 (76.9)	293	199 (67.9)	9.0	[1.7; 16.3]
OP - Observed	230	208 (90.4)	214	188 (87.9)	2.6	[-3.2; 8.4]
ITT - Observed	250	224 (89.6)	227	198 (87.2)	2.4	[-3.4; 8.1]
ITT - LOCF-DCPW for LPV/RTV, TLOVR for DRV/RTV	298	228 (76.5)	297	205 (69.0)	7.5	[0.3; 14.6]
ITT - LOCF-DC for LPV/RTV, TLOVR for DRV/RTV	298	228 (76.5)	297	217 (73.1)	3.4	[-3.5; 10.4]

N = number of patients; n = number of observations.
[a] Observed proportion of responders.
[b] Based on a normal approximation to the difference in % response.

The MAH illustrated also that the virological response (percentage of patients with viral load < 400 copies/ml) at Week 48 with LPV/RTV was comparable with the virological response rates observed in previous trials performed with LPV/RTV 400/100 mg b.i.d. in treatment-experienced HIV-1 infected patients. The difference in virological response at Week 48 between the DRV/RTV and LPV/RTV treatment groups was apparently maintained across several subgroups by baseline e.g. DRV FC and LPV FC, number of DRV and LPV RAMs at baseline, STI at screening, number of susceptible NRTIs and susceptible ARVs in the OBR. See the following table.

Table 8 Subgroup Analyses for Virological Response (% of Patients With Viral Load < 400 copies/ml at Week 48)- ITT – TLOVR

Baseline Parameter	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]
Baseline log_{10} Viral Load (copies/ml)						
< 100,000	242	193 (79.8)	247	169 (68.4)	11.3	[3.6; 19.1]
≥ 100,000	56	35 (62.5)	50	30 (60.0)	2.5	[-16.3; 21.3]
Baseline CD4+ Cell Count (x 10^6/L)						
< 50	27	16 (59.3)	24	16 (66.7)	-7.4	[-34.6; 19.8]
[50 - 100[	28	17 (60.7)	30	16 (53.3)	7.4	[-18.6; 33.4]
[100 - 200[	61	46 (75.4)	65	43 (66.2)	9.3	[-6.7; 25.2]
[200 - 350[	97	80 (82.5)	88	63 (71.6)	10.9	[-1.2; 22.9]
≥ 350	81	66 (81.5)	88	59 (67.0)	14.4	[1.3; 27.6]
Baseline DRV FC						
≤ 10	287	219 (76.3)	286	190 (66.4)	9.9	[2.5; 17.2]
> 10	5	3 (60.0)	4	2 (50.0)	10.0	[-68.4; 88.4]
Baseline LPV FC						
≤ 10	263	200 (76.0)	261	181 (69.3)	6.7	[-0.9; 14.3]
> 10	29	22 (75.9)	29	11 (37.9)	37.9	[13.9; 62.0]
≤ 40	287	218 (76.0)	282	189 (67.0)	8.9	[1.5; 16.3]
> 40	5	4 (80.0)	8	3 (37.5)	42.5	[-14.6; 99.6]
Number of DRV RAMs at Baseline[c]						
0	238	181 (76.1)	252	176 (69.8)	6.2	[-1.7; 14.1]
1	35	31 (88.6)	21	14 (66.7)	21.9	[0.8; 43.1]
2	11	8 (72.7)	13	4 (30.8)	42.0	[3.4; 80.6]
≥ 3	12	6 (50.0)	11	5 (45.5)	4.5	[-38.8; 47.9]

Table 8 Subgroup Analyses for Virological Response (% of Patients With Viral Load < 400 copies/ml at Week 48)- ITT – TLOVR (cont'd)

Baseline Parameter	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]
Number of LPV RAMs at Baseline[c]						
< 6	264	201 (76.1)	262	186 (71.0)	5.1	[-2.4; 12.7]
≥ 6	32	25 (78.1)	35	13 (37.1)	41.0	[18.9; 63.0]
Number of Primary PI Mutations[c]						
0	199	148 (74.4)	204	149 (73.0)	1.3	[-7.3; 10.0]
≥ 1	97	78 (80.4)	93	50 (53.8)	26.6	[13.8; 39.5]
Number of PIs Previously Used						
0	94	73 (77.7)	93	75 (80.6)	-3.0	[-14.7; 8.7]
1	108	80 (74.1)	115	77 (67.0)	7.1	[-4.9; 19.1]
≥ 2	96	75 (78.1)	89	47 (52.8)	25.3	[12.1; 38.6]
Structured Treatment Interruption at Screening						
No	234	181 (77.4)	226	151 (66.8)	10.5	[2.4; 18.7]
Yes	64	47 (73.4)	71	48 (67.6)	5.8	[-9.7; 21.4]
Use of an NNRTI in the OBR						
Efavirenz	26	21 (80.8)	15	12 (80.0)	0.8	[-25.2; 26.8]
Nevirapine	5	4 (80.0)	8	4 (50.0)	30.0	[-28.5; 88.5]
Not used	267	203 (76.0)	274	183 (66.8)	9.2	[1.6; 16.8]
Number of Susceptible NRTIs in the OBR[d]						
0	30	23 (76.7)	42	27 (64.3)	12.4	[-9.4; 34.2]
1	70	59 (84.3)	75	53 (70.7)	13.6	[0.0; 27.2]
≥ 2	188	139 (73.9)	171	112 (65.5)	8.4	[-1.1; 17.9]
Number of Susceptible ARVs (NNRTIs and NRTIs) in the OBR[d]						
0	24	18 (75.0)	32	21 (65.6)	9.4	[-15.4; 34.1]
1	55	48 (87.3)	75	51 (68.0)	19.3	[4.7; 33.9]
≥ 2	209	155 (74.2)	181	120 (66.3)	7.9	[-1.2; 16.9]
Gender						
Male	229	177 (77.3)	241	165 (68.5)	8.8	[0.8; 16.9]
Female	69	51 (73.9)	56	34 (60.7)	13.2	[-3.2; 29.6]
Age						
≤ 30	30	17 (56.7)	35	25 (71.4)	-14.8	[-38.3; 8.7]
]30 - 45]	189	142 (75.1)	196	126 (64.3)	10.8	[1.7; 20.0]
]45 - 55]	61	53 (86.9)	46	30 (65.2)	21.7	[6.1; 37.3]
]55 - 65]	17	15 (88.2)	17	16 (94.1)	-5.9	[-25.6; 13.8]
> 65	1	1 (100.0)	3	2 (66.7)	33.3	[-200.9; 267.5]
Race						
Black	54	35 (64.8)	51	25 (49.0)	15.8	[-3.1; 34.7]
Caucasian/White	161	120 (74.5)	168	113 (67.3)	7.3	[-2.6; 17.1]
Hispanic	44	38 (86.4)	43	32 (74.4)	11.9	[-4.8; 28.7]
Oriental/Asian	28	27 (96.4)	28	23 (82.1)	14.3	[-1.8; 30.4]
Other	11	8 (72.7)	6	5 (83.3)	-10.6	[-56.3; 35.1]
Region						
Africa	10	5 (50.0)	12	11 (91.7)	-41.7	[-76.8; -6.6]
Asia	26	25 (96.2)	24	20 (83.3)	12.8	[-3.9; 29.5]
Europe & Australia	92	72 (78.3)	112	78 (69.6)	8.6	[-3.6; 20.8]
Latin America	75	59 (78.7)	66	45 (68.2)	10.5	[-4.1; 25.1]
North-America	95	67 (70.5)	83	45 (54.2)	16.3	[2.2; 30.4]

