25 September 2014
EMA/664598/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Prezista

International non-proprietary name: DARUNAVIR

Procedure No. EMEA/H/C/000707/II/0063

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 10 January 2014 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Prezista	darunavir	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1, 4.2, 4.5 and 5.1 of the SmPC for the 100mg/ml oral suspension and the 400mg, 800mg film-coated tablets with information on the use of darunavir with cobicistat as pharmacokinetic enhancer. Consequential changes have been introduced in the SmPC and the PL of all formulations. Furthermore, there is a proposed update of the Annex II with a correction to the address of one of the manufacturers responsible for batch release and update of the PL with the local representatives' contact information for France, Romania, Ireland and Cyprus.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/138/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/138/2010 was completed.

The PDCO issued an opinion on compliance for the PIP P/138/2010 and the compliance statement was included in the technical dossier during procedure X-41G.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Greg Markey

Submission date:	10 January 2014
Start of procedure:	25 January 2014
Rapporteur's initial Assessment Report dated:	20 March 2014
Co-Rapporteur's initial Assessment Report	18 March 2014
PRAC Rapporteur's initial Assessment Report	18 March 2014
Rapporteur's updated assessment report circulated on:	18 April 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2014
MAH's responses submitted to the CHMP on:	22 May 2014
PRAC Rapporteur Assessment Report on the MAH's responses circulated on:	5 June 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on :	10 June 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 June 2014
Joint Rapporteur/Co-Rapporteur's assessment report on the MAH's responses circulated on:	20 June 2014
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	26 June 2014
MAH's responses submitted to the CHMP on:	27 July 2014
PRAC Rapporteur's assessment report on the MAH's responses circulated on:	25 August 2014
Joint Rapporteur/Co-Rapporteur's assessment report on the MAH's responses circulated on:	2 September 2014
Final Joint Rapporteur/Co-Rapporteur's updated assessment report on the MAH's responses circulated on:	22 September 2014
CHMP opinion:	25 September 2014

2. Scientific discussion

2.1. Introduction

The current PREZISTA Product Information (PI) states that darunavir (DRV) can only be administered in combination with low-dose ritonavir (rtv) as a pharmacokinetic enhancer (booster): *"PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight (see section 4.2)."*

Tybost, (Cobicistat, COBI) has been registered in September 2013 to be co-administered at a dose of 150 mg as an alternative pharmacokinetic enhancer of DRV 800 mg once daily as part of antiretroviral (ARV) combination therapy in HIV-1 infected adults.

As a consequence, the MAH applies for a type II variation to include the use of Tybost (Cobicistat, COBI) in the SmPC of Prezista, and proposed to add to section 4.1 *"PREZISTA, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients (see section 4.2)."*

In addition, modifications to section 4.2 and all other sections of the SmPC are proposed to include the use of COBI next to that of ritonavir as a booster of DRV.

As such, the SmPC of DRV will reflect that of COBI and allows combination with COBI once daily as an alternative to rtv once daily and in the same indication as the one that is already approved for PREZISTA, i.e. for the treatment of HIV-1 infection in HIV-1 infected treatment-naïve adult subjects and treatment-experienced adult subjects with no DRV resistance-associated mutations (RAMs), and with plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count ≥100x10^6 cells/L.

This type II variation is built on information which has already been reviewed as part of the existing Prezista supplemented with pivotal information to support the use of COBI as alternative booster for DRV: studies GS-US-216-0115 and GS-US-216-0130. The latter study reports are included in this type II variation, in line with the advice obtained from the EMA on 26 September 2013, and have been partly reviewed by CHMP as part of the COBI MAA.

In addition, an application of a new Fixed Dose Combination (FDC) of DRV/COBI is reviewed for the same indication as requested for Prezista.

All study data of GS-US-216-0115 and week 48 study results of GS-US-216-0130 that are now presented in the current AR have already been assessed in the application of the FDC DRV/COBI.

The CHMP proposes to bring all SmPCs in line and to incorporate week 48 efficacy data of study GS-US-216-0130 and week 48 safety data in section 5.1 and section 4.8, respectively, of the SmPC of Prezista, Tybost and the new FDC DRV/COBI once the concerns have been adequately addressed in the FDC DRV/COBI procedure.

2.2. Clinical Pharmacology aspects

As indicated, for this type II variation reference is made to the application of Tybost and is built on information which has already been reviewed as part of the existing Prezista eCTD, supplemented with pivotal information to support the use of COBI as alternative booster for DRV: studies GS-US-216-0115 and GS-US-216-0130. The results of these studies will be here addressed only shortly, as these 2 studies have been assessed before within the context of COBI MAA.

Study GS-US-216-0115

GS-US-216-0115 was an open-label, randomized, 2-period crossover Phase 1 study in 33 healthy subjects to evaluate, under fed conditions, the oral bioavailability of DRV 800 mg when co-administered as single agents with either COBI 150 mg or rtv 100 mg, both of which are PK enhancers of DRV.

