EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/834202/2010
Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/000707/II/0032

Invented name/name:	Prezista
International non-proprietary name/common name:	darunavir
Indication summary (as last approved):	Treatment of HIV-1 infection
Marketing authorisation holder (MAH):	Janssen-Cilag International N.V.

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

1. Scope of the variation and changes to the dossier

Scope of the variation:	Extension of indication to add the treatment of antiretroviral experienced patients with no DRV resistance associated mutations (RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/l to Section 4.1 of the 400mg tablet SmPC. Consequential changes have been introduced to sections 4.2, 4.4, 4.5 and 5.1 of the SmPC. Sections 4.4 and 4.5 of the SmPC have been updated to include information on interaction with efavirenz. In fulfilment of FUM 59, editorial changes have been made in section 5.1 of the SmPC. The other strengths are already authorised in ART-experienced adults i.e. 600/100 mg twice daily regimen for all other ART-experienced adults, including patients with ≥ 1 DRV RAMs and patients with no data on genotype. However, sections 4.1, 4.2, 4.4, 4.5, 5.1 have been updated in line with the changes on 400mg tablets. Annex IIB has been updated with a new version of the RMP. The DDPS version number has been removed. The PL has been updated accordingly.

Rapporteur: Co-Rapporteur:	Barbara van Zwieten-Boot Ian Hudson
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Module 1, 2 and 5
Product Information affected:	SmPC, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	12 February 2010
Start of procedure:	1 March 2010
Co-Rapporteur's assessment report circulated on:	14 April 2010
Rapporteur's assessment report circulated on:	21 April 2010
Rapporteur's and Co-Rapporteur's joint preliminary assessment circulated on:	14 May 2010
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 May 2010
MAH's responses submitted to the CHMP on:	22 July 2010
Rapporteur's and Co-Rapporteur's joint preliminary assessment report on the MAH's responses circulated on:	6 September 2010
Rapporteur's and Co-Rapporteur's joint updated assessment report on the MAH's responses circulated on:	20 September 2010
Follow-on Request for supplementary information and extension of timetable adopted by the CHMP on:	23 September 2010
MAH's responses submitted to the CHMP on:	14 December 2010
Rapporteur's and Co-Rapporteur's joint preliminary assessment report on the MAH's responses circulated on:	4 January 2011
Rapporteur's and Co-Rapporteur's joint updated assessment report on the MAH's responses circulated on:	18 January 2011
CHMP opinion:	20 January 2011

3. Scientific discussion

3.1. Introduction

Prezista (darunavir), co-administered with 100 mg ritonavir is indicated in combination with other antiretroviral (ARV) medicinal products for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adult patients.

Variation(s) requested		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The scope of the variation is as follows:

Extension of indication to add the treatment of antiretroviral experienced patients with no DRV resistance associated mutations (RAMs) to Section 4.1 of the 400mg tablet SmPC. Consequential changes have been introduced to sections 4.2, 4.4, 4.5 and 5.1 of the SmPC. Sections 4.4 and 4.5 of the SmPC have been updated to include information on interaction with efavirenz. In fulfilment of FUM 59, editorial changes have been made in section 5.1 of the SmPC.

The other strengths are already authorised in ART-experienced adults, including patients with ≥ 1 DRV RAMs and patients with no data on genotype and who are PI experienced.

However, sections 4.1, 4.2, 4.4, 4.5, 5.1 have been updated in line with the changes on 400mg tablets. Annex IIB has been updated with a new version of the RMP. The DDPS version number has been removed. The PL has been updated accordingly.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision P/138/2010 for the following condition(s):

Treatment of human immunodeficiency virus (HIV-1) infection in pediatric patients when coadministered with low-dose ritonavir and in combination with other antiretroviral (ARV) medicinal products in patients from 3 to less than 18 years of age.

The MAH submitted with this application the EMA/PDCO decision compliance report on this agreed PIP which is currently partially completed and the corresponding letter (EMA/17805/2010).

3.2. Clinical aspects

3.2.1. Rationale for the proposed change

The MAH submitted an application to add the use of once daily 800 mg darunavir (DRV) + 100 mg ritonavir (rtv) for treatment of anti-retroviral therapy (ART)-experienced adults with no DRV resistance associated mutations (RAMs). Currently the 800/100 mg once daily regimen is restricted to use in ART-naïve adults. The application primarily concerns submission of the study report on Week 48 data from study TMC114-C229 [ODIN].

It should be noted that the MAH maintains the approved 600/100 mg twice daily regimen for all other ART-experienced adults, including patients with ≥ 1 DRV RAMs and patients with no data on genotype and who are PI experienced.

Although the regimen proposed for this application requires the use of the approved 400 mg film-coated tablet in order to deliver a dose of 800 mg once daily darunavir, this variation also proposes to modify the SmPC for all strengths due to the need to reflect the usage in sections 4.1 and 4.2 and to update sections 4.4, 4.5, 4.8 and 5.1 in each case. Corresponding changes are proposed in the PL for each of the tablet strengths.

During the evaluation of this procedure, the CHMP requested the MAH to update the Section 4.5 of the SmPC with new information regarding an interaction with efavirenz.

To support this variation, the MAH submitted a dossier in CTD format including Module 1 (application form, proposed product information, information relating to the clinical trial, information relating to paediatrics: EMA/PDCO decision compliance report on an agreed PIP partially completed), Module 2 (clinical overview and clinical summary) and Module 5 (report of study TMC114-C947CPK Bayesian analysis of population PK data from study TMC114-C229, report of the 48-week data from study TMC114-C229, including population PK data and virological analysis).

In filing this application the MAH also addresses FUM 059 regarding modification of section 5.1 as previously requested by the CHMP.

3.2.2. Analysis of data submitted

Study TMC114-C229 (ODIN) Week 48 report pertains to a randomised (1:1 ratio), open-label non-inferiority trial comparing DRV/ rtv 800/100 mg q.d versus drv/rtv 600/100 mg b.i.d (both in combination with an individually selected OBR consisting of ≥ 2 NRTIs) in treatment-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (data up to the cut-off date of the Week-48 primary analysis, 27 August 2009). See table 1:

Table 1. Overview of Trial TMC114-C229

Location	Design	Indication / Population	DRV/rtv Dose/ Duration	Number of Patients
Asia, Australia, Europe, South Africa, South America, US, Canada	Phase III, randomised, open-label trial	HIV-1 infection/ treatment-experienced patients with 0 DRV RAMs*	800/100 mg q.d. 600/100 mg b.i.d. For 48 weeks	Total: 590 Randomised to DRV/rtv 800/100 mg q.d.: 294 Randomised to DRV/rtv 600/100 mg b.i.d.: 296

*V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V

Methods

This randomised, controlled, open-label multi-centre trial was not blinded due to the non-availability of rtv placebo. Additional sensitivity analyses for efficacy were performed to compensate at least partly for this lack of blinding. The trial started in September 2007; 113 investigators were involved in the sites in the continents mentioned in table 1.

Forty eight weeks report on the primary analysis is provided for the main phase of the study.

The study included an extension phase to provide DRV/rtv access as a 600/100 mg b.i.d regimen to patients who completed the 48 weeks of treatment with DRV/rtv in the main phase of the trial and continue to benefit from this treatment, and who live in a region where DRV is not yet commercially available, not yet reimbursed by the public and/or private health system or cannot be accessed from another source (e.g., access program, government program). The extension phase for this trial is ongoing.

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).

Study Participants

Main inclusion criteria were:

- Male or female, aged 18 years or older.
- Stable treatment with current HAART regimen for ≥ 12 weeks.
- Pre-screening and screening plasma HIV-1 RNA > 1000 copies/ml (assayed by RNA PCR standard specimen procedure) on current HAART regimen.
- Screening genotype resistance test results showing none of the following mutations in the protease gene V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V, known as DRV RAMs.
- In the investigator's opinion, NNRTIs were not a valid treatment option, because of the subject's ARV treatment history, ARV resistance testing, medication-taking behaviour, safety and tolerability concerns, or other subject-related factors.
- CD4+ cell count > 50 x 103 cells/ml (50 cells/µL).

Main exclusion criteria were:

- Active AIDS-defining illness with the following exceptions: stable cutaneous Kaposi's sarcoma or wasting syndrome. [Primary and secondary prophylaxis for an AIDS defining illness was allowed if the medication used was not part of the disallowed medication.]
- Previous or current use of enfuvirtide (ENF), tipranavir (TPV), or DRV.
- Use of any non-ARV investigational agents within 60 days prior to screening.
- Use of disallowed concomitant therapy.
- Pregnant or breastfeeding.
- Patients with clinical or laboratory evidence of significantly decreased hepatic function or decompensation (i.e., liver insufficiency), irrespective of liver enzyme levels. [Coinfected patients 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.]
- Grade 3 or 4 abnormality as defined by Division of AIDS (DAIDS) grading tables, with the following exceptions unless clinical assessment foresaw an immediate health risk to the patient:
  - patients with asymptomatic triglycerides or cholesterol elevations of grade 3 or 4;
  - patients with grade 3 or 4 bilirubin increases who used atazanavir as part of their HAART regimen at screening.

- Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of the study medication DRV or ritonavir.
- Any active clinically significant disease (e.g., tuberculosis, cardiac dysfunction, pancreatitis, acute viral infections), or findings that would compromise the patient's safety or outcome of the trial.

Treatments

During the screening period patients continued HAART regimen (4 weeks). At baseline, patients changed their screening regimen. An optimised background regimen (OBR) was initiated and consisted of ≥ 2 NRTIs selected by the investigator. Additionally, patients were randomised at baseline in a 1:1 ratio to receive a new PI regimen consisting of drv/rtv (along with the selected OBR) as summarised in table 2:

Table 2. Randomisation at baseline

DRV/rtv 600/100 mg b.i.d.	**Treatment period (48 weeks):*** Orally** 600-mg tablet of DRV + 1x100-mg capsule of ritonavir twice daily. DRV formulation used was F032.
DRV/rtv 800/100 mg q.d.	**Treatment period (48 weeks):** Orally** two 400-mg tablets of DRV + 1x100-mg capsule of ritonavir once daily. DRV formulation used was F030.

* and if applicable during the extension period.
** within 30 minutes after completion of a meal, every 12 hours (b.i.d. group) or 24 hours (q.d. group).

During the treatment period, the disallowed ARVs after the screening period and baseline in both treatment groups were as follows:

- PIs: All other PIs
- NRTIs: Investigational NRTIs except tenofovir and emtricitabine
- NNRTIs: all NNRTIs
- Fusion Inhibitors: ENF
- Entry inhibitors: maraviroc
- Integrase inhibitors: raltegravir

Disallowed concomitant non-ARV medications were as follows:

- From screening until the end of the treatment period:
  - investigational agents (from 60 days before screening onwards);
  - experimental vaccines (approved vaccines were allowed if they were given ≥ 4 weeks before a viral load measurement).
- From baseline until the end of the treatment period:
  - stimulants: amphetamines, amphetamine derivatives, modafinil;
  - herbal supplements: all products containing *Hypericum perforatum*(St John's Wort);

- and many other medications which are contraindicated for use with Prezista or due to clinically relevant significant interaction or impact on immune constitution of the patient (e.g. immunosuppressants).

Compliance

Compliance to DRV/rtv q.d. or DRV/rtv b.i.d. was assessed by 3 different methods:

- The Modified Medication Adherence Self-Report Inventory (M-MASRI) questionnaire,
- Based on DRV plasma concentrations being above or below the detection limit,
- By pill-count based on the number of pill dispensed and returned.

Patient-reported adherence rates were transformed to a binary variable using a 95% cut-off to define adherent (> 95%) and non-adherent (≤ 95%) patients.

Outcomes/endpoints

Efficacy

The primary endpoint was virological response, defined as a confirmed plasma viral load of < 50 copies/ml at Week 48 (using the FDA time to loss of virological response – TLOVR - algorithm).

The TLOVR algorithm consisted of the following: 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. Re-suppression after confirmed virologic failure was considered as failure in this algorithm.

Plasma viral load levels were determined using Roche Amplicor HIV-1 monitor TM test (Version 1.5).

Secondary endpoints included:

- virologic response defined as a viral load < 400 copies/ml (using the TLOVR algorithm);
- virologic response defined as a change in log10 viral load compared with the baseline value;
- immunologic parameters (CD4+ cell count change from baseline);
- Comparison of the QoL questionnaire results: 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/viremia, vital signs (pulse, SBP, and DBP) and ECG readings in accordance with ICH E14 (heart rate, PR interval, QRS interval, RR interval, QTc interval).

Resistance determinations

The number of all protease (PR) mutations [primary PI mutations, PI RAMs, DRV RAMs, and number of all reverse transcriptase (RT) mutations (NRTI RAMs and NNRTI RAMs) as defined by the International AIDS Society (IAS)-USA guidelines 2008], were tabulated per treatment group. The incidence of all individual protease and RT mutations was also tabulated.