N = number of patients; n = number of responders.

[a] Observed proportion of responders. [b] Based on a normal approximation to the difference in % response.

[c] Based on the 2006 IAS-USA list of mutations[3]. [d] Based on Antivirogram®.

[3] 43. Johnson VA, Brun-Vezinet F, Clotet B. Update of the drug resistance mutations in HIV-1. Top HIV Med 2006; 14 (3): 125-130.

It should be noted that for certain subgroups, the number of patients was relatively limited and these comparisons should be interpreted with caution.

Secondary endpoints

Week 48 results of main secondary virological response parameters such as the percentage of patients with confirmed plasma viral load < 50 copies/ml, and the percentage of patients with a confirmed decrease in plasma viral load ≥ 1.0 log_{10} copies/ml from baseline are displayed in the following two tables.

Table 9 Percentage of Patients With Viral Load < 50 copies/ml, and the Percentage of Patients With a Decrease in Viral Load of ≥ 1.0 log_{10} copies/ml From Baseline at Week 48 (ITT– TLOVR)

Treatment Group	Estimated[a] % Response	Estimated Difference in % Response	95% CI of Difference in % Response[b]	p-Value of Noninferiority	p-Value of Superiority
Viral Load < 50 copies/ml					
DRV/RTV LPV/RTV	72.0 60.9	11.1	[3.4; 18.8]	< 0.001	0.005
Decrease in Viral Load of ≥1.0 log_{10} copies/ml From Baseline					
DRV/RTV LPV/RTV	78.1 70.4	7.8	[0.73; 14.8]	< 0.001	0.028

a Percent response estimated from a logistic regression model including use of an NNRTI in the OBR as factor and baseline log_{10} plasma viral load as covariate.

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

The different sensitivity analyses demonstrated that the results for virological response defined as the percentage of patients with confirmed viral load < 50 copies/ml were robust and consistent across the different populations and imputation methods used.

The difference in virological response (viral load < 50 copies/ml) at Week 48 between the DRV/RTV and LPV/RTV treatment groups was maintained across several subgroups by baseline e.g. viral load, baseline DRV FC and LPV FC, number of DRV and LPV RAMs at baseline, STI at screening, use of an NNRTI in the OBR, number of susceptible NRTIs and susceptible ARVs in the OBR.

Table 10 Subgroup Analyses for Virological Response (% of Patients With Viral Load < 50 copies/ml at Week 48)- ITT – TLOVR

Baseline Parameter	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]
Baseline Viral Load (copies/ml)						
< 100,000	242	180 (74.4)	247	155 (62.8)	11.6	[3.4; 19.8]
≥ 100,000	56	31 (55.4)	50	24 (48.0)	7.4	[-11.9; 26.6]
Baseline CD4+ Cell Count (x 10^6/L)						
< 50	27	13 (48.1)	24	12 (50.0)	-1.9	[-30.0; 26.3]
[50 -100[	28	15 (53.6)	30	15 (50.0)	3.6	[-22.7; 29.9]
[100 -200[	61	41 (67.2)	65	40 (61.5)	5.7	[-11.2; 22.6]
[200 -350[	97	75 (77.3)	88	58 (65.9)	11.4	[-1.5; 24.4]
≥ 350	81	64 (79.0)	88	52 (59.1)	19.9	[6.1; 33.7]
Baseline DRV FC						
≤10	287	202 (70.4)	286	170 (59.4)	10.9	[3.2; 18.7]
> 10	5	3 (60.0)	4	2 (50.0)	10.0	[-68.4; 88.4]

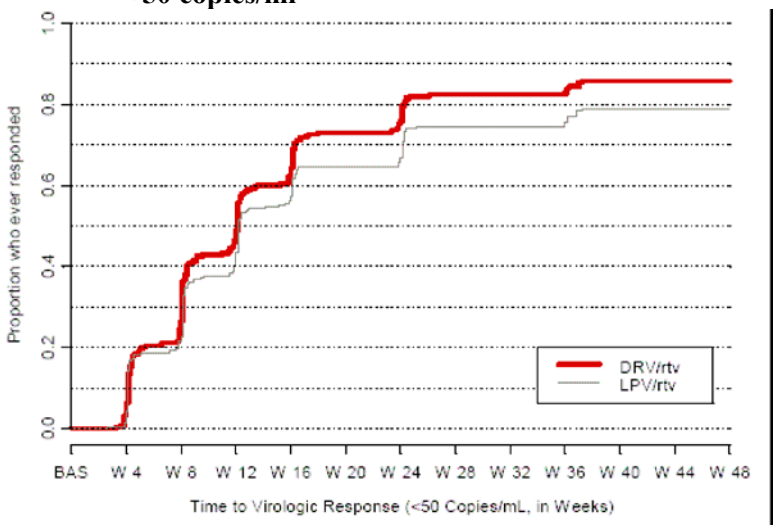
Table 10 Subgroup Analyses for Virological Response (% of Patients With Viral Load < 50 copies/ml at Week 48)- ITT – TLOVR (cont'd)