The DRV AUC24h and Cmax, were similar for DRV/COBI 800/150 mg once daily and DRV/rtv 800/100 mg once daily (both regimens co-administered as single agents); the 90% confidence intervals (CIs) for the least square (LS) means ratios were contained within the 80.00% to 125.00% bounds. The DRV Ctau was lower in the COBI group compared to the rtv group (mean [SD]: 1,333 [890] ng/ml versus 1,867 [1,555] ng/ml), but this is not expected to be clinically relevant based on pharmacokinetic/pharmacodynamic (PK/PD) analyses of the effect of DRV exposure on virologic response in studies TMC114-C211 and TMC114-C229 with DRV/rtv.

Table PK 1. Pharmacokinetic parameters [mean (%CV)] of DRV following multiple-dose administration with Cobicistat (GS-9350) 150 mg once daily or RTV 100 mg once daily.

DRV Plasma PK Parameters	Treatment A DRV+GS-9350 (N=31)	Treatment B DRV+RTV (N=31)	Geometric Least-Squares Means Ratio (%) of Test/Reference (Treatment A/Treatment B) (90% CI)
C_{max} (ng/mL) Mean (%CV)	7737.1 (21.8)	7464.2 (20.3)	103.36 (100.34, 106.48)
AUC_{tau} (ng·h/mL) Mean (%CV)	81,084.2 (31.0)	79,987.0 (34.0)	101.78 (97.40, 106.36)
C_{tau} (ng/mL) Mean (%CV)	1332.7 (66.8)	1866.7 (83.3)	69.43 (59.02, 81.68)
C_{0h} (ng/mL) Mean (%CV)	2395.5 (50.7)	2483.8 (34.3)	89.39 (80.36, 99.44)

C_{0h}, predose concentration following observed, multiple doses of study drug at steady-state; CI, confidence interval; CV, coefficient of variation; DRV, darunavir; PK, pharmacokinetic; RTV, ritonavir.
Treatment A: DRV (2 × 400 mg tablets) + GS-9350 (1 x 150 mg tablet); Treatment B: DRV (2 × 400 mg tablets) + RTV (1 × 100 mg capsule)
Note: Ratios were estimated as the geometric LSmeans ratio of Test vs. Reference.

This study was also submitted for the application of Cobicistat and will not be discussed here in detail.

Bioequivalent DRV exposures (AUCtau and Cmax) were observed following once-daily dosing of DRV 800 mg + Cobicistat (GS-9350) 150 mg versus DRV 800 mg + RTV 100 mg. The geometric least-squares (GLS) mean ratio for Ctau was lower because of unexpected increasing DRV concentrations at the 24-hour time point in the DRV+RTV treatment. DRV predose concentrations (C0h) following observed, multiple doses of study drug at steady-state were equivalent for both treatments and > 37-fold above the protein-adjusted EC50 for wild-type virus (55 ng/mL). Collectively, the data indicate that cobicistat 150 mg sufficiently boosts DRV similarly to RTV 100 mg.

The combination of darunavir 800 mg and cobicistat 150mg was therefore considered acceptable.

Study GS-US-216-130

Study GS-US-216-130, is an open-label, single arm, multi-centre, study that evaluates the safety and efficacy of a regimen of DRV+COBI (800 mg + 150 mg q.d. with food) plus 2 fully active NRTIs in HIV-1 infected, ARV treatment-naive and treatment- experienced adult subjects with no DRV RAMs (see for further

description the clinical part of this assessment report). Pharmacokinetics were evaluated for DRV, COBI, emtricitabine (FTC) and tenofovir (TFV) (dosed as Truvada 200mg/300mg) based on intensive sampling between Weeks 2 and 8 in a subset of subjects (n = 60) at selected sites (PK sub-study) and a single pharmacokinetic blood sample at all visits through Week 48 is planned for all subjects for patient population pharmacokinetic analysis.

Pharmacokinetic data were obtained form 60 subjects (57 treatment-naïve and 3 treatment-experienced) in the sub-study and 301 subjects (284 treatment-naïve and 17 treatment-experienced) in the overall study.

The steady-state DRV pharmacokinetic parameters following administration of DRV+COBI are shown in table PK 2 and for COBI in table PK 3.

Table PK 2. Summary of darunavir pharmacokinetic parameters in the PK sub-study (PK sub-study analysis set).

DRV PK Parameter[a]	DRV+COBI (N = 59)
AUC_{tau} (ng·h/mL), mean (%CV)	81,645.9 (32.2)
C_{max} (ng/mL), mean (%CV)	7663.2 (25.1)
C_{tau} (ng/mL), mean (%CV)	1310.7 (74.0)
C_{0h} (ng/mL), mean (%CV)	1559.8 (85.1)
T_{max} (h), median (Q1, Q3)	3.50 (2.49, 4.29)
$t_{1/2}$ (h), median (Q1, Q3)	7.24 (5.35, 11.54)

a For C_{max}, n = 60; for T_{max}, n = 60; for C_{tau}, n = 59; for C_{0h}, n = 60; for AUC_{tau}, n = 59, and for $t_{1/2}$, n = 55

Table PK 3. Summary of cobicistat pharmacokinetic parameters in the PK sub-study (PK sub-study analysis set).