The Fold-Change in IC50 (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.

PK/PD

Blood samples (sparse sampling) at Weeks 4, 8, 24, 48 (or withdrawal) were analysed.

PK/PD relationships between the DRV pharmacokinetic parameters AUC24h and C0h versus antiviral activity and safety parameters, PK/PD relationships between the rtv pharmacokinetic parameters AUC24h and C0h versus the predetermined safety parameters were evaluated.

All PK/PD analyses were performed by treatment group. In addition, for efficacy as well as for some selected safety parameters (see below), a pooled analysis across the DRV/rtv q.d. and DRV/rtv b.i.d. treatment groups was performed.

Sample size

Assuming a virological response (confirmed viral load < 50 copies/ml) rate of 70% at 48 weeks in both treatment arms, 306 patients were required per treatment arm to establish non-inferiority of DRV/rtv 800/100 mg q.d versus DRV/rtv 600/100 mg b.i.d with a maximum allowable difference (delta) of 12%, with a 1-sided significance level of $\alpha = 0.025$ and 90% power.

A delta of 12 % was considered appropriate, as it was small relative to observed differences between DRV/rtv and control PIs.

Randomisation

Subjects were randomised in a 1:1 ratio to treatment with DRV/rtv 800/100 mg q.d or DRV/rtv 600/100 mg b.i.d and according to stratification for screening plasma viral load (< 50,000 or ≥ 50,000 copies/ml).

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

Statistical methods

The Intent-to-treat (ITT) and on-protocol (OP) analyses included descriptive statistics, frequency tabulations, ANCOVA, general linear mixed model, logistic regression, Kaplan-Meier curves, Cox proportional hazards model, Mann-Whitney-U test, Wilcoxon's matched pairs signed ranks test, Fisher's exact test.

The primary efficacy analysis was performed when all subjects 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 < 50 copies/ml with DRV/rtv 800/100 mg q.d versus DRV/rtv 600/100 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 HRQoL, and to evaluate pharmacokinetics, effects of covariates, and pharmacokinetic / pharmacodynamic relationships and safety and tolerability over time.

Two populations were defined for the analyses:

- ITT population: all patients who where randomised and who received at least 1 dose of trial medication, regardless of their compliance with the Protocol.
- OP population: all randomised patients who received trial medication (excluding patients noncompliant for the trial medication for ≥ 1 week), and who did not take any disallowed ARV medication as described in the Protocol for > 1 week.

The ITT was considered as the primary population for the efficacy analysis. A logistic regression model including treatment as fixed factor and baseline plasma viral load as a covariate was applied to estimate the difference in virologic response rate (defined as a confirmed plasma viral load < 50 HIV-1 RNA copies/ml) between DRV/rtv 800/100 mg q.d. and DRV/rtv 600/100 mg b.i.d. For this purpose, 95% 2-sided confidence intervals (CIs) were derived to compare treatment groups at all time points. If at Week 48, the lower limit of this 95% 2-sided CI of the difference between DRV/rtv q.d. and DRV/rtv b.i.d. exceeded -12%, non-inferiority of DRV/rtv q.d. to DRV/rtv b.i.d. 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.

As additional sensitivity analysis, some efficacy analyses were also performed on an OP population excluding all major protocol violators.

The safety analysis was performed on the ITT population.

In addition, several sensitivity analyses were performed (e.g. observed response defined as a viral load < 50 copies/ml (without requiring confirmation of response or loss of response) and NC = F analysis). 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. last observed virological response was carried forward to Week 48 for subjects discontinuing due to patient wish).

Functional Assessment of HIV Infection (FAHI) scores (actual data and changes versus baseline) were presented descriptively and graphically. To analyze and compare treatments with respect to this QoL questionnaire, an ANCOVA was applied including factors for treatment, baseline plasma viral load, baseline CD4 counts and baseline FAHI (sub)total as covariate. In addition, a longitudinal mixed effects model was used to further describe the QoL changes over time. This model allowed testing for time effects, treatment effects, and their interaction. The same factors as in the ANCOVA above were included as fixed effects, and an unstructured variance-covariance matrix accounting for serial correlation. FAHI response, defined as the proportion of subjects with a clinically meaningful difference in Total FAHI score (i.e., a relative increase of 10%) was calculated.

One non-formal per protocol interim analysis was performed based on continued monitoring and assessment of the efficacy and safety in the trial when 50% of all patients had completed the 24-weeks assessment or discontinued earlier in order to assist the DSMB for human subject protection purpose. The results of this Week-24 interim analysis were confidential and available to only 3 persons: the Head Biometrics who presented the results to the DSMB, the interim Analysis Statistician and the Clinical Programmer supporting the interim analyses. No multiplicity correction was

implemented.

Results

Patient disposition

In this study 590 patients of the planned 612 were randomised and treated, 89 (15%) patients prematurely discontinued the study. For disposition of the patients in the ITT and OP populations see table 3. The difference between the ITT and OP analysis populations was 55 patients. At the CHMP request, the MAH provided a list of the detailed reason for the exclusion of these subjects. They were either noncompliant for the investigational medication for $\geq$ 1 week, either taking any disallowed ARV medication for $\geq$1 week, either both. Hence, they were excluded from the OP population as these events were coded as major protocol deviations in the protocol.

Table 3. Patient Disposition

	DRV/rtv 800/100 mg q.d.	**DRV/rtv 600/100 mg b.i.d.**	**Total DRV/rtv**
Intent-To-Treat Population, n			
Screened	-	-	1092
Randomised - not treated	6	3	9
Randomised - treated	294	296	590
Completed, n (%)	**253 (86.1)**	**248 (83.8)**	**501 (84.9)**
Discontinuations - Reason	**41 (13.9)**	**48 (16.2)**	**89 (15.1)**
AE/HIV-related event [a]	10 (3.4)	12 (4.1)[b]	22 (3.7)
Subject lost to follow-up	9 (3.1)	13 (4.4)	22 (3.7)
Subject noncompliant	8 (2.7)	9 (3.0)	17 (2.9)
Subject withdrew consent	4 (1.4)	5 (1.7)	9 (1.5)
Subject ineligible to continue the trial	2 (0.7)	5 (1.7)	7 (1.2)
Other	3 (1.0)	2 (0.7)	5 (0.8)
Subject reached a virologic endpoint [a]	3 (1.0)	2 (0.7)	5 (0.8)
Sponsor's decision	2 (0.7)	0	2 (0.3)
On-Protocol Population, n			
Randomised - treated	259	276	535
Completed, n (%)	**224 (86.5)**	**233 (84.4)**	**457 (85.4)**
Discontinuations - Reason	**35 (13.5)**	**43 (15.6)**	**78 (14.6)**
Subject lost to follow-up	9 (3.5)	13 (4.7)	22 (4.1)
AE/HIV-related event a	8 (3.1)	10 (3.6) b	18 (3.4)
Subject noncompliant	6 (2.3)	7 (2.5)	13 (2.4)
Subject withdrew consent	3 (1.2)	5 (1.8)	8 (1.5)
Subject ineligible to continue the trial	2 (0.8)	4 (1.4)	6 (1.1)
Other	3 (1.2)	2 (0.7)	5 (0.9)
Subject reached a virologic endpoint a	2 (0.8)	2 (0.7)	4 (0.7)
Sponsor's decision	2 (0.8)	0	2 (0.4)

N = number of subjects; n = number of observations.
a As assessed by the investigator
b Not taking into account subjects CRF ID 229-0116 who discontinued due to an AE (thrombocytopenia) but for whom the reason of discontinuation was reported as 'noncompliant', and 229-0466 who completed the treatment phase but had an AE (hypercholesterolemia) that started before the end of the treatment phase and that led to discontinuation during the extension phase.

As shown above, the overall discontinuation rate (for any reason) was slightly lower in the DRV/rtv q.d than in the DRV/rtv b.i.d treatment group. The majority of discontinuations were due to AE/HIV-related events, and lost to follow up in both groups in the ITT and OP populations.

Discontinuations due to virological failure occurred less in < 1% of all patients with no apparent difference between the two treatment groups in the ITT and OP populations.

The rate of discontinuations in both treatment groups remained relatively constant throughout the trial period with slightly more discontinuations in the group on the b.i.d regimen past week 8 as compared to the q.d regimen. The median (range) duration of exposure for the respective treatment groups was 48.4 (0.1; 56.0) and 48.4 (0.1; 63.0) weeks.

Conduct of the study

GCP

The MAH declared that 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.

Compliance / Major Protocol deviations

- Based on the M-MASRI, 59% of all patients were adherent to the trial medication over the course of the treatment period. At all measured time points, the percentage of adherent patients was greater in the DRV/rtv q.d group (ranging between 67% and 71%) than in the DRV/rtv b.i.d group (ranging between 59% and 65%).
- Calculated by pill count, the adherence rates were generally lower (56% overall assessment), and at all time points, the percentage of adherent patients was also greater in the DRV/rtv q.d group (ranging between 58% and 63%) than in the DRV/rtv b.i.d group (ranging between 42% and 59%).
- Based on DRV plasma concentrations, 85% of all patients were adherent to the trial medication overall. The difference in adherence to the trial medication between the treatment groups was very small at all time points (DRV/rtv q.d ranging between 86% and 94%, DRV/rtv b.i.d ranging between 90% and 96%).

The apparent differences in the results of the 3 different adherence measures used in trial TMC114-TMC114-C229 can be explained by the differences inherent in the data collection methods, and the way in which dichotomous levels of adherence ('adherent' versus 'non-adherent') were derived. The results obtained from the 3 different methods should only be compared qualitatively, not quantitatively.

Major protocol deviations were defined as relevant non-compliance with the trial medication, disallowed ARV use, 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 14.6% of patients in the DRV/rtv q.d group and 7.8% of patients in the DRV/rtv b.i.d group. The difference between the treatment groups was mostly due to the higher incidence of non-compliance with the trial medication.

Baseline data

Main demographic and disease characteristics of the patients in the treatment groups are shown in table 4.

Table 4. Main demographic and disease characteristics of the patients in TMC114-C229 (ITT population)

Baseline Characteristics - Subject Disposition	**DRV/rtv**	**DRV/rtv**	**Total**
(ITT Population)	800/100 mg q.d.	600/100 mg b.i.d.	DRV/rtv
Number of Subjects Treated (M/F)[a]	294 (179/115)	296 (198/98)	590 (377/213)
Age (yrs), median (range)	40 (18; 70)	40 (18; 77)	40 (18; 77)
Race, n (%)			
Black	83 (28.2)	72 (24.3)	155 (26.3)
Caucasian/White	102 (34.7)	110 (37.2)	212 (35.9)
Hispanic	47 (16.0)	59 (19.9)	106 (18.0)
Oriental/Asian	48 (16.3)	41 (13.9)	89 (15.1)
Other	14 (4.8)	14 (4.7)	28 (4.7)
Log10 Plasma Viral Load (copies/ml), mean (SE)	4.19 (0.05)	4.13 (0.05)	4.16 (0.03)
Viral Load (Copies/ml), n (%), N	294	296	590
< 100.000	255 (86.7)	265 (89.5)	520 (88.1)
≥ 100.000	39 (13.3)	31 (10.5)	70 (11.9)
CD4+ Cell Count (x 106/L), median (range)	219 (24; 1306)	236 (44; 864)	228 (24; 1306)
CD4+ Cell Count (x 106/L), n (%), N			
< 50	13 (4.4)	3 (1.0)	16 (2.7)
50 - < 100	36 (12.2)	35 (11.8)	71 (12.0)
100 - < 200	76 (25.9)	77 (26.0)	153 (25.9)
200 - < 350	108 (36.7)	107 (36.1)	215 (36.4)
≥ 350	61 (20.7)	74 (25.0)	135 (22.9)
Known Duration of HIV Infection (yrs), median (range)	7.9 (0.4; 23.1)	7.4 (0.6; 23.3)	7.5 (0.4; 23.3)
WHO Clinical Stage of HIV Infection, n (%)			
Stage 1 (asymptomatic)	107 (36.4)	102 (34.5)	209 (35.4)
Stage 2 (mild symptoms)	59 (20.1)	66 (22.3)	125 (21.2)
Stage 3 (advanced symptoms)	43 (14.6)	45 (15.2)	88 (14.9)
Stage 4 (severe symptoms)	85 (28.9)	83 (28.0)	168 (28.5)
Number of Mutations, median (range)			
Primary PI mutations	0 (0; 5)	0 (0; 4)	0 (0; 5)
PI RAMs	3 (0; 13)	4 (0; 14)	3 (0; 14)
DRV RAMs	0 (0; 2)	0 (0; 1)	0 (0; 2)
NRTI RAMS	1 (0; 7)	1 (0; 8)	1 (0; 8)
NNRTI RAMS	2 (0; 5)	1 (0; 5)	2 (0; 5)
Previously Used ARVs, n (%)			
NNRTI: ≥1	258 (87.8)	258 (87.2)	516 (87.5)
NRTI: ≥3	174 (59.1)	164 (55.4)	338 (57.2)
PI: 0	135 (45.9)	137 (46.3)	272 (46.1)
PI: 1	74 (25.2)	77 (26.0)	151 (25.6)
PI: ≥2	85 (28.9)	82 (27.7)	167 (28.3)
Fusion inhibitor: 1	1 (0.3)	0	1 (0.2)

Integrase inhibitor: 1	1 (0.3)	0	1 (0.2)
Hepatitis B or C Coinfection Status, n (%), N	292	292	584
Negative	267 (91.4)	255 (87.3)	522 (89.2)
Positive	25 (8.6)	37 (12.7)	62 (10.6)

n = number of observations
a The on-protocol population comprised 535 patients: 259 and 276 patients in the DRV/rtv q.d. and DRV/rtv b.i.d groups, respectively.