Baseline Parameter	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]
Baseline LPV FC						
≤10	263	184 (70.0)	261	164 (62.8)	7.1	[-1.0; 15.2]
> 10	29	21 (72.4)	29	8 (27.6)	44.8	[21.3; 68.3]
≤40	287	201 (70.0)	282	170 (60.3)	9.8	[1.9; 17.6]
> 40	5	4 (80.0)	8	2 (25.0)	55.0	[2.1; 107.9]
Number of DRV RAMs at Baseline[c]						
0	238	168 (70.6)	252	161 (63.9)	6.7	[-1.6; 15.0]
1	35	28 (80.0)	21	11 (52.4)	27.6	[3.3; 51.9]
2	11	7 (63.6)	13	3 (23.1)	40.6	[2.4; 78.7]
≥3	12	6 (50.0)	11	4 (36.4)	13.6	[-29.0; 56.3]
Number of LPV RAMs at Baseline[c]						
< 6	264	185 (70.1)	262	168 (64.1)	6.0	[-2.1; 14.0]
≥6	32	24 (75.0)	35	11 (31.4)	43.6	[21.6; 65.5]
Number of Primary PI Mutations[c]						
0	199	139 (69.8)	204	137 (67.2)	2.7	[-6.4; 11.8]
≥1	97	70 (72.2)	93	42 (45.2)	27.0	[13.5; 40.5]
Number of PIs Previously Used						
0	94	67 (71.3)	93	70 (75.3)	-4.0	[-16.8; 8.8]
1	108	72 (66.7)	115	69 (60.0)	6.7	[-6.0; 19.4]
≥2	96	72 (75.0)	89	40 (44.9)	30.1	[16.6; 43.6]
Structured Treatment Interruption at Screening						
No	234	168 (71.8)	226	138 (61.1)	10.7	[2.1; 19.3]
Yes	64	43 (67.2)	71	41 (57.7)	9.4	[-7.0; 25.9]
Use of an NNRTI in the OBR						
Efavirenz	26	20 (76.9)	15	10 (66.7)	10.3	[-18.6; 39.1]
Nevirapine	5	4 (80.0)	8	3 (37.5)	42.5	[-14.6; 99.6]
Not used	267	187 (70.0)	274	166 (60.6)	9.5	[1.4; 17.5]
Number of Susceptible NRTIs in the OBR[d]						
0	30	22 (73.3)	42	23 (54.8)	18.6	[-4.1; 41.2]
1	70	54 (77.1)	75	46 (61.3)	15.8	[0.8; 30.8]
≥2	188	128 (68.1)	171	103 (60.2)	7.9	[-2.1; 17.8]
Number of Susceptible ARVs (NNRTIs and NRTIs) in the OBR[d]						
0	24	17 (70.8)	32	19 (59.4)	11.5	[14.3; 37.2]
1	55	44 (80.0)	75	43 (57.3)	22.7	[6.6; 38.7]
≥2	209	143 (68.4)	181	110 (60.8)	7.6	[-1.9; 17.1]
Region						
Africa	10	4 (40.0)	12	11 (91.7)	-51.7	[-86.3; -17.1]
Asia	26	24 (92.3)	24	19 (79.2)	13.1	[-6.2; 32.5]
Europe & Australia	92	69 (75.0)	112	67 (59.8)	15.2	[2.3; 28.1]
Latin America	75	54 (72.0)	66	42 (63.6)	8.4	[-7.1; 23.9]
North-America	95	60 (63.2)	83	40 (48.2)	15.0	[0.4; 29.5]

N = number of patients; n = number of responders.
[a] Observed proportion of responders. [b] Based on a normal approximation to the difference in % response.
[c] Based on the 2006 IAS-USA list of mutations [d] Based on Antivirogram.

The Kaplan-Meier estimate showed that virological response defined as plasma viral load < 50 copies/ml was achieved more frequently in the DRV/RTV group than in the LPV/RTV group, see the following figure. The difference between the treatment groups in time to virological response defined as plasma viral load < 50 copies/ml was statistically significant (p = 0.0005), with a greater probability of responding to DRV/RTV treatment compared to LPV/RTV treatment (hazard ratio [95% CI]: 1.40 [1.16; 1.68]).

Figure 1 Time Virological Response: Proportion of Patients Achieving Plasma Viral Load < 50 copies/ml



Similar, the Kaplan-Meier estimate showed that the proportion of patients never achieving a plasma viral load < 50 copies/ml was smaller in the DRV/RTV group than in the LPV/RTV group, and that loss of virological response over time occurred 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 loss of virological response defined as plasma viral load < 50 copies/ml was statistically significant (p = 0.0268), with a smaller probability of failing under DRV/RTV treatment compared to LPV/RTV treatment (hazard ratio [95% CI]: 0.74 [0.56; 0.97]).

Similar results were obtained for time to loss of virological response defined as a decrease of ≥ 1.0 $\log_{10}$ versus baseline, where the difference between the treatment groups was statistically significant (p = 0.0397), and the hazard ratio for failing under DRV/RTV treatment relative to LPV/RTV treatment [95% CI] was 0.73 [0.54; 0.99].

Furthermore, the Week 48 mean change in $\log_{10}$ viral load from baseline in the ITT population was -1.95 and -1.72 $\log_{10}$ copies/ml for the DRV/RTV and LPV/RTV treatment groups, respectively. See the following table.

Table 11 Change in $\log_{10}$ Viral Load at Week 48 (ITT – NC = F)

Treatment Group	LS Means[a] (SE)	Difference in LS Means	95% CI of Difference in LS Means	P-Value
DRV/RTV LPV/RTV	-1.98 (0.0979) -1.78 (0.1013)	-0.20	[-0. 39; -0.00]	0.046

[a] Least square means estimated from an ANCOVA including use of an NNRTI in the OBR and treatment group as factors, and baseline $\log_{10}$ plasma viral load as covariate.

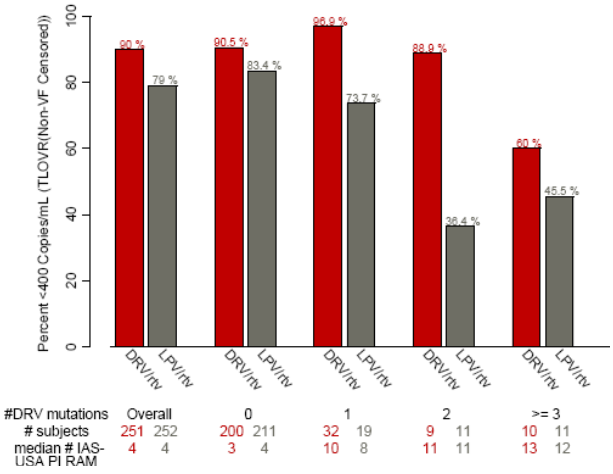
These results for the mean viral load DAVG were similar: at Week 48 this was -1.96 and -1.78 copies/ml for the DRV/RTV and LPV/RTV treatment groups, respectively.