COBI PK Parameter[a]	DRV+COBI (N = 59)
AUC_{tau} (ng·h/mL), mean (%CV)	7596.3 (48.1)
C_{max} (ng/mL), mean (%CV)	991.4 (33.4)
C_{tau} (ng/mL), mean (%CV)	32.8 (289.4)
T_{max} (h), median (Q1, Q3)	3.50 (2.01, 4.50)
$t_{1/2}$ (h), median (Q1, Q3)	3.25 (2.91, 3.81)

a For C_{max}, n = 60; for T_{max}, n = 60; for C_{tau}, n = 59; for AUC_{tau}, n = 59, and for $t_{1/2}$, n = 59

The results for darunavir were in line with those observed in study GS-US-216-0115, although in this study the Ctau and C0h values were comparable, while in study -115 C0h was higher than Ctau. Most important is that the lowest darunavir plasma concentrations are comparable.

The results for COBI were in line with those observed in study GS-US-236-0102, -0103, and -0104, i.e. historical data in HIV-1 infected patients, steady-state COBI PK parameters after once-daily administration of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild) in the intensive PK sub-studies (see table below).

COBI	AUC_{tau} [a, b] (ng•h/mL)	C_{max} [c] (ng/mL)	C_{tau} [a, d, e] (ng/mL)
HIV-1 infected Subjects (N = 62)	8300 (46)	1140 (36)	49.1 (260)

As can be observed, the Ctau values of COBI in study GS-US-216-130 were considerably lower than in the combined data used for comparison (i.e. 32.8 vs 49.1 ng/ml). The overall exposure data for DRV with COBI are in line with previous obtained data of DRV boosted with rtv (see below) and do not indicate that the observed lower Ctau for COBI may affect DRV exposure. However it cannot be excluded that due to low COBI Ctau values, also DRV exposure is lower and therefore the likelihood that patients fail increase. This has been raised as a concern in the Tybost/Prezista FDC application and is still under assessment.

The steady-state emtricitabine pharmacokinetic parameters following administration of DRV+COBI are shown in table PK 4.

Table PK 4. Summary of emtricitabine pharmacokinetic parameters in the PK sub-study (PK sub-study analysis set).

FTC PK Parameter[a]	DRV+COBI+TVD (N = 59)
AUC_{tau} (ng·h/mL), mean (%CV)	11,792.7 (29.6)
C_{max} (ng/mL), mean (%CV)	1861.5 (26.4)
C_{tau} (ng/mL), mean (%CV)	112.5 (89.9)
T_{max} (h), median (Q1, Q3)	2.02 (2.00, 3.50)
$t_{1/2}$ (h), median (Q1, Q3)	7.14 (6.44, 7.86)

a For C_{max}, n = 59; for T_{max}, n = 59; for C_{tau}, n = 58; for AUC_{tau}, n = 58, and for $t_{1/2}$, n = 56

Considering the metabolic pathway of emtricitabine, it is expected that the pharmacokinetics are not influenced by DRV/COBI. The results are in line with those indicated for Emtriva, i.e. in 20 HIV infected subjects receiving 200 mg emtricitabine daily as hard capsules, steady-state plasma emtricitabine peak concentrations (Cmax), trough concentrations (Cmin) and area under the plasma concentration time curve over a 24-hour dosing interval (AUC) were 1.8±0.7 µg/ml, 0.09±0.07 µg/ml and 10.0±3.1 µg•h/ml, respectively. Steady-state trough plasma concentrations reached levels approximately 4-fold above the in vitro IC90 values for anti-HIV activity.

The steady-state tenofovir pharmacokinetic parameters following administration of DRV+COBI are shown in table PK 5.

Table PK 5. Summary of tenofovir pharmacokinetic parameters in the PK sub-study (PK sub-study analysis set).

TFV PK Parameter[a]	DRV+COBI+TVD (N = 59)
AUC_{tau} (ng·h/mL), mean (%CV)	3612.8 (33.3)
C_{max} (ng/mL), mean (%CV)	382.4 (30.9)
C_{tau} (ng/mL), mean (%CV)	77.5 (42.5)
T_{max} (h), median (Q1, Q3)	2.00 (1.00, 3.05)
$T_{1/2}$ (h), median (Q1, Q3)	13.34 (11.68, 15.35)

a For C_{max}, n = 59; for T_{max}, n = 59; for C_{tau}, n = 58; for AUC_{tau}, n = 58, and for $t_{1/2}$, n = 56

From study TMC114-C124 it is known that co-administration of DRV/COBI with tenofovir may increase concentrations of tenofovir (inhibition of P-gp) (see table below).