The study groups were generally well balanced with regard to demographic characteristics. The same holds for baseline disease characteristics as displayed in table 5. Approximately 11 % of the patients were co-infected with hepatitis B or C with relatively more co-infected patients on the b.i.d regimen. There were no notable differences between the treatment groups with respect to susceptibility to PIs, NRTIs, NNRTIs at baseline, or with respect to the number of susceptible NRTIs in the underlying OBR. See table 5.

Table 5. Number of Susceptible Drugs per Class at Baseline, Based on Antivirogram

Number of Subjects With Susceptible Drugs per Class, n (%)	**DRV/rtv 800/100 mg q.d.**	**DRV/rtv 600/100 mg b.i.d.**	**Total DRV/rtv**
PI			
Total Susceptible Drugs ≥ 1 susceptible 8 [a] susceptible	291 291 (100) 248 (85.2)	287 286 (100) 247 (86.1)	578 577 (100) 495 (85.6)
Total Susceptible Drugs in Regimen DRV susceptible	291 291 (100)	286 286 (100)	577 577 (100)
NRTI			
Total Susceptible Drugs	291	287	578
0 susceptible	5 (1.7)	3 (1.0)	8 (1.4)
1 susceptible	2 (0.7)	5 (1.7)	7 (1.2)
≥ 2 susceptible	284 (97.6)	279 (97.2)	563 (97.4)
Total Susceptible Drugs in Underlying OBR	290	284	574
0 susceptible	19 (6.6)	15 (5.3)	34 (5.9)
1 susceptible	53 (18.3)	75 (26.4)	128 (22.3)
≥ 2 susceptible	218 (75.2)	194 (68.3)	412 (71.7)
NNRTI			
Total Susceptible Drugs0 susceptible	291 187 (64.3)	287 180 (62.7)	578 367 (63.5)
≥ 1 susceptible	104 (35.7)	107 (37.3)	211 (36.5)

N = number of subjects; n = number of observations
a All currently available PIs = (fos)amprenavir, atazanavir, indinavir, LPV, nelfinavir, saquinavir, TPV, DRV.

Overall, the median FC for DRV in the ITT population was 0.5, and the median FC for the other PIs ranged from 0.6 (LPV, [fos]amprenavir, atazanavir, indinavir) to 0.9 (nelfinavir). There were no relevant differences between the DRV/rtv q.d. and DRV/rtv b.i.d. treatment groups with respect to FC values.

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. This is line with the observation that 65% of

patients had at least WHO clinical stage 2. The most common were dermatologic conditions (21%) and conditions related to the GI system (21%). These conditions had similar frequencies in both DRV/rtv treatment groups. Other conditions were generally similarly presented in the treatment groups.

The majority of non-ARV concomitant therapies used during this trial were for the treatment of underlying disease. The use of antifungals for dermatologic use was higher in the DRV/rtv q.d group (15%) than in the DRV/rtv b.i.d group (9%), while the use of lipid modifying agents and stomatologic preparations was lower in the DRV/rtv q.d group (5% and 13% resp.) than in the DRV/rtv b.i.d group (11% and 17% resp.). There were no important differences between the DRV/rtv q.d and DRV/rtv b.i.d treatment groups with respect to other non-ARV concomitant therapies.

Discussion on Design, Methods & Demographics

The general study design is acceptable given that the test regimen was compared against the approved twice daily regimen, which is already approved for use in ART-experienced subjects.

The open label study design is acceptable given that, if the study had been double-blind, the QoL assessment could not have taken into account the treatment simplification.

3.2.3. Clinical Efficacy

Primary endpoint

The percentage of patients with confirmed plasma viral load < 50 copies/ml at Week 48 in the ITT population was 72.1% for the DRV/rtv q.d group and 70.9% for the DRV/rtv b.i.d group. Statistical comparison using the logistic regression model for the ITT and OP populations is shown in table 6.

Table 6. Virological Response: Percentage of Patients With Viral Load < 50 Copies/ml at Week 48 (ITT & OP– TLOVR)

Population	Treatment Group	Estimated[a] % Response	Estimated Difference in % Response	95% CI of Difference in % Response[b]	p-Value of Non-inferiority
ITT	DRV/rtv q.d DRV/rtv b.i.d	73.4 71.5	1.9	-5.4; 9.2	< 0.001
OP	DRV/rtv q.d DRV/rtv b.i.d	74.8 73.0	1.8	-5.8; 9.3	< 0.001

a Percent response estimated from a logistic regression analysis including baseline log10 viral load as covariate.
b Confidence limits based on standard error obtained by application of the delta method.

The lower limit of the 95% CI of the difference between the treatment groups was > -12% in both analysis populations at Week 48; therefore, non-inferiority of DRV/rtv q.d versus DR/rtv b.i.d regimen was concluded.

The percentages of patients with confirmed plasma viral load < 50 copies/ml per time point (ITT – TLOVR) is summarised in table 7.

Table 7. Percentage of Subjects With Viral Load< 50 Copies/ml (ITT – TLOVR) per Time Point

Time Point	DRV/rtv 800/100 mg q.d		DRV/rtv 600/100 mg b.i.d		DRV/rtv q.d – DRV/rtv b.i.d	
	N	n (%)	N	n (%)	Difference in % Response	95% CI of Difference in % Response[a]
Week 4	294	57 (19.4)	296	51 (17.2)	2.2	-4.1; 8.4
Week 8	294	126 (42.9)	296	115 (38.9)	4.0	-3.9; 11.9
Week 12	294	167 (56.8)	296	160 (54.1)	2.7	-5.3; 10.8
Week 24	294	201 (68.4)	296	206 (69.6)	-1.2	-8.7; 6.3
Week 36	294	212 (72.1)	296	209 (70.6)	1.5	-5.8; 8.8
Week 48	294	212 (72.1)	296	210 (70.9)	1.2	-6.1; 8.5

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

The results obtained for the OP population were consistent with those of the ITT population. These comparative results of DRV/rtv were also consistent with results of virological response according to the TLOVR algorithm as per FDA guidance. See table 8.

Table 8. Virological Response: Percentage of Patients With Viral Load < 50 Copies/ml at Week 48 ITT-TLOVR algorithm as per FDA guidance

Patients With Virologic Response (< 50 Copies/ml) as per FDA Guidance, n (%)	DRV/rtv 800/100 mg q.d N = 294	DRV/rtv 600-100 mg b.i.d N = 296
Confirmed virologic response at Week 48	210 (71.4)	208 (70.3)
Virologic failures:		
Initial lack of response	31 (10.5)	24 (8.1)
Rebounder	7 (2.4)	6 (2.0)
Never suppressed	14 (4.8)	13 (4.4)
Discontinuations :		
Due to virologic failure (never suppressed)	0	2 (0.7)
Due to AE	7 (2.4)	6 (2.0)
Death	1 (0.3)	5 (1.7)
Due to other reasons	24 (8.2)	32 (10.8)

N = number of subjects; n = number of responders
Note: the numbers represented in this table reflect only the status at Week 48.

The different sensitivity analyses indicated 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. Except for the longitudinal mixed model, the lower limit of the 95% CI of the difference between the treatment groups was consistently > -12%, confirming non-inferiority of DRV/rtv q.d. versus DRV/rtv b.i.d. See table 9. However, the CHMP considered that the results obtained from the longitudinal mixed model analysis of virologic response should be interpreted with caution given the parameters of this modelling methodology.

Table 9. Sensitivity Analyses for Virological Response: Percentage of Patients With Viral Load < 50 Copies/ml at Week 48

Population Analysis	DRV/rtv 800/100 mg q.d.		DRV/rtv 600/100 mg b.i.d.		DRV/rtv q.d. – DRV/rtv b.i.d.	
	N	Number of Responders[a], n (%)	N	Number of Responders[a], n (%)	Difference in % Response	95% CI of Difference in % Response[b]
ITT - TLOVR	294	212 (72.1)	296	210 (70.9)	1.2	-6.1; 8.5
OP - TLOVR	259	190 (73.4)	276	200 (72.5)	0.9	-6.7; 8.4
ITT - Observed case	253	203 (80.2)	243	205 (84.4)	-4.1	-10.9; 2.6
OP - Observed case	223	181 (81.2)	228	195 (85.5)	-4.4	-11.2; 2.5
OP excluding all major PVs - TLOVR	251	188 (74.9)	273	199 (72.9)	2.0	-5.5; 9.6
ITT - TLOVR Non-VF censored	258	212 (82.2)	253	210 (83.0)	-0.8	-7.4; 5.8
ITT - LOCF-DCPW for DRV/rtv b.i.d., TLOVR for DRV/rtv q.d.	294	212 (72.1)	296	216 (73.0)	-0.9	-8.1; 6.4
ITT - NC = F	294	205 (69.7)	296	209 (70.6)	-0.9	-8.3; 6.5
ITT - M = F	294	203 (69.1)	296	205 (69.3)	-0.2	-7.7; 7.3
Longitudinal mixed model[c]	NA	79.7	NA	84.7	-5.0	-12.2; 2.2

The results in virological response at Week 48 for the DRV/rtv treatment groups across several subgroups by baseline are displayed in table 10.

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

	DRV/rtv 800/100 mg q.d		DRV/rtv 600/100 mg b.i.d		DRV/rtv q.d. – DRV/rtv b.i.d	
					Difference in	95% CI of Difference in
Subgroup	**N**	**n (%)**	**N**	**n (%)**	**% Response**	**% Response[a]**
Screening Plasma Viral Load (Copies/ml)b						
≤ 50,000	222	174 (78.4)	224	172 (76.8)	1.6	-6.2; 9.4
> 50,000	72	38 (52.8)	72	38 (52.8)	0.0	-16.4; 16.4
Baseline Viral Load						
(Copies/ml)						
<100,000	255	198 (77.6)	265	194 (73.2)	4.4	-3.0; 11.9
≥100,000	39	14 (35.9)	31	16 (51.6)	-15.7	-39.2; 7.7
Baseline CD4+ Cell Count						
(x 10^6/L)						
< 50	13	7 (53.8)	3	3 (100)	-46.2	-109.6; 17.3
50 - < 100	36	21 (58.3)	35	20 (57.1)	1.2	-22.2; 24.6
100 -< 200	76	59 (77.6)	77	52 (67.5)	10.1	-4.1; 24.3
200 - < 350	108	78 (72.2)	107	80 (74.8)	-2.5	-14.4; 9.3
≥ 350	61	47 (77.0)	74	55 (74.3)	2.7	-12.0; 17.4
Baseline Primary PI						
Mutations						
0	247	175 (70.9)	250	175 (70.0)	0.9	-7.2 ; 8.9
≥ 1	47	37 (78.7)	46	35 (76.1)	2.6	-14.6; 19.9
Number of Previously Used						

PIs						
0	135	111 (82.2)	137	109 (79.6)	2.7	-6.7; 12.0
1	74	48 (64.9)	77	49 (63.6)	1.2	-14.2; 16.6
≥ 2	85	53 (62.4)	82	52 (63.4)	-1.1	-15.8; 13.7
Clade B Versus Non-B						
B	179	126 (70.4)	199	128 (64.3)	6.1	-3.4; 15.6
Non-B	115	86 (74.8)	97	82 (84.5)	-9.8	-20.7; 1.2
Number of Susceptible NRTIs						
in the OBR						
0	19	17 (89.5)	15	14 (93.3)	-3.9	-23.8; 16.1
1	53	42 (79.2)	75	59 (78.7)	0.6	-13.9; 15.1
2	202	143 (70.8)	177	117 (66.1)	4.7	-4.7; 14.1
≥ 3	16	6 (37.5)	17	10 (58.8)	-21.3	-56.0; 13.4
Gender						
Female	115	80 (69.6)	98	68 (69.4)	0.2	-12.3; 12.7
Male	179	132 (73.7)	198	142 (71.7)	2.0	-7.0; 11.1
Age						
≤ 30	35	25 (71.4)	35	21 (60.0)	11.4	-11.0; 33.9
30 -≤ 45	180	136 (75.6)	169	123 (72.8)	2.8	-6.4; 12.0
45 -≤ 55	64	39 (60.9)	72	52 (72.2)	-11.3	-27.2; 4.6
55 -≤ 65	14	11 (78.6)	18	12 (66.7)	11.9	-20.6; 44.4
> 65	1	1 (100)	2	2 (100)	0.0	0.0; 0.0
Region Africa	35	26 (74.3)	28	22 (78.6)	-4.3	-25.9; 17.3
Asia	47	42 (89.4)	38	33 (86.8)	2.5	-11.4; 16.5
Australia + Europe	40	32 (80.0)	28	23 (82.1)	-2.1	-21.5; 17.2
North America	47	29 (61.7)	54	25 (46.3)	15.4	-4.1; 34.9
South America	125	83 (66.4)	148	107 (72.3)	-5.9	-16.9; 5.1
Race						
Black	83	52 (62.7)	72	47 (65.3)	-2.6	-17.9; 12.7
Caucasian/White	102	73 (71.6)	110	76 (69.1)	2.5	-9.9; 14.9
Hispanic	47	34 (72.3)	59	40 (67.8)	4.5	-13.2; 22.3
Oriental/Asian	48	43 (89.6)	41	36 (87.8)	1.8	-11.6; 15.1
Other	14	10 (71.4)	14	11 (78.6)	-7.1	-40.7; 26.4

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

In response to the 1st RSI, the MAH provided Table 11 which shows the evaluation of heterogeneity of the treatment effects based on tests for statistical interactions for various subgroup parameters.