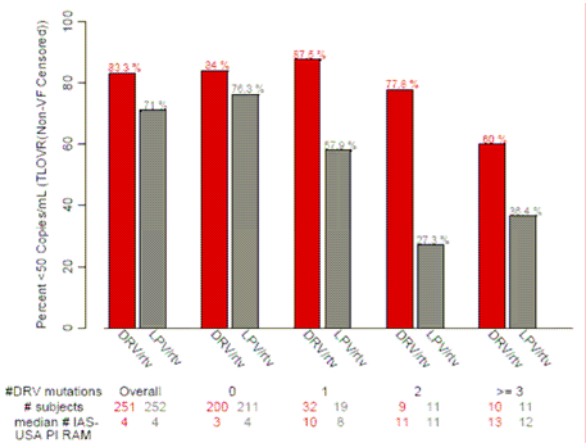
The majority of subjects harboured HIV-1 clade B (81.8% and 80.8 % in the DRV/RTV and LPV/RTV group, respectively). Other clades that were found in at least 10 subjects in each treatment group were clade C (4.7% and 4.0 % in the DRV/RTV and LPV/RTV group, respectively) and clade CRF01_AE (7.4% and 9.1 % in the DRV/RTV and LPV/RTV group, respectively). Other clades were present in less than 10 subjects in each treatment group. It should be noted that for all the clades except for clade B, the number of subjects was relatively limited and therefore those results should be interpreted with caution.

The virologic response in the DRV/RTV group or in the LPV/RTV group in subjects harbouring clade C, clade CRF01_AE or 'other clades' was not significantly different from the response in subjects harbouring clade B.

Influence of the number of DRV or LPV RAMs on virological response.
A diminished virological response rate defined by the % of patients with confirmed viral load < 400 copies/ml at Week 48 (TLOVR [Non-VF Censored]) was observed for the DRV/RTV subgroup of patients with ≥ 3 DRV RAMs (60%, representing < 75% of the overall response rate for the DRV/RTV group). The same was observed for the LPV/RTV subgroups of patients with 2 or ≥ 3 DRV RAMs (36% and 46%, respectively, representing < 75% of the overall response rate for the LPV/RTV group). The median number of IAS-USA PI RAMs was 3 and 4 for the subgroups of patients with no DRV RAMs at baseline in the DRV/RTV or LPV/RTV groups, respectively. A higher median number of IAS-USA PI RAMs (range 8 - 13) was observed for all subgroups of patients with ≥ 1 DRV RAM at baseline. Note that the number of patients in the subgroups with > 1 DRV RAM at baseline was low. Similar results were observed for virological response defined as the percentage of patients with viral load < 50 copies/ml at Week 48 (TLOVR [Non-VF Censored]). See the figures below.

Figure 2 Virological Response Defined as the Percentage of Patients with Viral Load < 400 copies/ml or < 50 copies/ml (TLOVR [Non-VF Censored]) at Week 48 versus Number of DRV RAMs at Baseline[a]



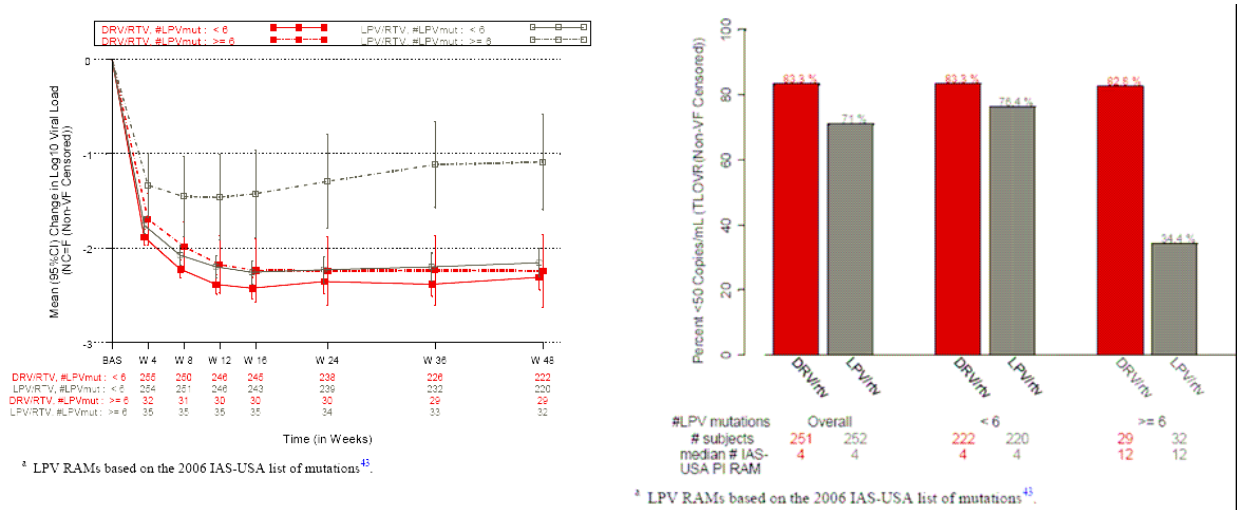


[a] DRV RAMs based on the 2006 IAS-USA list of mutations

A similar trend was also observed for the mean change in $\log_{10}$ viral load.

A diminished virological response rate (percentage of patients with viral load < 400 copies/ml at Week 48) was observed for the LPV/RTV subgroup of patients with ≥ 6 LPV RAMs (41%, representing < 75% of the overall response rate for the LPV/RTV group). The presence of LPV RAMs at baseline did not influence virological response to DRV/RTV, even if the median number of IAS-USA PI RAMs was 12 in the subgroup of patients with ≥ 6 LPV RAMs. Similar results were seen for virological response rate defined as percentage of patients with viral load < 50 copies/ml at Week 48 and for mean change in $\log_{10}$ viral load. See illustrations below.

Figure 3 Mean Change in log_{10} Viral Load From Baseline (NC = F [Non-VF Censored]) OR Virological Response Defined as the Percentage of Patients with Viral Load < 50 copies/ml (TLOVR [Non-VF Censored]) at Week 48 Versus Number of LPV RAMs at Baseline[a]



[a] LPV RAMs based on the 2006 IAS-USA list of mutations[43].

Proportionally fewer virological failures in the DRV/RTV group than in the LPV/RTV group developed DRV RAMs (18% versus 23%), LPV RAMs (25% versus 36%), IAS-USA primary PI mutations (21% versus 36%), IAS-USA PI RAMs (36% versus 48%), FDA defined PI mutations (21% versus 38%), or IAS-USA NRTI-RAMs (14% versus 27%). See the following table.