Parameter	Mean (SD); t_{max}: Median (Range) Test	Reference	Test/Reference Least Square Means Ratio, % (90% CI)
	TDF 300 mg qd + DRV/rtv 300/100 mg bid	TDF 300 mg qd	
N	12	12	
t_{max}, h	1.0 (1.0-4.0)	1.5 (0.5-2.5)	-
C_{min}, ng/mL	86.8 (15.7)	65.6 (13.4)	136.6 (119; 157)
C_{max}, ng/mL	528 (106)	423 (75.2)	123.9 (108; 142)
AUC_{24h} ng.h/mL	4,633 (735)	3,789 (499)	121.8 (110; 135)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.

These data are more or less in line with the steady-state mean tenofovir Cmax, AUCtau and Ctrough (mean ± SD) following multiple doses of Stribild in HIV-1 infected subjects, i.e. 0.45 ± 0.16 µg/ml, 4.4 ± 2.2 µg •h/ml, and 0.1 ± 0.08 µg/ml, respectively.

The data from study -130 are lower than reported in the interaction study and for Stribild, however are comparable to the Reference arm in study C124 (tenofovir only). As such, the results of study -130 for tenofovir are not raising a concern.

Patient population pharmacokinetic analyses

Based on a previously developed population PK model for DRV, an updated model was developed using a subset of richly sampled PK data collected in study GS-US-216-0130 (i.e., the PK sub-study). Model parameters were then re-estimated using the rich sampled data available from the Week 24 dataset. All subjects had sparse sampling data for DRV at Week 24, and some subjects had sparse sampling data beyond Week 24. The final model was then used together with those sparse and rich sampled data for the Bayesian feedback analysis to estimate the individual PK parameters (AUC24h and C0h) of DRV. A total of 53 subjects were included in the initial model build dataset, with 55 subjects included in the parameter re-estimation dataset. All subjects with available PK data (298 subjects) were included in the Week-24 Bayesian feedback analysis dataset.

The model build and Bayesian feedback analysis were performed using mixed-effects modelling methods, as implemented in NONMEM (version VII level 2.0). Models were fitted to untransformed data using the first-order conditional estimation method in NONMEM with the INTERACTION option. For the empirical Bayes estimation, MAXEVAL was set to 0.

The best model to describe the PK of DRV was a 2-compartment disposition model with a sequential zero-order-first-order absorption. The effects of total daily dose and AAG on CL/F were retained from the original model. The relative bioavailability term was corrected for the commercial formulation (compared to the tablet used in previous clinical studies), and was fixed to a value of 1.18, as determined in the previously developed model. This allowed CL/F and central volume of distribution (Vc/F) to be directly compared with previous estimates.

Intersubject variability terms were included on the disposition parameters CL/F, Vc/F, and intercompartmental clearance (CLp/F), with an ISV term also included on the zero-order absorption duration parameter D1. The ISV term on the peripheral volume of distribution (Vp/F) was fixed to 55.7 %CV, a value previously determined for DRV. The median prediction error for the model was 2.61%, and the median absolute prediction error was 7.43%. The model was therefore considered acceptable for determination of individual DRV exposure metrics in the Bayesian feedback analysis. Parameter estimates for the final model are shown in table PK 6. No significant covariate was identified so that the final model was the same as the base model.

Table PK 6. Final population PK model parameter estimates of DRV following multiple-dose administration of DRV/COBI 800/150 mg once daily co-administered as single agents in study GS-US-216-0130.

Parameter		Parameter Estimate	Parameter SE (%CV)	ISV Estimate (%CV)	ISV SE (%CV)
CL_{INT}/F (L/h)	θ_1	51.6	3.4	24.9	18.3
Effect of TDD on CL_{INT}/F	θ_2	0.388 [a]	-	-	-
Effect of AAG on CL_{INT}/F (dL/mg)	θ_3	0.030 [a]	-	-	-
V_c/F (L)	θ_4	35.6	19.9	15.6	210
CL_p/F (L/h)	θ_5	24.0	19.4	51.0	34.3
V_p/F (L)	θ_6	90.0	10.4	55.7 FIXED	-
KA (/h)	θ_7	0.393	18.5	-	-
F_{REL}	θ_8	1.18 [a]	-	-	-
D1(h)	θ_9	1.49 [b]	11.1	88.4	27.4
RUV (%CV)	-	18.2	20.5	-	-

CL_{INT} /F=intrinsic clearance; D1=zero-order duration of input; F_{REL}=relative bioavailability; KA=absorption rate constant; RUV=residual unexplained variability; TDD=total daily dose.