Table 11. Tests for Heterogeneity of Treatment Effects Across Subgroups – Trial TMC114-C229 - Week-48 Analyses

Subgroup	DRV/rtv 800/100 mg q.d.		DRV/rtv 600/100 mg b.i.d.		DRV/rtv q.d. – DRV/rtv b.i.d.		
	N	Virologic Responsea n (%)	N	Virologic Responsea n (%)	Difference in % Response	95% CI of Difference in % Response	P-Valueb
Baseline Viral Load (Copies/mL)							
< 100,000	255	198 (77.6)	265	194 (73.2)	4.4	-3.0; 11.9	0.094
≥ 100,000	39	14 (35.9)	31	16 (51.6)	-15.7	-39.2; 7.7	
Baseline CD4+ Cell Count (x 106/L)							
< 50	13	7 (53.8)	3	3 (100)	-46.2	-109.6; 17.3	0.258
50 -< 100	36	21 (58.3)	35	20 (57.1)	1.2	-22.2; 24.6	
100 -< 200	76	59 (77.6)	77	52 (67.5)	10.1	-4.1; 24.3	
200 -< 350	108	78 (72.2)	107	80 (74.8)	-2.5	-14.4; 9.3	
≥ 350	61	47 (77.0)	74	55 (74.3)	2.7	-12.0; 17.4	
Baseline CD4+ Cell Count (x 106/L)							
< 50	13	7 (53.8)	3	3 (100)	-46.2	-109.6; 17.3	0.064
≥ 50	281	205 (73.0)	293	207 (70.6)	2.3	-5.1; 9.7	
Baseline CD4+ Cell Count (x 106/L)							
< 100	49	28 (57.1)	38	23 (60.5)	-3.4	-24.5; 17.8	0.569
≥ 100	245	184 (75.1)	258	187 (72.5)	2.6	-5.1; 10.3	
Clade							
B	179	126 (70.4)	199	128 (64.3)	6.1	-3.4; 15.6	0.031
Non-B	115	86 (74.8)	97	82 (84.5)	-9.8	-20.7; 1.2	
Region							
Africa	35	26 (74.3)	28	22 (78.6)	-4.3	-25.9; 17.3	0.428
Asia	47	42 (89.4)	38	33 (86.8)	2.5	-11.4; 16.5	
Australia + Europe	40	32 (80.0)	28	23 (82.1)	-2.1	-21.5; 17.2	
North America	47	29 (61.7)	54	25 (46.3)	15.4	-4.1; 34.9	
South America	125	83 (66.4)	148	107 (72.3)	-5.9	-16.9; 5.1	
Region							
South America	125	83 (66.4)	148	107 (72.3)	-5.9	-16.9; 5.1	0.090
Other	169	129 (76.3)	148	103 (69.6)	6.7	-3.0; 16.5	
Number of Susceptible NRTIs in the OBR							
0	19	17 (89.5)	15	14 (93.3)	-3.9	-23.8; 16.1	0.491
1	53	42 (79.2)	75	59 (78.7)	0.6	-13.9; 15.1	
2	202	143 (70.8)	177	117 (66.1)	4.7	-4.7; 14.1	
≥ 3	16	6 (37.5)	17	10 (58.8)	-21.3	-56.0; 13.4	
Number of Susceptible NRTIs in the OBR							
0	19	17 (89.5)	15	14 (93.3)	-3.9	-23.8; 16.1	0.656
≥ 1	271	191 (70.5)	269	186 (69.1)	1.3	-6.4; 9.1	

OBR = optimized background regimen
a Plasma viral load < 50 copies/mL

b P-value for treatment by subgroup interaction

It is acknowledged that study TMC114-C229 was not statistically powered for comparative analyses at subgroup level. However, the data indicate that this regimen might not be appropriate for patients with HIV RNA >100,000 copies/ml and for patients with non-clade B virus. In addition, there are insufficient data to determine whether this regimen is appropriate for patients with CD4 counts <50-100 x 106/L and for those with virus not susceptible to potentially suitable NRTIs.

In addition, the data suggest that the 800/100 mg DRV/rtv q.d regimen had variable efficacy in comparison to the approved twice daily regimen according to region (e.g. in South America).

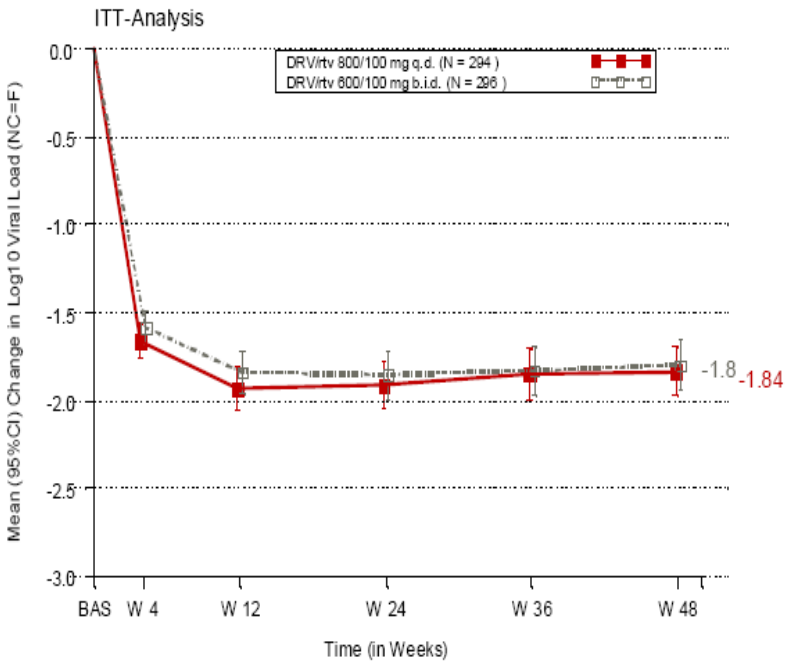
Secondary endpoints

Virologic response – other parameters

Week 48 results of main secondary virologic response parameters such as the percentage of patients with confirmed plasma viral load < 400 copies/ml, and statistical comparisons between the treatment groups at Week 48 for this secondary virologic response parameter (logistic regression model, ITT and OP – TLOVR) showed similar patterns as for the primary endpoint. The same holds for the sensitivity analyses for virologic response < 400 copies/ml (TLOVR) performed as for the primary virologic response parameter.

Results for patients with a confirmed decrease in plasma log10 viral load from baseline are displayed in figure 1.

Figure 1. Mean Change in Log10 Viral Load From Baseline (ITT – NC = F) Over Time



A decrease in log10 viral load from baseline was observed for both treatment groups as early as Week 4. At all time points, the mean decrease in log10 viral load was similar for the DRV/rtv q.d. and the DRV/rtv b.i.d. groups.

For other secondary virological parameters such as the time to first virologic response: percentage of patients achieving <50 copies/ml or <400 copies/ml (FDA-TLOVR algorithm), the time to virologic

failure and decrease of mean viral load difference in average (DAVG) at Week 48 the results were comparable for both DRV/rtv treatment groups.

Immunological response

Increases in mean CD4+ cell count from baseline were observed for both treatment groups at all time points; these increases were similar for both treatment groups except at Week 8 with DRV/rtv q.d showing a similar value as for week 4 whereas in group DRV/rtv b.i.d the values showed further increase.

Statistical comparison between the treatment groups at Week 48 (ANCOVA) for the change in CD4+ cell count from baseline (ITT and OP – LOCF) is summarised in table 12.

Table 12. Change in CD4+ Cell Count from baseline at Week 48 (ITT and OP – LOCF)

Analysis Population	Treatment Group	LS-means[a] (SE)	Difference in LS-Means (95% CI[b])
ITT	DRV/rtv q.d. DRV/rtv b.i.d.	106.85 (7.261) 112.80 (7.236)	-5.95 (-26.09; 14.20)
OP	DRV/rtv q.d. DRV/rtv b.i.d.	109.36 (7.748) 114.14 (7.506)	-4.78 (-25.98; 16.43)

a Percent response estimated from an ANCOVA including baseline log10 plasma viral load as covariate and treatment as cofactor.
b Confidence limits based on standard error obtained by application of the delta method

In both groups the increase in CD4 cell count was similar. The findings for CD8+ cell count and CD4+/CD8+ ratio were consistent with those for CD4+ cell count.

Development of Resistance - Virological Failure

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. The TLOVR (non-VF censored) algorithm was used for the identification of virologic failures (with HIV-1 RNA ≥ 50 copies/ml). The virologic failures group consisted of:

- Rebounders: patients 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,
- Patients who were never suppressed: patients who were still in the trial at Week 12 and never achieved 2 consecutive viral load values of < 50 copies/ml.

The numbers of rebounders and patients who were never suppressed are displayed in table 13.

Table 13. Number of rebounders, patients who were never suppressed and virologic failures not achieving virologic Response i.e. Viral Load < 50 Copies/ml (ITT – TLOVR non-VF Censored)

	DRV/rtv	**DRV/rtv**
Number of Patients, n (%)	**800/100 mg q.d N = 294**	**600/100 mg b.i.d N = 296**
Virologic failure*:	65 (22.1)	54 (18.2)
Rebounder	11 (3.7)	11 (3.7)
Non-responder	54 (18.4)	43 (14.5)

N = number of patients; n = number of observations
* Only 60 and 42 cases in the q.d and b.i.d groups, respectively had endpoint and baseline genotype data.

The observed small difference between the treatment groups can mainly be explained by a higher frequency of early discontinuations (≤ 12 weeks) in the DRV/rtv b.i.d. group (10 patients) compared to the DRV/rtv q.d group (3 patients). These early discontinuations (i.e. ≤ 12 weeks) were not counted as non-responders, therefore the DRV/rtv b.i.d group contained less non-responder than the DRV/rtv q.d group.

Paired baseline/endpoint genotypes were available for 60 and 42 virologic failure patients in the DRV/rtv q.d and DRV/rtv b.i.d groups, respectively.

- Only 1 patient, in the DRV/rtv q.d group, developed primary (major) PI mutations (V32I, M46I, L76V, and I84V), which included 3 DRV RAMs (V32I, L76V, and I84V).
- In the virologic failures with baseline and endpoint genotype, 7 (11.7%) out of 60 patients developed PI RAMs at endpoint in the DRV/rtv q.d group versus 4 (9.5%) out of 42 in the DRV/rtv b.i.d. group. Four (6.7%) and 3 (7.1%) virologic failures developed 1 or 2 NRTI RAMs in the DRV/rtv q.d and DRV/rtv b.i.d groups, respectively.

Phenotypic data (with Antivirogram®) at baseline and endpoint for virologic failures were available for 59 cases in DRV/rtv q.d group and 41 cases in DRV/rtv b.i.d group.

In the DRV/rtv q.d group, one patient lost susceptibility to DRV at endpoint (FC changed from 0.4. to 24.4) and another patient lost susceptibility to 2 PIs.