Table 12 Development of Mutations in Virological Failures at Endpoint

Patients Developing Mutations at Endpoint, n (%)	DRV/RTV	LPV/RTV
Total Number of Virological Failures	**31[a] (10.4)**	**65[b] (21.9)**
DRV RAMs[c]	5 (17.9)	13 (23.2)
LPV RAMs[c]	7 (25.0)	20 (35.7)
IAS-USA primary PI mutations[c]	6 (21.4)	20 (35.7)
IAS-USA PI RAMs[c]	10 (35.7)	27 (48.2)
FDA-defined PI RAMs	6 (21.4)	21 (37.5)
IAS-USA NRTI RAMs[c]	4 (14.3)	15 (26.8)

n = number of observations.
a Baseline and endpoint genotype was available for 28 of 31 virological failures; n = 28 was used to calculate the % for each mutation list.
b Baseline and endpoint genotype was available for 56 of 65 virological failures; n = 56 was used to calculate the % for each mutation list.
c Based on the IAS-USA list of mutations.

Among the 5 patients in the DRV/RTV group who developed DRV RAMs endpoint, 1 patient had 2 DRV RAMs at baseline, while the other 4 patients already had ≥ 3 DRV RAMs at baseline. Two of these 5 patients were already resistant to DRV (FC > 10) at baseline, and the other 3 patients became resistant to DRV after the development of the additional DRV RAMs. All 5 patients were resistant to LPV (FC > 10) at baseline.

Among the 20 patients in the LPV/RTV group who developed LPV RAMs at endpoint, 10 patients had < 6 LPV RAMs at baseline. Seven patients were already resistant to LPV (FC > 10) at baseline, and all other patients except 2 became resistant to LPV after the development of the LPV RAMs.

Analyses to identify the protease mutations that developed in > 10% of virological failures on DRV/RTV treatment showed that the V32I mutation developed in 11% (3/28) of virological failures.

Fewer virological failures treated with DRV/RTV than with LPV/RTV lost susceptibility to PIs or NRTIs after treatment: 4/31 (14%) patients in the DRV/RTV group were susceptible to fewer PIs (excluding DRV) after treatment compared to 18/65 (33%) patients in the LPV/RTV group. See the following table

Table 13 Loss of Susceptibility to ARVs in Virological Failures at Endpoint

Subjects with Less Susceptible ARVs at Endpoint Compared to Baseline, n (%)	DRV/RTV	LPV/RTV
Total Number of Virologic Failures	31[a] (10.4)	65[b] (21.9)
PI		
All	4 (14.3)[c]	18 (33.3)[d]
In treatment regimen	3 (10.7)[e]	13 (24.1)[f]
NRTI		
All	4 (14.3)[g]	17 (31.5)[h]
In underlying OBR	3 (10.7)[i]	14 (25.9)[j]

n = number of observations.
[a] Baseline and endpoint phenotype was available for 28 of 31 virologic failures.
[b] Baseline and endpoint phenotype was available for 54 of 65 virologic failures.
[c] 3 patients had baseline viruses with no susceptibility to a PI.
[d] 2 patients had baseline viruses with no susceptibility to a PI.
[e] 2 patients had baseline viruses with no susceptibility to DRV.
[f] 12 patients had baseline viruses with no susceptibility to LPV.
[g] 1 patient had baseline viruses with no susceptibility to a NRTI.
[h] 2 patients had baseline viruses with no susceptibility to a NRTI.
[i] 4 patients had baseline viruses with no susceptibility to a NRTI from the OBR.
[j] 11 patients had baseline viruses with no susceptibility to a NRTI from the OBR.
Note: Phenotypes determined by Antivirogram.

Immunological response
Statistical comparison between the treatment groups at Week 48 (ANCOVA) for the change in CD4+ cell count from baseline (ITT – NC = F) is summarised in the following table. In both groups the median change (increase) in CD4 cell count was similar.

Table 14 Change in CD4+ Cell Count at Week 48 (ITT – NC = F)

Treatment Group	LS Means[a] (SE)	Difference in LS Means	95% CI of Difference in LS Means	p-Value
DRV/RTV	94 (10.8)	-11	[-32; 11]	0.330
LPV/RTV	105 (11.2)			

[a] Least square means estimated from an ANCOVA including use of an NNRTI in the OBR and treatment group as factors, and baseline $\log_{10}$ plasma viral load as covariate.

QoL- FAHI score
FAHI imputed score at baseline was rather high (124 and 121 for the DRV/RTV and LPV/RTV treatment groups, respectively), leaving relatively limited room for improvement. There were no statistically or clinically relevant differences between the two treatment groups for the slight observed changes.

Population PK/PD data (These were already assessed in the CHMP renewal AR).
Of the 298 patients randomised and treated with DRV/RTV, 285 patients with sparse sampling data were included in the population pharmacokinetic analysis for DRV. The Bayesian estimates of the DRV pharmacokinetic parameters from the sparse sampling data are summarised in the below table.

Table 15 Population PK Estimates of DRV

Parameter	Median (Range)
N	285
AUC_{12h}, ng·h/ml	55816 (32437; 177680)
C_{0h}, ng/ml	3306.5 (1516.9; 13198)

N = number of patients.

The analysis concluded that plasma trough DRV concentrations (C0h) exceeded the predefined target trough concentration of 550 ng/ml (based on the EC50 value for PI-resistant HIV-1 strains when corrected for protein binding) in all patients. Results from this analysis confirm previous findings in treatment-experienced HIV-1 infected patients following dosing with DRV/RTV 600/100 mg b.i.d.

Concomitant use of EFV and NVP at baseline, age, and weight did not influence the DRV AUC12h or C0h values. A trend toward higher DRV exposure in females (approximately 8%, N = 67) compared to males (N = 218), and higher exposure in Blacks (approximately 15%, N = 49) and lower exposure in Asian patients (approximately 16%, N = 27) compared to Caucasian patients (N = 154) was observed. These differences were not considered clinically relevant.

No apparent relationships were observed between the DRV pharmacokinetic parameters AUC12h and C0h, and the occurrence of AEs leading to permanent discontinuation of the trial medication, or rash-, cardiac-, GI-, liver-, lipid- and glucose-related AEs, or AEs of the SOCs Nervous System Disorders, and Psychiatric Disorders.

Discussion on Efficacy

Study C214 demonstrated the non-inferiority of the efficacy of DRV/RTV at the recommended dosage of DRV/RTV 600/100 mg b.i.d. compared to LPV/RTV both in combination with an OBR in the studied ART-experienced HIV-1 infected patients based on the primary virological endpoint (i.e. the percentage of patients with confirmed plasma viral load < 400 copies/ml at Week 48 in the OP population) at the chosen delta of 12%. DRV/RTV was at least as efficacious as LPV/RTV based on the results for secondary virological and immunological response parameters. In this comparison, DRV/RTV treatment appeared to be associated with more favourable virological response as defined by the primary endpoint (77% for the DRV/RTV group and 68% for the LPV/RTV group). This was also evident from the results for the percentage of patients with confirmed plasma viral load < 50 copies/ml at Week 48 (which was a secondary endpoint) and other secondary virological parameters.