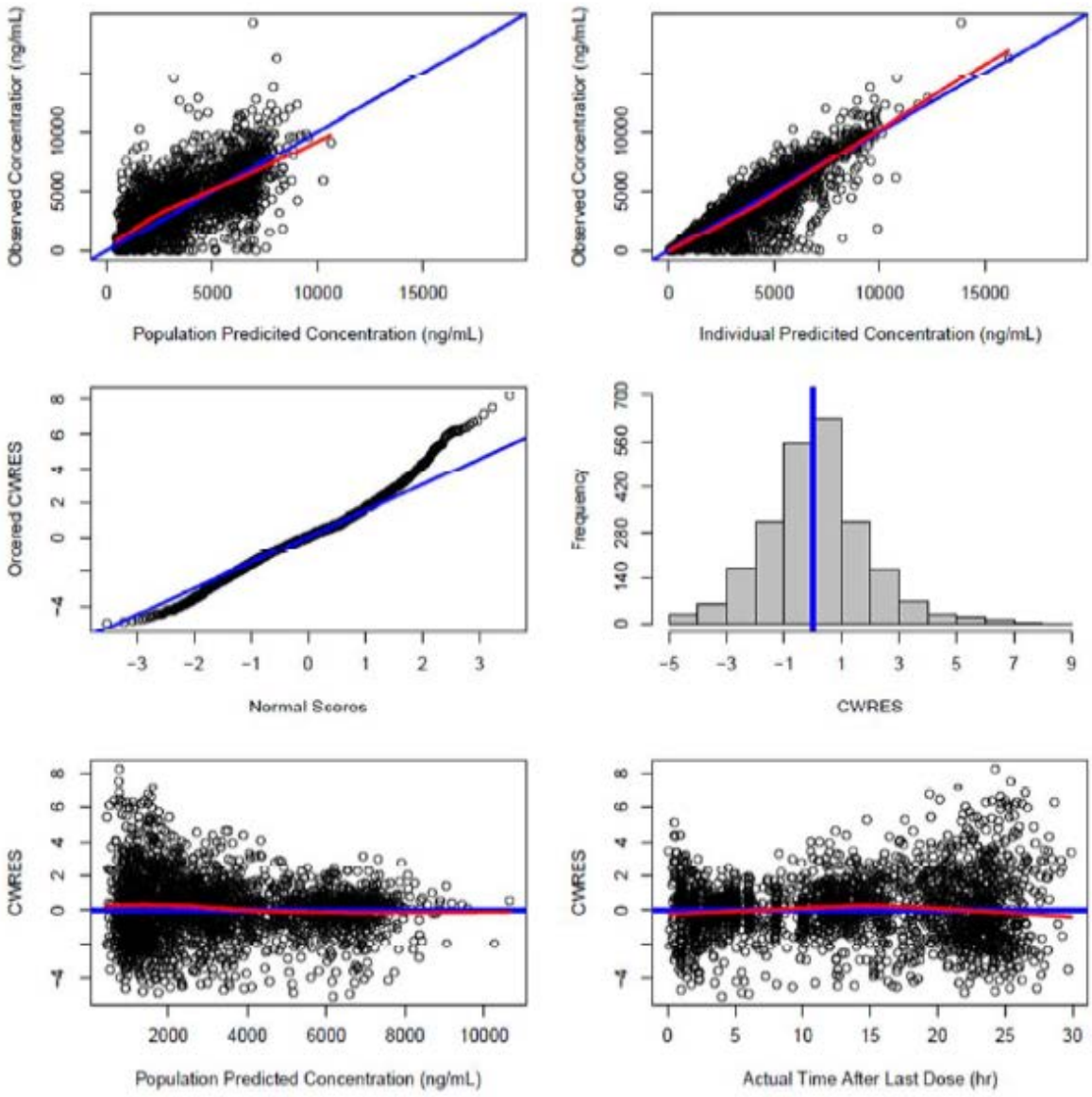
[a] Parameter fixed.

[b] Estimate shown has been converted out of logit domain.

There were a total of 2,364 PK samples available for the Bayesian feedback analysis. The mean (range) number of PK samples per subject was 7.9 (1 to 19). The final model was fitted to the Week-24 Bayesian feedback dataset with parameters fixed to those obtained during the estimation process. Plots of observed versus population predicted plasma concentrations and observed versus individual predicted plasma concentrations of DRV for the Bayesian feedback at Week 24 were similar to the plots for the final model and showed no obvious bias (figure PK 1). However, the distribution of observations around the line of unity when compared to individual predicted concentrations was wider for the final model, suggesting that the model was less precise when applied to this dataset. The conditional weighted residuals were evenly distributed, with no skewness. A visual predictive check showed that the model adequately described the data (figure PK 2).