Seven out of 59 (11.9%) patients in this group lost susceptibility to an NRTI in the OBR, compared to 4 out of 41 (9.8%) in the DRV/rtv b.i.d group. Loss of susceptibility to an NRTI in the OBR was associated with developing NRTI RAMs in 3 of the 7 virologic failures in the DRV/rtv q.d group. Endpoint FC values were just above the biological cut-offs for 3 other patients. Loss of susceptibility to an NRTI in the OBR in the 4 virologic failures in the DRV/rtv b.i.d group was associated with developing NRTI RAMs in 2 patients.

Virologic response by adherence/compliance to therapy

Virologic response by adherence as assessed by the 3 different methods mentioned earlier is summarised in the table 14.

Table 14. Virologic Response (Viral Load < 50 copies/ml) at Week 48 (ITT – TLOVR) by Adherence[a]

Parameter	DRV/rtv 800/100 mg q.d		DRV/rtv 600/100 mg b.i.d		DRV/rtv q.d – DRV/rtv b.i.d	
	N	Number of Responders[a], n (%)	N	Number of Responders, n (%)	Difference in % Response	95% CI of Difference in % Response[b]
Adherence Measured by M-MASRI						
Adherent	166	141 (84.9)	149	127 (85.2)	-0.3	[-8.2; 7.6]
Nonadherent	97	55 (56.7)	119	74 (62.2)	-5.5	[-18.7; 7.7]
Adherence Based on DRV Concentrations						
Adherent	238	197 (82.8)	248	203 (81.9)	0.9	[-5.9; 7.7]
Nonadherent	48	15 (31.3)	35	7 (20.0)	11.3	[-8.1; 30.6]
Adherence Measured by Pill Count						
Adherent	169	139 (82.2)	160	134 (83.8)	-1.5	[-9.7; 6.7]
Nonadherent	125	73 (58.4)	136	76 (55.9)	2.5	[-9.6; 14.6]

N = number of patients; n = number of observations
a Overall assessment
b Based on a normal approximation of the difference in % response

As shown above virologic response at Week 48 was greater in adherent patients than in non adherent patients (adherence based on the overall assessment). In all subgroups by adherence, virologic response was similar in both treatment groups. The response data of the subgroups of adherent patients assessed by the 3 different methods supported the non-inferiority of DRV/rtv q.d versus DRV/rtv b.i.d regimen. In non adherent patients, non-inferiority in virologic response of DRV/rtv q.d was supported when compliance was assessed by pill count and DRV plasma concentrations but not by the (M-MARSI) method.

QoL- FAHI score

FAHI imputed score at baseline was rather high (124 for the DRV/rtv q.d and 121 DRV/rtv b.i.d treatment groups), leaving relatively limited room for improvement. There were no notable statistically or clinically relevant differences between the two treatment groups for the slight observed mean changes at week 48 compared to baseline values.

There were also no relevant differences between the DRV/rtv q.d and DRV/rtv b.i.d treatment groups in FAHI response.

Discussion on Efficacy

The response rates for DRV/rtv q.d regimen in the subgroups such as high viral load $\geq$ 100000 copies/ml, CD4 counts at the lowest range <50 even <100 cells (x 10^6/L), 0 number of susceptible NRTIs in the OBR, and clade non-B seems to indicate that in such groups the 800/100 mg DRV/rtv q.d regimen might not result in comparable efficacy with the approved 600 /100 mg DRV/rtv b.i.d regimen in ART experienced patients, although the number of involved patients are limited.

Regional differences are also apparent in the presented data: In North America the q.d regimen of Prezista was favoured whereas in South America the b.i.d regimen seems to be favoured in the comparison. Despite the outcome of the formal test for treatment heterogeneity which indicated no significant interaction between treatment group and region (see Table 11), the lower efficacy of the

800/100 mg DRV/rtv q.d regimen in comparison to the approved b.i.d regimen in this relatively large subgroup of patients is of concern.

The long-term efficacy of DRV/rtv q.d regimen is unknown in ART-experienced adult patients with 0 DRV RAMs. At some time point before or post week 48 a certain proportion of the patients might develop resistance to DRV resulting ultimately in failure of DRV/rtv treatment.

The results for the secondary efficacy endpoints were consistent with the results of the primary endpoint for both treatment groups.

The paired baseline/endpoint genotypes for virologic failure patients are rather limited. The comparative results with both DRV/rtv treatment regimens should be interpreted with caution; yet 1 patient in the DRV/rtv q.d group developed primary (major) DRV mutations lost susceptibility to DRV at endpoint based on phenotyping analysis. The latter patient lost susceptibility also to other PIs. The development of this resistance was possibly related to previous failure of LPV/rtv treatment. However, the patient was compliant according to DRV concentration levels and did not have any structured treatment interruptions. This point reveals some of the difficulties and risks to use the proposed once daily dosage of DRV/rtv in an appropriate patient-tailored fashion.

The sensitivity analysis results of adherent versus non-adherent patients by treatment regimen, by adherence measurement method and differences between treatment groups confirm the importance of the adherence to ART therapy to obtain optimal benefit from the treatment. However, the extent of non-compliance/ non-adherence is of concern and it does impact on the global primary outcome of the study. Although, the findings in adherent patient groups by adherence measurement method do not compromise the robustness of non-inferiority conclusion. In adherent patients, the response rate was approximately 10% higher than in the ITT or OP TLOVR populations of the primary analysis. However, these results did not reveal clinically relevant difference between the two treatment groups.

3.2.4. Population PK/PD data

Sparse sampling data of 280 patients on the q.d regimen and 278 patients on the b.i.d regimen were included in the population pharmacokinetic analysis for DRV. DRV and rtv plasma concentrations were analysed by a validated LC-MS/MS method.

The summary of the available data included in the population pharmacokinetic analysis and the covariates are shown in table 15:

Table 15. Summary of the available data included in the population pharmacokinetic analysis and the covariates

Item	ODIN, TMC114-TiDP31-C229
Tibotec code	TMC114-TiDP31-C229
No. and type of subjects	558 HIV-1+ patients
No. of PK samples	2792 Darunavir Concentrations
	2799 Ritonavir Concentrations
Darunavir dose	278 subjects with 600 mg bid dosing
	280 subjects with 800 mg qd dosing
Ritonavir dose	278 subjects with 100 mg bid dosing
	280 subjects with 100 mg qd dosing
Background Regimen	Individually optimized background regimen
Single/Multiple dose	Multiple
Study periods	Week 4, 8, 24, 48 and early withdrawal visits
Sampling time windows	Week 4 and 24: pre- and 1 hr post-dose
	Week 8, 48, withdrawal at any time
No samples	1-2 samples per visit;
Assay (LLOQ)	LC-MS/MS (Darunavir and Ritonavir: 5 ng/mL)

	600/100 mg BID (n=278)		800/100 mg QD (n=280)	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
AAG (mg/dL)	92.7 (27.9)	89.0 (31.0-240)	95.7 (31.3)	90.0 (45.0-315)
Age (yrs)	40.7 (9.57)	40.0 (18.0-77.0)	40.5 (9.00)	40.0 (18.0-70.0)
WT (kg)	70.4 (15.7)	69.0 (36.0-140)	70.6 (16.3)	69.5 (37.5-136)
CRCL (mL/min)	116 (29.4)	113 (47.4-230)	116 (32.4)	115 (41.0-232)
SEX (n)				
Males	185		170	
Females	93		110	
RACE (n)				
Caucasian	105		98	
Black	65		77	
Hispanic	53		45	
Asian	41		47	
Other	14		13	

The model applied is based upon the model developed before. The parameter estimates from the original population PK model used in this analysis are in table 16.

Table 16. Parameter estimates from the original population PK model

Parameter (Units)	Population Mean (SE*)	CV% Inter-Individual Variance (SE*)
CL/F (L/hr)	41.9 (13)	26 (8)
Influence of TDD[1]	0.388 (8.8)	-
Kaff of AAG (dL/mg)	0.0304 (18)	-
V/F (L)	122 (8.2)	88[2] (17)
Q/F (L/hr)	15.0 (11)	65 (30)
Vp/F (L)	84.3 (11)	56 (36)
Ka	0.455 (8.1)	74 (23)
F(rel)	1.18 (1.6)	-
Residual Error	0.122 (4.2)	-

* - SE given as CV%

1. Change in clearance based on total daily dose (TDD)
2. Correlation between the variance estimates of apparent central volume and absorption rate constant estimated at 0.61.

For DRV, for the 600 mg BID arm a slight bias for the individual predicted concentrations (IPRED) is observed. These are under-predicted at high concentrations and somewhat over-predicted at low concentrations. This was also observed for the typical predicted concentrations (PRED). However, the less smooth lines for all plots indicate little bias in the structural model as the smooth is similar to the expected trend. The weighted residuals (WRES) are approximately normally distributed although there is a trend for the WRES to increase for time after dosing (TAD) beyond 20 hrs. However, this may be attributed to compliance or inaccuracies in dosing history, as time after dosing in this study would be expected to be not greater than 12h. For the 800/100 mg QD arm there is almost no bias for IPRED and a slight over-prediction for PRED as concentrations increase. The WRES values are again approximately normally distributed. There is no trend for the WRES to increase as TAD increases. The distribution of etas on CL/F appears to be approximately normal distributed. The individual random effects (ETA) for clearance plotted against age, body weight (WT), creatinine clearance (CRCL), sex, race and dose, showed no clear apparent trends.

For RTV, it appeared that the dependent (DV) vs. PRED plots indicate that the population model cannot predict higher concentrations, which was not seen during model development. This can be attributed to the fact that for model development Cmax values were lower compared to this study. In addition, the WRES are also skewed and not normally distributed.

The Bayesian estimates of the DRV and rtv pharmacokinetic parameters from the sparse sampling data are summarised in table 17.

Table 17. Population PK Estimates of DRV and rtv

Parameter	**DRV/rtv 800/100 mg q.d. Median (Range)**	**DRV/rtv 600/100 mg b.i.d. Median (Range)**
N	**280**	**278**
DRV:		
AUC24h, ng•h/ml C0h, ng/ml	87788 (45456; 236920) 1896 (184; 7881)	109401 (48934; 323820) 3197 (250; 11865)
rtv:		
AUC24h, ng•h/ml C0h, ng/ml	5776 (1801; 39027) 59 (6; 1049)	12588 (3404; 44762) 307 (41; 1657)

N = number of patients

As expected dosing with DRV/rtv q.d resulted in lower AUC24h and C0h values compared to dosing with DRV/rtv b.i.d. Similar findings were obtained for rtv. Results from this study were consistent with findings from studies previously submitted by the MAH. Likewise, the findings with respect to the DRV pharmacokinetic parameters by subgroups for gender, age, race, region, and weight are consistent with previous pharmacokinetic analyses.

There were some differences between the treatment groups regarding exposure (AUC) to DRV in the above mentioned subgroups. The MAH stated that despite the lower DRV trough and overall exposure following DRV/rtv 800/100 mg q.d, comparable efficacy to the DRV/rtv b.i.d group was observed, confirming that adequate DRV exposures were achieved following DRV/rtv q.d dosing in this population.

At the CHMP request, analyses of the numbers of patients with plasma trough DRV concentrations (C0h) that 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) and those who did not achieve this target concentration in both treatment groups and subgroups defined by gender, age, race, region, and weight were provided. See tables 18 and 19.