Justification of the chosen non-inferiority margin was based on trials with other PIs and not on a discussion of potential clinical relevance in the context of morbidity or survival. However, the observed lower bound of the 95% CI was > -10% and therefore there is no reason for concern in that regard.

Virological response tends to decrease over time at least partly due to viral resistance associated with RAM, as noted also in the original pre-registration assessment for the highly pre-treated HIV-1 infected patients. The results of the Week 96 of the present ongoing trial are of interest for the further evaluation of the development of resistance and evaluation of the long-term safety of DRV/RTV in this HIV-1 infected population. In this regard there is an ongoing FUM, to which the MAH committed; in this context, the MAH should also present the virologic response by clade (see also Letter of Undertaking).

The submitted population pharmacokinetic analysis did not reveal unexpected findings. Some small differences in plasma concentrations were observed between studied groups, but this is considered not clinically relevant.

2.3 Safety

Trial TMC114-C214 showed that the overall AE profile of DRV/RTV 600/100 mg b.i.d. was comparable to that of LPV/RTV 400/100 mg b.i.d, which represents a standard of care for treatment-

experienced patients. Except for diarrhoea, which was less frequent with DRV/RTV than with LPV/RTV and rash which was more frequent with DRV/RTV, the incidence of the most common AEs was comparable for the 2 treatment groups. See the following table.

Table 16 Adverse Events: Summary Table

n (%) of Subjects With	DRV/RTV N = 298	LPV/RTV N = 297
Mean Exposure (weeks)	***53.5***	***51.5***
Most common AEs (preferred terms)[a]		
Diarrhoea	95 (31.9)	124 (41.8)
Nausea	55 (18.5)	62 (20.9)
Nasopharyngitis	37 (12.4)	33 (11.1)
Headache	33 (11.1)	22 (7.4)
Upper respiratory infection	30 (10.1)	22 (7.4)
Most common AEs at least grade 2 in severity and at least possibly related to DRV/RTV		
Diarrhoea	23 (7.7)	43 (14.5)
Nausea	12 (4.0)	13 (4.4)
Hypertriglyceridaemia	16 (5.4)	24 (8.1)
Hypercholesterolemia	9 (3.0)	13 (4.4)
Blood triglycerides increased	9 (3.0)	13 (4.4)
Blood cholesterol increased	8 (2.7)	4 (1.3)
AEs of specific interest		
≥ 1 Rash-related AEs	48 (16.1)	20 (6.7)
≥ 1 Cardiac-related AE	19 (6.4)	21 (7.1)
≥ 1 GI-related AE	165 (55.4)	177 (59.6)
≥ 1 Liver-related AE	24 (8.1)	19 (6.4)
≥ 1 Lipid-related AE	59 (19.8)	62 (20.9)
≥ 1 Glucose-related	AE 9 (3.0)	13 (4.4)
≥ 1 AE	277 (93.0)	273 (91.9)
≥ 1 SAE	28 (9.4)	31 (10.4)
≥ 1 AE leading to death	2 (0.7)	3 (1.0)
≥ 1 AE leading to permanent discontinuation	20 (6.7)	20 (6.7)[a]
≥ 1 grade 3 or 4 AE	80 (26.8)	89 (30.0)

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

[a] AEs reported in ≥ 10% of DRV/RTV-treated patients.

[b] Not taking into account one patient who discontinued due to an AE (diarrhoea) after 17 January 2007, the cut-off date for the primary analysis.

The incidence of cardiac-related AEs was generally comparable for the DRV/RTV and LPV/RTV groups. Heart-failure-related AEs were reported in 0.3% and 1% of patients in the respective treatment groups, ischemia-related AEs in 0.3% and 2%, and rhythm disturbance- or ECG- related AEs in 6% and 5%, respectively. The most frequent cardiac-related AE by preferred term was ECG QTc interval prolonged (2% and 0.3% with DRV/RTV and LPV/RTV, respectively). All other cardiac-related AEs occurred in ≤ 1% of patients in the DRV/RTV and/or LPV/RTV group.

QTcF values of > 500 ms were not observed. QTcB values of > 500 ms were observed in 2% and 1% of patients in the DRV/RTV and LPV/RTV groups, respectively. Increases in QTcF of > 60 ms were observed in 2% and 1% of patients in the DRV/RTV and LPV/RTV groups, respectively. Increases in QTcB of > 60 ms were observed in 4% and 2% of patients in the DRV/RTV and LPV/RTV groups, respectively. In 2 DRV/RTV-treated patients, an increase in QTcB of > 60 ms resulted in a QTcB value of > 500 ms (509 and 502 ms, respectively). No other increases in QTc of > 60 ms resulted in QTc values of > 500 ms. No patients presented any clinical events related to QTc prolongation.

The incidence of liver-related AEs was generally comparable between both treatment groups. The most frequent liver-related AEs (preferred term) were alanine aminotransferase (ALT) increased (2% in both groups), gamma-glutamyl tranferase (GGT) increased (2% and 1% with DRV/RTV and LPV/RTV, respectively), aspartate aminotransferase (AST) increased (1% and 3%) and jaundice (1%

and 0%). All other liver-related AEs occurred in < 1 % of patients in the DRV/RTV and/or LPV/RTV group. Grade 3 or 4 liver-related AEs occurred in 4% of patients in both treatment groups.

Hyperbilirubinemia (increase in total bilirubin) was observed less frequently in the DRV/RTV group (2%) than in the LPV/RTV group (6%). Grade 3 or 4 hyperbilirubinemia was observed in 2 DRV/RTV-treated patients and not in LPV/RTV-treated patients.

In both treatment groups, the overall incidence of liver-related AEs was higher in patients with hepatitis B or C co-infection (25% and 24% with DRV/RTV and LPV/RTV, respectively) than in patients not co-infected with hepatitis B or C virus (5% and 4%).

The incidence of lipid-related AEs was generally comparable between both treatment groups. The most frequent lipid-related AEs (preferred term) were hypertriglyceridaemia (7% and 10% with DRV/RTV and LPV/RTV, respectively), hypercholesterolaemia (4% and 6%), blood triglycerides increased (4% in both groups), blood cholesterol increased (4% and 3%), and hyperlipidaemia (3% and 4%). All other lipid-related AEs occurred in ≤ 2 % of patients in the DRV/RTV and/or LPV/RTV group.