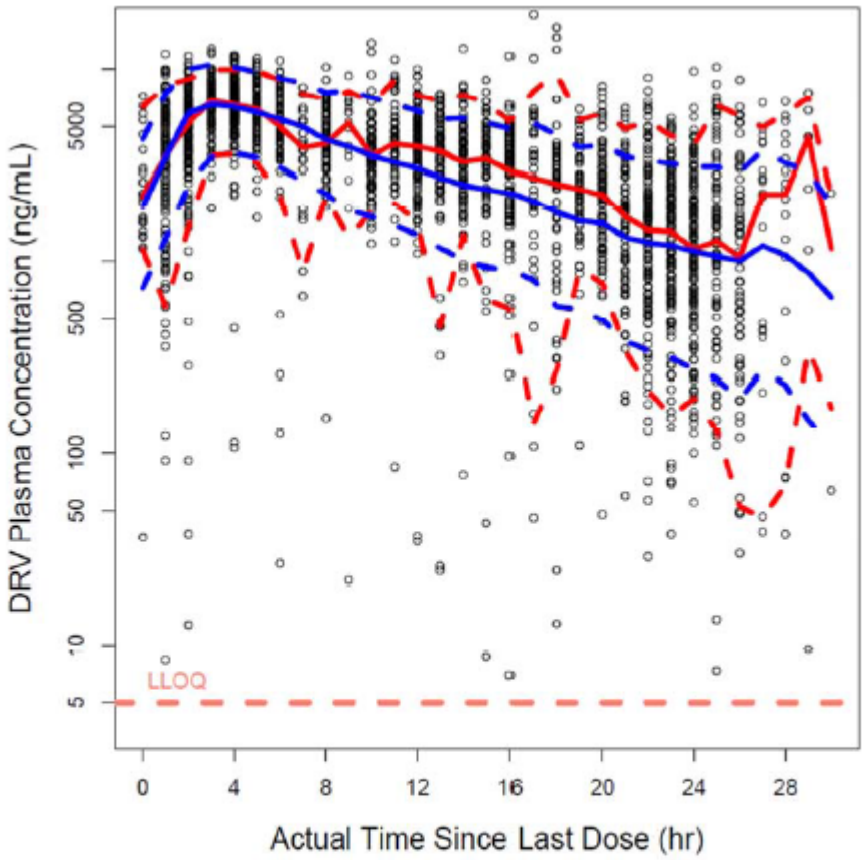
The median prediction error and median absolute prediction error for the model when fitted to the Bayesian feedback dataset were -1.83% and 17.3%, respectively. This indicated that the model was suitable for determination of individual DRV exposure metrics.

Figure PK 1. Goodness of fit plots for the updated population PK model of study GS-US-216-0130 at Week 24.



CWRES=conditional weighted residual.
The blue solid line in the top panel represents the line of unity with the solid red line representing a smoother of the data.

Figure PK 2. Visual predictive check for the Bayesian feedback at Week 24.



Black circles=observed data; lower and upper red dashed lines=5th and 95th percentiles for the observed data; red solid line=50th percentile for the observed data; lower and upper blue dashed lines=5th and 95th percentiles for the simulated data; blue solid line=50th percentile for the simulated data; dashed horizontal pink line=lower limit of quantification.

The population PK parameter estimates for DRV are summarized in table PK 7.

Table PK 7. Population PK parameter estimates for DRV following multiple-dose administration of DRV/COBI 800/150 mg once daily co-administered as single agents + background regimen in HIV-1 infected subjects (Study GS-US-216-0130).

Parameter	Mean (SD); Median (Range)
N	298
C_{0h}, ng/mL	2,043 (1,257)
	1,875 (70-6,890)
AUC_{24h}, ng.h/mL	100,152 (32,042)
	96,900 (34,500-224,000)

N=maximum number of subjects with data.

Further covariates that were assessed for their potential to explain variability in the PK of DRV included age, height, weight, body surface area, body mass index, creatinine clearance, sex, and race. Graphical analyses between individual parameters and these covariates suggested that age and sex may explain some of the variability in CL/F, although no significant covariate could be identified during the model building process. Similar findings were also observed for Vp/F.

It is commented by CHMP that the model developed in this analysis was similar to the previously developed model based on DRV/RTV, with the primary difference associated with the absorption process. The previous model included a single first-order parameter to describe absorption, whereas the model presented in this analysis described absorption via a sequential zero-order-first-order process. In addition, the BSV term on KA in the previous model was replaced with a BSV term on D1. Finally, the correlation between Vc/F and KA in the previous model was removed. Parameter estimates for the updated model in this analysis, together with the previously developed model using data with DRV boosted RTV, are shown in the table below. All fixed effects parameters were similar, excluding Vc/F, which was estimated to be 35.6 l in this analysis compared to 122 l in the previous analysis. In case the prior model was fitted to the model development dataset, Vc/F was estimated at 37.1 l, suggesting that the final estimate obtained was driven by the data, rather than the model (possibly due to the fact that the data were modelled at steady-state, which is in contrast to the original model development).

Comparison of parameter estimates between prior and current models.