Table 18. Overview of subjects with DRV C0h below (<) and equal to or above (≥) 550 ng/mL overall, and by subgroups for gender, age, race, region, and weight

	DRV/rtv 800/100 mg q.d. N = 278		DRV/rtv 600/100 mg b.i.d. N = 280	
(Sub)groups	≥ 550 ng/mL n (%)	< 550 ng/mL n (%)	≥ 550 ng/mL n (%)	< 550 ng/mL n (%)
All Subjects	273 (97.5)	7 (2.5)	277 (99.6)	1 (0.4)
Gender				
Female	109 (99.1)	1 (0.9)	92 (98.9)	1 (1.1)
Male	164 (96.5)	6 (3.5)	185 (100.0)	0
Age (years)				
≤ 30	32 (100.0)	0	33 (100.0)	0
]30 - 45]	165 (96.5)	6 (3.5)	158 (100.0)	0
]45 - 55]	62 (100.0)	0	67 (98.5)	1 (1.5)
]55 - 65]	13 (92.9)	1 (7.1)	17 (100.0)	0
> 65	1 (100.0)	0	2 (100.0)	0
Race				
Black	77 (100.0)	0	64 (98.5)	1 (1.5)
Caucasian/White	97 (99.0)	1 (1.0)	105 (100.0)	0
Hispanic	43 (95.6)	2 (4.4)	53 (100.0)	0
Oriental/Asian	43 (91.5)	4 (8.5)	41 (100.0)	0
Other	13 (100.0)	0	14 (100.0)	0
Region				
Africa	33 (100.0)	0	26 (100.0)	0
Asia	42 (91.3)	4 (8.7)	38 (100.0)	0
Australia + Europe	39 (100.0)	0	28 (100.0)	0
North America	42 (97.7)	1 (2.3)	46 (100.0)	0
South America	117 (98.3)	2 (1.7)	139 (99.3)	1 (0.7)
Weight (kg)				
≤ 58.6	73 (98.6)	1 (1.4)	65 (98.5)	1 (1.5)
]58.6 - 69.0]	63 (96.9)	2 (3.1)	77 (100.0)	0
]69.0 - 79.5]	68 (95.8)	3 (4.2)	69 (100.0)	0
> 79.5	68 (98.6)	1 (1.4)	66 (100.0)	0

N = number of subjects, n = number of observations

Table 19. Summary of the clinical outcome for subjects in both treatment groups (overall) who did not achieve a DRV C0h of < 550 ng/mL (corresponding values for baseline viral load, viral load change from baseline, and virologic response [HIV-RNA < 50 copies/mL, TLOVR and observed case])

CRF ID	Treatment Group	Baseline Viral Load[a]	Trough Concentration	Viral Load Change From Baseline[a]	Virologic Response[b] (TLOVR)	Virologic Response[b] (Observed Case)
229-0165	DRV/rtv q.d.	3.80	345.12	-2.11	Yes	Yes
229-0219	DRV/rtv q.d.	3.87	444.43	-2.18	Yes	Yes
229-0379	DRV/rtv q.d.	3.41	485.3	-1.72	Yes	Yes
229-0527	DRV/rtv q.d.	4.29	184.39	-2.60	Yes	Yes
229-0545	DRV/rtv q.d.	4.48	534.55	-2.79	Yes	Yes
229-0640	DRV/rtv q.d.	4.47	345.4	-2.78	Yes	Yes
229-0850	DRV/rtv q.d.	4.29	490.97	-2.60	Yes	Yes
229-0729	DRV/rtv b.i.d.	4.91	250.47	-0.69	No	No

[a] Log_{10} copies/mL
[b] Confirmed plasma viral load < 50 copies/mL

The number of patients with C0h values below 550 ng/ml is low (8/558) of whom 7 patients were in the 800/100 mg qd group vs. 1 in the 600/100 mg bid group. Moreover, 7 out of 8 patients had a virologic response at week 48; the only patient not having a response was from the bid group. Suboptimal exposure in the 800 mg q.d group associated with suboptimal trough concentrations seems to be limited to a minority of the patients.

The MAH was of the opinion that there were no relationships between the DRV C0h and the change in log10 viral load or virologic response defined as plasma viral load < 50 copies/ml from baseline at Week 48 were observed in either treatment group. The regression analyses showed no relevant relationships between the DRV pharmacokinetics and virologic response at Week 48. Baseline log10 viral load and number of susceptible NRTIs were predictors of response.

There were no apparent/consistent relationships between the DRV and rtv pharmacokinetic parameters AUC24h 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 or laboratory lipid abnormalities.

Nevertheless, this target concentration was used by the MAH in support of the PK/PD rationale of the DRV/rtv 800/100 mg q.d regimen. In the present ODIN study the number of patients with trough concentration values below 550 ng/ml is low and perhaps too small to detect any relationship between the pharmacokinetics of DRV and its efficacy in the absence of studies of prolonged duration. Furthermore, the quoted trials in other populations in other studies used the DRV/rtv 600/100 b.i.d regimen where this might not be an issue. The validity of the concern discussed above with regard to the risk of suboptimal exposure to DRV/rtv with the once daily regimen is further emphasized by the findings of Soon GH et al (2010, see below). Based on the importance of the observations in this study on the target trough concentration the MAH accepted to include an appropriate warning in the SmPC.

A recently published study (Soon GH et al.2010. Antimicrob. Agents Chemother. 54:2775– 2780) on the interaction of very similar dosage of DRV/ rtv (i.e. 900/100 mg once daily regimen of DRV/rtv with efavirenz) revealed that efavirenz impacted adversely on the DRV plasma concentrations in healthy volunteers. The trough levels of DRV [by 57% to 1,180 ng/ml (SD: 1,138 ng/ml)] and half-life were reduced significantly; the effect on AUC 0-24 was less pronounced (reduced by 14%; see table 20). As implied from the large SD value, many individuals will have suboptimal trough levels.

Table 20. Pharmacokinetics of DRV when 900mg was given once daily with rtv at 100mg once daily, before and after administration of efavirenz at 600mg once daily

Parameter	DRV-RTV		DRV-RTV + EFV		LS means		*P* value
	Mean	SD	Mean	SD	Ratio	90% CI	
C_{min} (ng/ml)	2,137	1,034	1,180	1,138	0.43	0.32–0.57	0.0003
C_{max} (ng/ml)	10,967	3,320	10,027	2,552	0.92	0.82–1.03	0.23
T_{max} (h)	4	2–6[b]	4	2–5[b]	NA		0.50
AUC (ng · h/ml)	103,261	32,963	89,498	33,889	0.86	0.75–0.97	0.049
$t_{1/2}$ (h)	15.3	7.4	8.5	4.6	0.56	0.49–0.65	0.00001
CL/*F* (ml/h)	9,657	3,466	11,392	4,127	1.17	1.03–1.33	0.047

[a] Abbreviations: RTV, ritonavir; DRV, darunavir; EFV, efavirenz; NA, not available; LS, least-squares; C_{min}, trough concentration in plasma; C_{max}, maximum concentration in plasma; T_{max}, time to the maximum concentration in plasma; AUC, area under the concentration-time curve; $t_{1/2}$, half-life; CL/*F*, clearance.
[b] Instead of SDs, the values for the time to the maximum concentration in plasma are ranges.

The observed effect of 600 mg q.d. efavirenz on DRV trough levels is more pronounced than the effect presently described in the section 4.5 of the approved SmPC. Therefore, combination therapy with efavirenz and DRV/rtv 800/100 mg q.d is disputable.

Of note, in the ODIN trial, no efavirenz was used.

Discussion on PK/PD data

The population pharmacokinetic model was adequate to describe the pharmacokinetics for DRV. With regard to rtv, the data were accepted earlier for the approved same dosing regimen recommended for ART naïve patients.

The problem of possible suboptimal exposure in the 800 mg q.d group associated with suboptimal trough concentrations seems to be limited to a minority of the patients; however, the number of patients with suboptimal exposure was higher than in the 600/100 mg bid group.

The findings from the study from Soon GH et al on the adverse interaction of efavirenz with the PK of the very similar dosage of DRV/ rtv (i.e. 900/100 mg q.d) are also based on the importance of this target trough level concentration.

A concentration below 550 ng/ml is one of the factors which may impact on the efficacy. The CHMP felt that this point was greater concern for the q.d dosing regimen in ART experienced patients. In addition, it may even be further affected by any large decrease in DRV concentrations for instance by co-medications. As requested by the CHMP, the MAH included an appropriate warning in the SmPC.

3.2.5. Clinical Safety

The most frequent adverse events (AEs) with at least possibly related to treatment (i.e. adverse drug reactions, ADRs) reported in both treatment groups were diarrhoea, nausea, vomiting, headache, and rash. See tables 21 and 22 for a summary and display of ADRs in both treatment groups.

Table 21. AE Summary Table

n (%) of Subjects With	**DRV/rtv 800/100 mg q.d N = 294**	**DRV/rtv 600/100 mg b.i.d N = 296**	**Total DRV/rtv N = 590**
Mean Exposure (Weeks)	***44.8***	***43.1***	***43.9***

≥ 1 AE	224 (76.2)	228 (77.0)	452 (76.6)
≥ 1 SAE	16 (5.4)	27 (9.1)	43 (7.3)
≥ 1 grade 3 or 4 AE	23 (7.8)	45 (15.2)	68 (11.5)
≥ 1 AE at least possibly related to DRV/rtv	90 (30.6)	112 (37.8)	202 (34.2)
≥ 1 AE leading to permanent discontinuation	10 (3.4)	14 (4.7)	24 (4.1)
Death*	2 (0.7)	6 (2.0)	8 (1.4)

N = number of patients n = number of observations
* None of the AEs with fatal outcome was considered related to the trial treatment by the investigator.

The proportion of patients with AEs and discontinuation rate were similar in both treatment groups.

Table 22. ADRs at Least Possibly Related* to DRV/rtv in ≥ 2 patients in Either Treatment Group during treatment period– TMC114-C229 (Week 48 Data)

System Organ Class Preferred Term, n (%)	**DRV/rtv 800/100 mg q.d N = 294**	**DRV/rtv 600/100 mg b.i.d N = 296**	**Total DRV/rtv N = 590**
Mean Exposure (Weeks)	*44.8*	*43.1*	*43.9*
Any ADR to DRV/rtv	*90 (30.6)*	*112 (37.8)*	*202 (34.2)*
Gastrointestinal Disorders	69 (23.5)	76 (25.7)	145 (24.6)
Abdominal discomfort	0	2 (0.7)	2 (0.3)
Abdominal distension	2 (0.7)	2 (0.7)	4 (0.7)
Abdominal pain	5 (1.7)	3 (1.0)	8 (1.4)
Diarrhoea	29 (9.9)	45 (15.2)	74 (12.5)
Dyspepsia	4 (1.4)	4 (1.4)	8 (1.4)
Flatulence	2 (0.7)	2 (0.7)	4 (0.7)
Gastritis	3 (1.0)	0	3 (0.5)
Nausea	32 (10.9)	31 (10.5)	63 (10.7)
Vomiting	9 (3.1)	16 (5.4)	25 (4.2)
General Disorders and Administration Site Conditions	4 (1.4)	5 (1.7)	9 (1.5)
Fatigue	2 (0.7)	4 (1.4)	6 (1.0)
Infections and Infestations	2 (0.7)	2 (0.7)	4 (0.7)
Gastroenteritis	0	2 (0.7)	2 (0.3)
Investigations	5 (1.7)	10 (3.4)	15 (2.5)
ALT increased	0	3 (1.0)	3 (0.5)
Blood cholesterol increased	1 (0.3)	3 (1.0)	4 (0.7)
Blood triglycerides increased	0	2 (0.7)	2 (0.3)
Metabolism and Nutrition Disorders	10 (3.4)	15 (5.1)	25 (4.2)
Anorexia	1 (0.3)	2 (0.7)	3 (0.5)
Hypercholesterolemia	2 (0.7)	3 (1.0)	5 (0.8)
Hyperglycaemia	1 (0.3)	2 (0.7)	3 (0.5)
Hyperlipidaemia	0	3 (1.0)	3 (0.5)
Hyperphagia	2 (0.7)	0	2 (0.3)
Hypertriglyceridemia	2 (0.7)	5 (1.7)	7 (1.2)
Musculoskeletal and Connective Tissue Disorders	1 (0.3)	2 (0.7)	3 (0.5)
Nervous System Disorders	12 (4.1)	14 (4.7)	26 (4.4)
Dizziness	4 (1.4)	3 (1.0)	7 (1.2)
Dysgeusia	0	2 (0.7)	2 (0.3)
Headache	4 (1.4)	6 (2.0)	10 (1.7)
Somnolence	4 (1.4)	1 (0.3)	5 (0.8)

Psychiatric Disorders Insomnia	2 (0.7) 1 (0.3)	3 (1.0) 2 (0.7)	5 (0.8) 3 (0.5)
Renal and Urinary Disorders	0	3 (1.0)	3 (0.5)
Skin and Subcutaneous Tissue Disorders Lipodystrophy acquired Pruritus Rash Rash maculopapular Urticaria	18 (6.1) 0 2 (0.7) 8 (2.7) 1 (0.3) 0	19 (6.4) 4 (1.4) 2 (0.7) 8 (2.7) 2 (0.7) 2 (0.7)	37 (6.3) 4 (0.7) 4 (0.7) 16 (2.7) 3 (0.5) 2 (0.3)

N = number of patients n = number of observations * Investigator-Assessed Causality

Except for diarrhoea and vomiting, which were less frequent with DRV/rtv q.d than with DRV/rtv b.i.d, the incidence of all these AEs was comparable between the treatment groups. However, most frequent ADRs ≥ grade 2 related to DRV/rtv q.d or DRV/rtv b.i.d, respectively occurred at similar rates in the treatment groups and were mainly gastrointestinal and related to nausea (3.7% and 4.4%), diarrhoea (3.7% in both groups), and vomiting (2.4% and 3.0%).

Cardiac-related AEs were reported with similar frequency in the DRV/rtv q.d group (2.7%) and DRV/rtv b.i.d group (1.7%). Only 1 cardiac-related AE was considered at least possibly related to DRV/rtv (ECG U-wave abnormality) this was a patient in the q.d group.