Glucose-related AEs were reported in 3% and 4% of patients in the DRV/RTV and LPV/RTV groups, respectively. None of the glucose-related AEs were reported in > 1% of patients in any treatment group and the incidence of glucose-related AEs was comparable between both treatment groups. One patient in the DRV/RTV group permanently discontinued the trial medication due to grade 2 diabetes mellitus (possibly related).

The incidence of increased amylase was higher in the DRV/RTV group (24%) than in the LPV/RTV group (17%); the incidence of increased lipase and creatinine was comparable for both treatment groups (8% versus 5%, and 6% versus 8%, respectively). There were no relevant differences between the treatment groups in the incidence of grade 3 or 4 abnormalities for amylase (6% versus 3%), lipase (2% versus 0.3%), or creatinine (0% for both treatment groups). The increases in amylase and lipase were asymptomatic in all cases.

The incidence of haematology laboratory abnormalities was generally comparable for the DRV/RTV and LPV/RTV treatment groups. The majority of haematology abnormalities in this trial were grade 1 or 2. The incidence of prothrombin time (PT) and activated partial thromboplastin time (PTT) abnormalities was low. Grade 4 increased PT was observed in 1 LPV/RTV-treated patient and not in DRV/RTV-treated patients; grade 4 increased PTT was observed in 1% of patients in both treatment groups. Grade 4 decreases in haemoglobin were observed in 1% of patients in the LPV/RTV group and not in the DRV/RTV group. There were no grade 3 or 4 decreases for white blood cell (WBC) count. Grade 3 decreases in platelet count were observed in 0.3% of patients in the DRV/RTV group and 1% of patients in the LPV/RTV group. Grade 3 or 4 decreases in neutrophil count were not observed in the DRV/RTV group and in 2% of patients in the LPV/RTV group.

The incidence of AEs related to urinalysis was low and comparable for the DRV/RTV and LPV/RTV treatment groups. The most frequent AE related to urinalysis was haematuria, reported in 1% of patients in both treatment groups. No AEs related to urinalysis were grade 3 or 4 in severity.

Serious Adverse Events were reported in 9% and 10% of patients in the DRV/RTV and LPV/RTV treatment groups, respectively. All SAEs, except 2 (anaemia and cardiorespiratory arrest), occurred in only 1 patient in the DRV/RTV and/or LPV/RTV group. The SAE anaemia occurred in 2 DRV/RTV-treated patients, and the SAE cardiorespiratory arrest occurred in 2 LPV/RTV-treated patients. The most frequent SAEs by SOC (in > 1% of patients in any treatment group) were Infections and Infestations (3% and 3%, with DRV/RTV and LPV/RTV, respectively), and Cardiac Disorders (0% and 2%).

Seven percent of patients of both treatment groups permanently discontinued treatment due to ≥ 1 AEs. The incidence of AEs leading to permanent discontinuation was generally comparable for the DRV/RTV and LPV/RTV treatment groups. AEs leading to permanent discontinuation were most

commonly from the SOC Gastrointestinal Disorders (2% of patients in both groups), of which the AE diarrhoea (1% and 2% with DRV/RTV and LPV/RTV, respectively) was reported most frequently, and the SOC Investigations (2% in both groups). All other AEs leading to permanent discontinuation occurred in ≤ 1% of patients in the DRV/RTV and/or LPV/RTV group.

AEs of all grades that were considered at least possibly related to DRV/RTV or LPV/RTV were reported in 58.7% and 64.3% of patients in the DRV/RTV and LPV/RTV groups, respectively. Grade ≥ 2 AEs at least possibly related to DRV/RTV or LPV/RTV were reported in 36.9% and 40.7% of patients, respectively. The majority of grade ≥ 2 AEs at least possibly related to DRV/RTV or LPV/RTV occurred in ≤ 1% of patients in any treatment group.

Table 17 Most Common (≥ 1% of patients in Either Treatment Group) Adverse Events with at Least Grade 2 and Considered at Least Possibly Related to PI

System Organ Class **Preferred Term, n (%)**	**DRV/RTV** **N = 298**	**LPV/RTV** **N = 297**
Mean Exposure (weeks)	***53.5***	***51.5***
Any ≥ Grade 2 AE at Least Possibly Related to PI[a]	***110 (36.9)***	***121 (40.7)***
Gastrointestinal Disorders	**44 (14.8)**	**55 (18.5)**
Diarrhea	23 (7.7)	43 (14.5)
Nausea	12 (4.0)	13 (4.4)
Vomiting	5 (1.7)	5 (1.7)
Abdominal pain	4 (1.3)	3 (1.0)
Abdominal distention	3 (1.0)	0
Dyspepsia	3 (1.0)	1 (0.3)
Flatulence	1 (0.3)	3 (1.0)
Metabolism and Nutrition Disorders	**29 (9.7)**	**44 (14.8)**
Hypertriglyceridemia	16 (5.4)	24 (8.1)
Hypercholesterolemia	9 (3.0)	13 (4.4)
Hyperlipidemia	3 (1.0)	7 (2.4)
Decreased appetite	1 (0.3)	3 (1.0)
Investigations	**28 (9.4)**	**28 (9.4)**
Blood triglycerides increased	9 (3.0)	10 (3.4)
Blood cholesterol increased	8 (2.7)	4 (1.3)
ALT increased	6 (2.0)	4 (1.3)
LDL increased	3 (1.0)	5 (1.7)
Weight decreased	1 (0.3)	3 (1.0)
AST increased	1 (0.3)	3 (1.0)
Skin and Cutaneous Tissue Disorders	**13 (4.4)**	**10 (3.4)**
Rash maculo-papular	3 (1.0)	0
Lipohypertrophy	0	3 (1.0)
Nervous System Disorders	**9 (3.0)**	**8 (2.7)**
Headache	3 (1.0)	4 (1.3)
General Disorders and Administration Site Disorders	**5 (1.7)**	**10 (3.4)**
Fatigue	2 (0.7)	3 (1.0)
Drug withdrawal syndrome	0	3 (1.0)
Musculoskeletal Disorders	**3 (1.0)**	**4 (1.3)**
Psychiatric Disorders 1 (0.3) 4 (1.3)	**1 (0.3)**	**4 (1.3)**

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

[a] Related to DRV/RTV or LPV/RTV.

Discussion on Safety

The relative AE profile of DRV/RTV emerging from this Week 48 analysis of the study results for trial TMC114-C214 indicates that DRV/RTV at the recommended dosage (as for the highly pre-treated patients) for this population is at least similar to the profile of LPV/RTV. The safety results of DRV/RTV from this study are in line with the earlier assessment of the safety of DRV/RTV during the renewal procedure in which the present results were integrated. An amendment of the SPC in that regard is not needed.