Parameter	Updated Model		Prior Model[1]	
	Parameter Estimate SE (CV%)	BSV Estimate (CV%) SE (CV%)	Parameter Estimate SE (CV%)	BSV Estimate (CV%) SE (CV%)
CL_{INT}/F (L/hr)	51.6 (3.4)	24.9 (18.3)	41.9 (13)	26 (8)
Effect of TDD on CL_{INT}/F	0.388*		0.388 (8.8)	
K_{AFF} of AAG (dL/mg)	0.0304*		0.0304 (18)	
V_c/F (L)	35.6 (19.9)	15.6 (210)	122 (8.2)	88 (23)
CL_p/F (L/hr)	24.0 (19.4)	51.0 (34.3)	15.0 (11)	65 (30)
V_p/F (L)	90.0 (10.4)	55.7 FIX	84.3 (11)	56 (36)
KA (/hr)	0.393 (18.5)		0.455 (8.1)	74 (17)
F_{REL}	1.18*		1.18 (1.6)	
D1(hr)	1.49 (11.1)	88.4 (27.4)		
R (V_c/F, KA)			0.61	
RUV (CV%)	18.2 (20.5)		34.9 (4.2)	

CLINT /F = intrinsic clearance, TDD = total daily dose, AAG = alpha-1 acid glycoprotein concentration, Vc/F = central volume of distribution, CLp/F = inter-compartmental clearance, Vp/F = peripheral volume of distribution, KA = absorption rate constant, FREL = relative bioavailability, D1 = zero-order duration of input, R = correlation between parameters, RUV = residual unexplained variability, * = parameter fixed, BSV = between subject variability, SE = standard error of the estimate, CV% = percent coefficient of variation.

The predicted pharmacokinetics for darunavir are in line with those observed in study C211 and C229 (Prezista; HIV-infected patients).

	PK Parameter	GS-US-216-0130 DRV 800 mg + COBI 150 mg (N = 298) QD	TMC114-C211[a] DRV 800 mg + RTV 100 mg (N = 335) QD	TMC114-C229[a] DRV 800 mg + RTV 100 mg (N = 280) QD
AUC_{24h} (ng·h/mL)	Mean (SD)	100152 (32042)	93026 (27050)	93334 (28626)
	Median (Range)	96900 (34500-224000)	87854 (45000-219240)	87788 (45456-236920)
C_{0h} (ng/mL)	Mean [SD]	2043 (1257)	2282 (1168)	2160 (1201)
	Median [Range]	1875 (70-6890)	2041 (368-7242)	1896 (184-7881)

2.2.1. Discussion

Study was 0115 was also submitted for the application of Cobicistat and hence is not discussed in detail in current variation.

Bioequivalent DRV exposures (AUCtau and Cmax) were observed following once-daily dosing of DRV 800 mg + Cobicistat (GS-9350) 150 mg versus DRV 800 mg + RTV 100 mg. The geometric least-squares (GLS) mean ratio for Ctau was lower because of unexpected increasing DRV concentrations at the 24-hour time point in the DRV+RTV treatment. DRV predose concentrations (C0h) following observed, multiple doses of study drug at steady-state were equivalent for both treatments and > 37-fold above the protein-adjusted EC50 for wild-type virus (55 ng/mL). Collectively, the data indicate that cobicistat 150 mg sufficiently boosts DRV similarly to RTV 100 mg.

The combination of darunavir 800 mg and cobicistat 150mg was therefore considered acceptable.

Regarding study 0130, the results for darunavir were in line with those observed in study GS-US-216-0115, although in this study the Ctau and C0h values were comparable, while in study -115 C0h was higher than Ctau. Most important is that the lowest darunavir plasma concentrations are comparable.

The results for COBI were in line with those observed in study GS-US-236-0102, -0103, and -0104, i.e. historical data in HIV-1 infected patients, steady-state COBI PK parameters after once-daily administration of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild) in the intensive PK sub-studies (see table below).

COBI	AUC_{tau} [a, b] (ng•h/mL)	C_{max} [c] (ng/mL)	C_{tau} [a, d, e] (ng/mL)
HIV-1 infected Subjects (N = 62)	8300 (46)	1140 (36)	49.1 (260)

As can be observed, the Ctau values of COBI in study GS-US-216-130 were considerably lower than in the combined data used for comparison (i.e. 32.8 vs 49.1 ng/ml). The overall exposure data for DRV with COBI are in line with previous obtained data of DRV boosted with rtv and do not indicate that the observed lower Ctau for COBI may affect DRV exposure. However it could not be excluded that due to low COBI Ctau values, also DRV exposure is lower and therefore the result in higher likelihood that patients' therapy fail (see further discussion under "efficacy") . This issue has also been raised as a concern in the Tybost/Prezista FDC application.

With respect to patient population pharmacokinetic analyses, as discussed in detail, the model developed in this analysis was similar to the previously developed model based on DRV/RTV, with the primary difference associated with the absorption process.