The incidence of laboratory abnormalities was low and generally similar in both treatment groups.

Liver-related AEs were considered at least possibly related to DRV/rtv in none in the DRV/rtv q.d group versus 4 in the DRV/rtv b.i.d group (1 hepatomegaly, 3 with increased LFT).

Overall, hyperbilirubinemia (increase in total bilirubin) was observed slightly less frequently in the DRV/rtv q.d group (1.0%) than in the DRV/rtv b.i.d group (3.2%). The small difference between the treatment groups in the incidence of hyperbilirubinemia appeared to be driven by hepatitis B or C co infection, which was less frequent in the DRV/rtv q.d group (see table 4). Furthermore, in contrast to the q.d regimen, the incidence of liver-related AEs was higher in co infected patients than in not co infected patients (8.1% versus 2.7%) in the b.i.d regimen.

Lipid-related AEs were considered at least possibly related to DRV/rtv in 7 (2.4%) in the DRV/rtv q.d group versus 14 (4.7%) in the DRV/rtv b.i.d group (mainly cases of hypercholesterolemia, hypertriglyceridaemia, hyperlipaemia).

The incidence of coagulation and haematology laboratory abnormalities was generally comparable between the treatment groups. The majority of coagulation and haematology abnormalities in this trial were grade 1 or 2. Grade 3 or 4 haematology related abnormalities occurred mostly in only 1 or 2 subjects in any treatment group.

The incidence of AEs related to urinalysis was low and similar for both treatment groups. The most frequent AEs related to urinalysis were haematuria, reported in 1.4% of patients in both treatment groups, and proteinuria (0.7% in both treatment groups). No other AEs related to urinalysis were reported in > 1 patient in any treatment group.

Small mean 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.

Comparison of the change from baseline in ECG parameters revealed small mean changes, which were sometimes statistically significant (Wilcoxon's matched pairs signed ranks test). None of the observed

within-group mean changes from baseline were considered clinically relevant. The incidence of the individual QTc interval abnormalities was generally comparable for both treatment groups.

Treatment emergent QTcF values of > 500 ms were observed in 1.7% and 1.3% of patients in the DRV/rtv q.d and DRV/rtv b.i.d groups, respectively. For QTcB values of > 500 ms were observed in 2.5% and 0.9% of patients, respectively. Isolated increases in QTcF of > 60 ms were observed in 3.7% and 3.5% of patients in the DRV/rtv q.d and DRV/rtv b.i.d treatment groups; similar rates were noted for increases in QTcB. No clinically relevant cases related to QTc prolongation were reported.

At the CHMP request, the MAH discussed the overall safety and tolerability profile for both DRV/rtv dose regimens which were generally consistent with the known overall safety profile for DRV/rtv. Smaller incidences were observed for DRV/rtv 800/100 mg q.d. compared to DRV/rtv 600/100 mg b.i.d. for the following AEs or laboratory abnormalities:

- SAEs (5.4% versus 9.1%);
- Grade 3 or 4 AEs (7.8% versus 15.2%);
- The GI disorders diarrhea (14.3% versus 22.3%) and vomiting (4.4% versus 8.4%); these differences were mainly driven by grade 1 events (see Table 23);
- Lipid abnormalities (see Table 24).

Table 23. Incidence of Diarrhea and Vomiting in trial TMC114-C229 – Week-48 Analyses

Incidence (%)	Diarrhea		Vomiting	
	DRV/rtv q.d.	DRV/rtv b.i.d.	DRV/rtv q.d.	DRV/rtv b.i.d.
Any grade	14.3	22.3	4.4	8.4
At least possibly related	9.9	15.2	3.1	5.4
At least possibly related & ≥ grade 2	3.7	3.7	2.4	3.0

Table 24. Incidence of Lipid-Related Laboratory Abnormalities in trial TMC114-C229 – Week-48 Analyses

	Triglycerides		Total cholesterol		LDLc	
Incidence (%)	DRV/rtv q.d.	DRV/rtv b.i.d.	DRV/rtv q.d.	DRV/rtv b.i.d.	DRV/rtv q.d.	DRV/rtv b.i.d.
Any grade	5.2	11.0	25.8	37.6	26.6	32.7
Grade 2 to 4 (or 3)	5.2	11.0	10.1	20.6	9.8	16.7

Serious Adverse Events

Most SAEs occurred in only 1 patient in any treatment group. Drug-related SAE (DRSAEs) reported for both treatment groups are displayed in table 25.

Table 25. SAEs at Least Possibly Related* to DRV/rtv in Either Treatment Group during treatment period– TMC114-C229 (Week 48 Data)

System Organ Class **Preferred Term, n (%)**	**DRV/rtv 800/100 mg q.d** **N = 294**	**DRV/rtv 600/100 mg b.i.d** **N = 296**	**Total DRV/rtv** **N = 590**
Mean Exposure (Weeks)	*44.8*	*43.1*	*43.9*
Any DRASE to DRV/rtv	*1 (0.3)*	*3 (1.0)*	*4 (0.7)*
Infections and Infestations	**1 (0.3)**	**0**	**1 (0.2)**
Pneumonia	1 (0.3)	0	1 (0.2)
Metabolism and Nutrition Disorders	**0**	**2 (0.7)**	**2 (0.3)**
Hyperamylasemia	0	1 (0.3)	1 (0.2)
Hypercholesterolemia	0	1 (0.3)	1 (0.2)
Renal and Urinary Disorders	**0**	**1 (0.3)**	**1 (0.2)**
Calculus ureteric	0	1 (0.3)	1 (0.2)

N = number of patients n = number of observations * Investigator-Assessed Causality

Overall frequency of AEs leading to permanent discontinuation was similar in the treatment groups (3.4% on q.d and 4.7% on b.i.d). ADRs leading to permanent discontinuation are displayed in table 26.

Table 26. ADRs at Least Possibly Related* to DRV/rtv leading to permanent treatment discontinuation in Either Treatment Group during treatment period– TMC114-C229 (Week 48 Data)

System Organ Class **Preferred Term, n (%)**	**DRV/rtv 800/100 mg q.d** **N = 294**	**DRV/rtv 600/100 mg b.i.d** **N = 296**	**Total DRV/rtv** **N = 590**
Mean Exposure (Weeks)	***44.8***	***43.1***	***43.9***
Any ADR Leading to Permanent Discontinuation	***5 (1.7)***	***3 (1.0)***	***8 (1.4)***
Gastrointestinal Disorders	**4 (1.4)**	**1 (0.3)**	**5 (0.8)**
Abdominal pain	0	1 (0.3)	1 (0.2)
Constipation	1 (0.3)	0	1 (0.2)
Flatulence	1 (0.3)	0	1 (0.2)
Nausea	2 (0.7)	1 (0.3)	3 (0.5)
Vomiting	1 (0.3)	0	1 (0.2)
Metabolism and Nutrition Disorders	**0**	**1 (0.3)**	**1 (0.2)**
Hypercholesterolemia	0	1 (0.3)	1 (0.2)
Nervous System Disorders	**2 (0.7)**	**1 (0.3)**	**3 (0.5)**
Dizziness	1 (0.3)	1 (0.3)	2 (0.3)
Headache	1 (0.3)	1 (0.3)	2 (0.3)
Skin and Subcutaneous Tissue Disorders	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Rash	1 (0.3)	0	1 (0.2)
Rash maculopapular	0	1 (0.3)	1 (0.2)

N = number of patients n = number of observations * Investigator-Assessed Causality

Discussion on Clinical Safety

The safety results of the present study are consistent with the known safety profile of DRV/rtv 600/100 mg b.i.d, with some differences with regard to frequencies. These can be explained by the difference in the intensity of prior ART therapy in the studied populations and also by the current knowledge on DRV safety.

The safety profile of the DRV/rtv 800/100 mg q.d in the present study is similar to that of the b.i.d regimen with diarrhoea and vomiting being less frequent with the q.d regimen in the tested patient population. The predicted higher rate of gastro-intestinal intolerance after q.d dosage was not clearly apparent, with the exception of a few more discontinuations due to ADRs such as nausea and vomiting.

However, the differences in incidences found in trial TMC114-C229 can not support a generalized claim that the safety profile of the q.d. regimen is "significantly superior" to the b.i.d regimen. Furthermore, the safety profile of the q.d regimen is consistent with earlier experience with this regimen in ART-naïve HIV1-infected patients. This safety profile is adequately reflected in the SmPC.

3.2.6. Risk Management Plan

At the request of the CHMP, an updated version of the RMP: version 10.3, dated 12 January 2011 was submitted. The updates to the RMP are presented in Table 27.

Table 27. Table Summary of the Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks		
Severe skin reactions	- Routine pharmacovigilance	Listed in the Special warnings and precautions for use section of the SmPC (Section 4.4), including recommendations to discontinue PREZISTA/rtv immediately if signs or symptoms of severe skin reactions develop and a caution statement for the use of PREZISTA in patients with a known sulphonamide allergy since darunavir contains a sulphonamide moiety. Rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus, angioedema, generalized rash, allergic dermatitis, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and (drug) hypersensitivity are listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Hepatotoxicity	- Routine pharmacovigilance	Hepatotoxicity is a subsection in the Special warnings and precautions for use section of the SmPC (Section 4.4), including: • a statement on increased risk of liver function abnormalities in patients with pre-existing liver dysfunction; • advice on appropriate laboratory test monitoring prior and during therapy with PREZISTA/rtv and on increased AST/ALT monitoring in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases; • recommendation to consider interruption or discontinuation of PREZISTA/rtv treatment in case of evidence of new or worsening liver dysfunction. Also hepatic impairment is listed in the Special warnings and precautions for use section of the SmPC (Section 4.4). Section 4.2 Posology and method of administration Section 4.4

		Special warnings and precautions for use, and Section 5.2 Pharmacokinetic properties of the SmPC includes a caution statement for the use of PREZISTA in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Section 5.2 Pharmacokinetic properties states that the effect of severe heaptic impairment on the pharmacokinetics of darunavir has not been studied. Section 4.2 Posology and method of administration, Section 4.3 Contraindications, and Section 4.4 Special warnings and precautions for use state that PREZISTA should not be used/is contraindicated in patients with severe (Child-Pugh Class C) hepatic impairment. Increased alanine aminotransferase, increased aspartate aminotransferase, hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased blood alkaline phosphatase, and increased gamma-glutamyltransferase are listed as ADR in Section 4.8 Undesirable effects of the SmPC. Details on undesirable effects in HIV/hepatitis B or C co-infected patients are also provided in Section 4.8 Undesirable effects of the SmPC.
Hyperglycemia	- Routine pharmacovigilance	Listed in the Special warnings and precautions for use section of the SmPC (Section 4.4). Diabetes mellitus, hyperglycemia, and insulin resistance are listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Lipid Abnormalities	- Routine pharmacovigilance	Hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia, and decreased high density lipoprotein are listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Pancreatitis	- Routine pharmacovigilance	Increased blood amylase, pancreatitis, and increased lipase are listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Fat Redistribution	- Routine pharmacovigilance	Listed in the Special warnings and precautions for use section of the SmPC (Section 4.4), including: • a statement on the increased risk of lipodystrophy associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. • recommendations on the monitoring and management of fat redistribution. Lipodystrophy (including lipohypertrophy, lipodystrophy and lipoatrophy) is listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Immune reconstitution	- Routine pharmacovigilance	Listed in the Special warnings and precautions for use section of the SmPC (Section 4.4). Immune reconstitution syndrome is listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Development of Drug Resistance	- Routine pharmacovigilance • Additionally, the dose regimen will be taken into account in all resistance monitoring reports (e.g., PSUR).	Section 4.1 Therapeutic indications of the SmPC mentions that in deciding to initiate treatment with PREZISTA/rtv 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.
Important Potential Risks		
Coronary Artery-Related Events	- Routine pharmacovigilance	Acute myocardial infaction, myocardial infarction, and angina pectoris are listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Cardiac Conduction-Related Events	- Routine pharmacovigilance	Prolonged electrocardiogram QT is listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Hyperbilirubinaemia	- Routine pharmacovigilance	Increased blood bilirubin is listed as ADR in Section 4.8 Undesirable effects of the SmPC.