3 Pharmacovigilance

Risk Management Plan
The Risk Management Plan (RMP) version 5.0, dated 7 February 2008 was assessed to evaluate the need for an update in relation to this extension of indication.

The MAH conducted a comparative phase III trial TMC114-C214 with 298 less treatment-experienced patients on DRV/RTV and 297 less treatment-experienced patients on LPV/RTV. The adverse events profile observed after 48 weeks (data cut-off date) was for the most part consistent with what is already known for DRV in (highly) treatment-experienced patients. In the DRV/RTV group, 26.8% reported any grade 3 or 4 adverse event. In the SPC of DRV/RTV the percentage of any grade 2, 3, or 4 adverse events is 30% and 9% of these patients (DRV/RTV) experienced a severe adverse event.

However, these figures cannot be compared accurately, because the MAH provided no clear data about the percentages of grade 3 and 4 adverse events separately in the study group. In the final study report, the MAH has to provide these figures per grade group (see also Letter of Undertaking).

The most common events were diarrhoea (32% and 42% with DRV/RTV and LPV/RTV, respectively), nausea (18% and 21%), nasopharyngitis (12% and 11%), headache (11% and 7%), abdominal pain (10% and 7%), upper respiratory tract infection (10% and 7%) and hypertriglyceridaemia (7% and 10%). This is consistent with the already known data for DRV/RTV.

The incidence and severity of the adverse events do not give cause for changes in the RMP, except for the rash-related adverse events.

In the comparative phase III trial TMC114-C214, the overall frequency of rash-related adverse events was higher during treatment with DRV/RTV (16.4%) than with LPV/RTV (7.1%). However, the incidence of grade 3 or 4 rash-related events was low in both groups (0.7% vs. 0%), but still higher than the already known percentage for DRV/RTV. Rash is reported in the SPC as common, and generalised rash, allergic dermatitis, urticaria, pruritus as uncommon.

Rash-related adverse events, including Stevens Johnson syndrome (SJS), are already an identified risk in the Risk Management Plan. In the complete dataset there have been 4 case reports of SJS, of which 1 ‘very likely related’, 1 ‘doubtfully related’, and 2 ‘not or doubtfully related’. Also, there is a higher incidence of rash-related events in the less treatment-experienced patients on DRV/RTV than in the control group.

The MAH therefore was requested to amend the RMP, section 2.2.1’ Important Identified Risks’: for all rash-related events that have occurred with DRV/RTV. It was also requested to be recorded whether the patients concerned were naïve, highly pre-treated or less pre-treated. The updated version 7.0 of the RMP dated 31 July 2008 was submitted in eCTD sequence 0079 in the framework of the PSUR covering the period PSUR 24 Dec 2007 - 23 Jun 2008.

The MAH consequently has also revised in this version of the RMP the presentation of the clinical data on rash-related events in Section 1.5.2.1.1 in order to distinguish the risk characteristics of the pooled safety data (n = 3063 subjects), from the less pre-treated subjects (TITAN trial) and from the naïve subjects (ARTEMIS trial). This updated version is currently being assessed with a CHMP conclusion awaited during the November 2008 CHMP meeting.

4 Changes to the Product Information

The CHMP agreed to the proposed extension of indication in section 4.1 of the SPC, however, requested a slight rewording to highlight both the new and the old patient population. The MAH agreed to this request and updated the SPC in accordance (see also attachment 1).

Regarding the proposed changes to section 5.1, the CHMP requested that references to superiority of DRV/RTV above LPV/RTV should be deleted, as the trial design was aimed at non-inferiority. The MAH agreed and revised the section accordingly.

Also, proposed changes regarding the mention that no new RAM or FC findings of clinical relevance were observed were requested to be deleted. The CHMP regarded this information as not informative for the prescriber. The MAH agreed and updated section 5.1 accordingly (see also attachment 1). In addition, the MAH committed to update the resistance section according to the new template B of the revision of the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection.

The CHMP agreed to the initially proposed changes in the Package Leaflet.

5 Overall conclusions, risk/benefit assessment and recommendation

Study C214 demonstrated the non-inferiority of the efficacy of DRV/RTV at the recommended dosage of DRV/RTV 600/100 mg b.i.d. compared to LPV/RTV both in combination with an OBR in the studied ART-experienced HIV-1 infected patients based on the primary virological endpoint (i.e. the percentage of patients with confirmed plasma viral load < 400 copies/ml at Week 48 in the OP population) at the chosen delta of 12%. DRV/RTV was at least as efficacious as LPV/RTV based on the results for secondary virological and immunological response parameters. In this comparison, DRV/RTV treatment appeared to be associated with more favourable virological response as defined by the primary endpoint (77% for the DRV/RTV group and 68% for the LPV/RTV group). This was also evident from the results for the percentage of patients with confirmed plasma viral load < 50 copies/ml at Week 48 (which was a secondary endpoint) and other secondary virological parameters.

Justification of the chosen non-inferiority margin was based on trials with other PIs and not on a discussion of potential clinical relevance in the context of morbidity or survival. However, the observed lower bound of the 95% CI was > -10% and therefore there is no reason for concern in that regard.

Virological response tends to decrease over time at least partly due to viral resistance associated with RAM, as noted also in the original pre-registration assessment for the highly pre-treated HIV-1 infected patients. The results of the Week 96 of the present ongoing trial are of interest for the further evaluation of the development of resistance and evaluation of the long-term safety of DRV/RTV in this HIV-1 infected population. In this regard there is an ongoing FUM, to which the MAH committed; in this context, the MAH should also present the virologic response by clade.

The submitted population pharmacokinetic analysis did not reveal unexpected findings. Some small differences in plasma concentrations were observed between studied groups, but this is considered not clinically relevant.

The relative AE profile of DRV/RTV emerging from this Week 48 analysis of the study results for trial TMC114-C214 indicates that DRV/RTV at the recommended dosage (as for the highly pre-treated patients) for this population is at least similar to the profile of LPV/RTV. The safety results of DRV/RTV from this study are in line with the earlier assessment of the safety of DRV/RTV during the renewal procedure in which the present results were integrated. Therefore, the CHMP agreed that no amendments to the Product Information are needed in the framework of this extension of indication.

The CHMP considered the benefit risk balance of Prezista positive for the sought indication variation:

"*PREZISTA, co-administered with 100 mg ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced~~highly pre-treated~~ adult patients, including those that have been highly pre-treated~~who failed more than one regimen containing a protease inhibitor (PI)~~.*
In deciding to initiate treatment with PREZISTA co-administered with 100 mg ritonavir careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of PREZISTA."