Overdose/ medication error with the 400 mg tablet	- Routine pharmacovigilance	The proposed SmPC of PREZISTA 400 mg in the context of the ODIN filing mentions in Section 4.2 Posology and method of administration that PREZISTA 400 mg tablets are only to be used to construct the once daily 800 mg regimen.
Important Missing Information		
Elderly	- Routine pharmacovigilance	Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use, and Section 5.2 Pharmacokinetic properties state that there is limited information available in patients above 65 years of age and therefore Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use state that PREZISTA should be used with caution in this age group.
Pregnant and Breast Feeding Women	- Routine pharmacovigilance - Continued evaluation through the ongoing study TMC114HIV3015 to assess the pharmaco-kinetics of DRV/rtv and/or ETR in 12 to 24 HIV-1 infected pregnant women. - Participation in the Antiretroviral Pregnancy Registry.	Section 4.6 Fertility, pregnancy and lactation of the SmPC states that there are no adequate and well-controlled studies with darunavir in pregnant women and it is not known whether darunavir is excreted in human milk. Therefore, PREZISTA/rtv should be used during pregnancy only if the potential benefit justifies the potential risk and, taking into account the potential of HIV transmission and the potential for adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed under any circumstances if they are receiving PREZISTA.
Children 3-6 years of age	- Routine pharmacovigilance - Continued evaluation through the ongoing Study TMC114-C228 in treatment experienced children.	Section 4.2 Posology and method of administration states that there are insufficient data on the use of PREZISTA with low dose ritonavir in children less than 6 years of age or less than 20 kg body weight. Hence, in Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use it is stated that PREZISTA is not recommended for use in this group. In addition, Section 5.3 Preclinical safety data states that due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, PREZISTA with low dose ritonavir should not be used in paediatric patients below 3 years of age.
Long-term safety data in children aged 6 to 17 years of age.	- Routine pharmacovigilance - Long-term observational study in children and adolescents with the PENTA group.	Section 4.8 Undesirable effects (subsection Children and adolescents) of the SmPC states that overall, the safety profile in the 80 children and adolescents included in the Phase II DELPHI trial was similar to that observed in the adult population. Section 5.1 Pharmacodynamic properties (subsection Clinical experience) of the SmPC provides information on duration of exposure to DRV in respective populations (up to 96 weeks for the adult population and up to 24 weeks for the paediatric population)

This version of the RMP does not yet reflect the currently approved SmPC (29/11/2010) nor does it take into account the final outcome of the label update related to present submission (e.g., the new efavirenz request) since this is not yet finalised. The MAH will submit a complete update of the RMP, addressing the approved labelling, with the next PSUR submission which is due 21 February 2011.

3.3. Changes to the Product Information

The following changes are highlighted in the product information in Annex I.

- Changes to sections 4.1, 4.2, 4.4, 4.5 and 5.1 of the SmPC of the 400mg tablet SmPC were introduced with the results of the study TMC114-C229 in treatment-experienced HIV-1 infected patients with 0 DRV RAMs. Changes to the SmPCs of all formulations were introduced in line with these changes (sections 4.1, 4.2, 4.4, 4.5, 5.1).
- Sections 4.4 and 4.5 of the SmPC have been updated to include information on an interaction with efavirenz.
- In fulfilment of FUM 59, editorial changes have been made in section 5.1 of the SmPC.
- Annex IIB has been updated with a new version of the RMP and the DDPS version number was removed.
- The PL has been updated accordingly.

3.4. Results and Discussion

3.4.1. Efficacy Conclusion

Overall, the 48 week results of study TMC114-C229 in treatment-experienced HIV-1 infected patients with 0 DRV RAMs showed non-inferiority of the efficacy of the newly proposed dosage of DRV/rtv at 800/100 mg q.d. to the DRV/rtv 600/100 mg b.i.d dosage both in combination with OBR based on the primary virologic endpoint (i.e. the percentage of patients achieving confirmed plasma viral load < 50 copies/ml in the ITT population) at the chosen delta of 12%. The results for the secondary virological and immunological response parameters were consistent with the results for the primary endpoint. The response rate was 72.1% for the DRV/rtv q.d group versus 70.9% in the DRV/rtv 600/100 mg b.i.d group. The sensitivity analyses results concerning adherent versus non-adherent patients confirmed the importance of adherence to ART therapy to obtain optimal benefit from the treatment. In adherent patients, the response rate was approximately 10% higher than in the overall ITT or OP TLOVR populations of the primary analysis.

However, the response rates for DRV/rtv q.d regimen in the subgroups such as high viral load > 100000 copies/ml, CD4 counts at the lowest range <50 cells (x 10^6/L) or even <100 cells (x 10^6/L), 0 number of susceptible NRTIs in the OBR, and clade non-B seem to indicate that the 800/100 mg DRV/rtv q.d regimen might not result in a comparable efficacy to the approved 600/100 mg DRV/rtv b.i.d regimen in ART experienced patients.

Furthermore, regional differences are also apparent in the presented data: In North America the q.d regimen of Prezista was favoured whereas in South America the b.i.d regimen seems to be favoured in the comparison.

Finally, the long-term efficacy of DRV/rtv q.d regimen is unknown in ART-experienced adult patients with 0 DRV RAMs. The extension phase for the ODIN trial is on-going. However, DRV/rtv 600/100 mg b.i.d is the only regimen used in this phase of the study. Hence, the data from the extension phase can therefore be considered only of supportive value.

Hence, at the CHMP request, the MAH restricted the originally claimed broad indication in "ART experienced adults with 0 darunavir resistance associated mutations (DRV-RAMs)" to "a subset of ART experienced adults" taking into account the CHMP's concerns in relation to relevant impacting factors e.g. high viral load (HIV RNA >100,000 copies/ml), low CD4 counts (<100 x 106/L) in Section 4.1 of the SmPC. In addition, since the long-term data on the efficacy of the DRV/rtv q.d regimen in this population is not available, the MAH reflected in section 4.4 of the SmPC that the data are derived

from a single clinical trial and the long-term efficacy of DRV/rtv q.d regimen is unknown in the sought indication.

The resistance data in this trial indicated that DRV/rtv 800/100 mg q.d. based therapy in this population results in a low rate of virologic failure and development of resistance. However, at some time point before or post week 48 a certain proportion of the patients will develop resistance to DRV resulting ultimately in failure of DRV/rtv treatment. Prescribers and patients should be alerted to this issue and should be advised to have regular reassessment of the resistance development to DRV conducted; and to assess the adequacy of the treatment regimen and to change timely to DRV/rtv 600/100 mg b.i.d or another appropriate ART combination therapy. At the CHMP request, the MAH updated the wording in relation to the reassessment of virologic response and resistance testing in the SmPC in Section 4.1, 4.2, 4.3, 4.4 and 5.1. In addition, the MAH proposes the twice-daily dose DRV/rtv 600/100 mg b.i.d as the recommended dosage in treatment-experienced adults with ≥ 1 DRV RAM(s) and "in the infrequent situations where for treatment-experienced patients a genotype is not available". Section 4.2 of the SmPC was updated accordingly.

Based on the provided population pharmacokinetic data, the MAH claimed that despite lower DRV and rtv trough concentrations and overall exposures, adequate DRV and rtv exposures were achieved following DRV/rtv 800/100 mg q.d dosing, as confirmed by the non-inferior efficacy with this regimen compared to that with DRV/rtv 600/100 mg b.i.d. Analyses of the numbers of patients with plasma trough DRV concentrations (C0h) that exceeded the predefined target trough concentration of 550 ng/ml and those who did not achieve this target concentration in both treatment groups and subgroups defined by gender, age, race, region, and weight were provided by the MAH. These data seem to indicate that this risk is limited to a minority of the patients; however, the number of patients with suboptimal exposure was higher than in the 600/100 mg b.i.d group. This issue was further discussed with MAH based on the recently published study of Soon GH et al. on the interaction of a very similar dosage of DRV/ rtv (i.e. 900/100 mg) once daily regimen with efavirenz. This study revealed that efavirenz impacted adversely on the DRV plasma concentrations, especially the trough plasma concentration, in healthy volunteers. Hence, at the CHMP request, the MAH updated sections 4.4 and 4.5 of the SmPC to inform the prescriber of the risks of suboptimal DRV plasma trough concentrations and recommend the use of DRV / rtv 600/100 mg b.i.d, instead of DRV / rtv 800mg q.d, when DRV is used in combination with efavirenz.

Overall, the extent of non-compliance/ non-adherence in this study is of concern although the findings in adherent patient groups did not seem to compromise the robustness of non-inferiority conclusion. These data do not allow an unequivocal conclusion that the q.d regimen provided a clinically relevant higher compliance rate versus the b.i.d dosage regimen.

3.4.2. Safety Conclusion

The AE profile of DRV/rtv 800/100 mg q.d emerging from this Week 48 analysis of study TMC114-C229 indicates that this dosage for treatment-experienced population with 0 DRV RAMs is at least similar to the approved DRV/rtv 600/100 mg b.i.d regimen.

The envisaged higher rate of gastro-intestinal intolerance after a q.d dosage was not clearly apparent, with the exception of a few more discontinuations due to ADRs such as nausea and vomiting.

Based on this single trial, in a relatively small patient population, the observed small differences in gastro-intestinal ADRs and metabolic lipid parameters do not allow the conclusion that the safety profile of q.d dosage regimen was significantly superior to the b.i.d dosage regimen in the tested ART–experienced patient population.

The safety profile for DRV/rtv in this study is in line with the known safety profile for DRV. Differences with regard to the frequencies of ADR can be explained by the difference in the intensity of prior ART therapy in the studied population. This is adequately reflected in the SmPC.

Regarding the risk of potential overdose and medication errors, the MAH included at the CHMP request wording on these risks in Sections 4.2 of the updated SmPC and Section 3 of the Patient Leaflet. In addition, these risks were added as potential risk in the RMP.

At the CHMP request, the MAH also committed to monitor the resistance to DRV and the risk of overdose and medication errors and to present them in the PSUR taking into account the dose regimen (see Follow Up Measures in Section 4).

Overall, the clinical safety profile of the DRV/rtv 800 mg strength q.d regimen in ART-experienced adult patients with 0 DRV RAMs can be considered acceptable.

3.5. Conclusions and Benefit / Risk Assessment

3.5.1. Benefit

The benefit of a simplified treatment regimen with once daily DRV/rtv that provides improved patient convenience with enhanced compliance in the proposed treatment-experienced population with 0 DRV RAMs would be of appreciable clinical relevance provided that this benefit is unambiguously proven throughout the sought indication at large (including patients with increased risk disease characteristics).

Uncertainties concerning the benefit

The claimed benefit is not unambiguously proven throughout the sought indication at large i.e. patients with increased risk disease characteristics such as high viral load > 100,000 copies/ml, CD4 counts at the lowest range <50 even <100 cells (x 10^6/L), 0 number of susceptible NRTIs in the OBR, and clade non-B. In response, the MAH restricted the claimed indication in line with the CHMP request.

The long-term efficacy of DRV/rtv q.d regimen is unknown in the sought target group i.e. ART experienced adult patients with 0 DRV RAMs. At the CHMP request, this point is reflected in the SmPC. Following discussions with the MAH, the CHMP agreed that the Week-48 data from trial TMC114-C229 sufficiently support the DRV/rtv 800/100 mg q.d. indication in the restricted treatment experienced population of the revised SmPC and that an additional trial in this population was not deemed necessary primarily due to the constrained feasibility and the duration of recruitment for such trial.

3.5.2. Risks

The simplified once lower dosage with DRV/rtv 800/100 mg q.d compared to the approved DRV/rtv 600/100 mg b.i.d regimen in ART-experienced patients may potentially increase the risk of virologic failure due to the development of resistance to DRV and other PIs. Furthermore, a higher single dose may induce a higher rate of gastro-intestinal intolerance.

Uncertainties concerning the Risks

There is no insurance that the simplified once daily lower dosage with DRV/rtv 800/100 mg q.d, compared to the approved DRV/rtv 600/100 mg b.i.d regimen, in ART-experienced patients will not

increase the risk of virologic failure due to the development of resistance to DRV and other PIs. Hence, at the CHMP request, the indication in section 4.1 of the SmPC was restricted.

At the CHMP request, additional PK/PD data were provided by the MAH. These data seem to indicate that this risk is limited to a minority of the patients. However, the number of patients with suboptimal exposure was larger in the 800/100 mg q.d group than in the 600/100 mg bid group. Hence, a warning in this regard was added in sections 4.4 and 4.5 of the SmPC for Prezista.

The larger number of patients with suboptimal exposure to q.d regimen compared to the 600/100 mg b.i.d regimen, which might increase the risk of virologic failure due to the development of resistance to DRV and other PIs, remain worrisome. Hence, the RMP was updated accordingly.

3.5.3. Benefit-Risk Conclusion

Based on the review of the clinical efficacy and safety, the CHMP considers that the benefit-risk balance for the variation application EMEA/H/C/707/II/32 for Prezista (darunavir) is positive for a restricted indication for "the treatment of HIV-1 infection in ART-experienced adults with no DRV resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 10^6/l. In deciding to initiate treatment with DRV in such ART-experienced adults genotypic testing should guide the use of DRV."

4. Conclusion

On 20 January 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.