2.3. Clinical Efficacy aspects

With DRV/COBI 800/150 mg once daily, similar DRV exposures are targeted as with the reference treatment DRV/rtv 800/100 mg once daily that was used in the

TMC114-C211 (ARTEMIS) study in treatment naïve patients and

TMC114 C229 (ODIN) study in treatment experienced patients,

With similar DRV exposures comparable outcomes in HIV-1 infected ART-naïve adults and in ART-experienced adults (without DRV RAMs and with plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥ 100x106 cells/L) can be expected of DRV/COBI, as well.

ART-naïve subjects: DRV/RTV 800/100 mg once daily

The randomized, active-controlled, open-label Phase 3 study TMC114-C211 compared DRV/rtv 800/100 mg once daily (n=343) with LPV/rtv 800/200 mg per day (given as a twice daily or as a once daily regimen) (n=346). Both arms used a fixed background regimen consisting of TDF 300 mg once daily and FTC 200 mg once daily.

Table E1: Virologic Response (<50 Copies/mL, TLOVR) in the Week-48 and Week-192 Analyses of Study TMC114-C211

	At Week 48[a]			At Week 192[b]		
Outcomes	**DRV/rtv 800/100 mg qd N = 343**	**LPV/rtv 800/200 mg per day N = 346**	**Treatment Difference (95% CI of Difference)**	**DRV/rtv 800/100 mg qd N = 343**	**LPV/rtv 800/200 mg per day N = 346**	**Treatment Difference (95% CI of Difference)**
HIV-1 RNA <50 Copies/mL, n (%)	287 (83.7%)	271 (78.3%)	5.3% (-0.5; 11.2)[c]	236 (68.8%)	198 (57.2%)	11.6% (4.4; 18.8)[c]

N=total number of subjects; n=number of observations; qd= once daily; CI=confidence interval.

[a] Data based on analyses at Week 48, intent-to-treat (ITT) population.

[b] Data based on analyses at Week 192, ITT population.

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

The noninferiority of DRV/rtv versus LPV/rtv was demonstrated (at the predefined 12% noninferiority margin; p<0.001). The Week 192 analysis demonstrated sustained efficacy of the DRV/rtv arm: virologic response was 68.8% and 57.2% in the DRV/rtv and LPV/rtv arms, respectively.

ART-experienced subjects: DRV/RTV 800/100 mg once daily

Study TMC114-C229 was a randomized, open label study comparing DRV/rtv 800/100 mg once daily (n=294) to DRV/rtv 600/100 mg twice daily (n=296) in HIV 1 infected treatment experienced subjects with screening genotype resistance testing showing no DRV RAMs, a viral load of >1,000 HIV 1 RNA copies/mL and a CD4+ cell count >50x106 cells/L at screening. Both arms used an optimized background regimen consisting of ≥ 2 NRTIs selected by the investigator.

Table E2: Virologic Response (<50 Copies/mL, TLOVR) in the Week-48 Analysis of Study TMC114-C229

Outcomes	DRV/rtv 800/100 mg qd + OBR N=294	DRV/rtv 600/100 mg bid + OBR N=296	Treatment Difference % (95% CI of Difference)
HIV-1 RNA <50 Copies/mL, n (%)[a]	212 (72.1)	210 (70.9)	1.2 (-6.1; 8.5)[b]

N=total number of subjects; n=number of observations; qd= once daily; bid=twice daily; OBR=optimized background regimen.

[a] Imputations according to the TLOVR algorithm, ITT population.

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

The noninferiority of DRV/rtv once daily versus DRV/rtv twice daily was demonstrated (at the predefined 12% noninferiority margin; p<0.001).

DRV/COBI 800/150 mg Once Daily

In the ongoing, single-arm, multicenter, Phase 3b study GS-US-216-0130, n=313 HIV-1 infected adult subjects (295 ART-naïve and 18 ART experienced with no DRV RAMs) are treated for a period of at least 48 weeks with DRV/COBI 800/150 mg once daily, and 2 fully active NRTIs.

The primary objective is to evaluate the safety and tolerability of DRV/COBI 800/150 mg plus 2 NRTIs in the studied population through 24 weeks of treatment. The secondary objectives are to assess the safety and tolerability of the regimen through 48 weeks of treatment, the efficacy of the regimen as determined by a virologic response of HIV-1 RNA <50 copies/mL at Weeks 24 and 48 of treatment, and the change from baseline in CD4+ cell counts at Weeks 24 and 48.

The overall median (range) duration of exposure to study medication was 31.4 weeks (0.1 to 42.4 weeks), with a median exposure of 31.9 weeks in the treatment-naïve subjects and a median exposure of 26.6 weeks in treatment-experienced subjects.

The majority of subjects received TDF-based ARV medication during the study (99.7% of treatment-naïve subjects and 94.4% of treatment-experienced subjects)

The majority of subjects were male (90.2% in the treatment naïve subgroup, 72.2% in the treatment-experienced subgroup) and most were white (59.7% and 61.1%, respectively) or black (34.2% and 38.9%, respectively). The median age was 34 years (range 18 to 72 years) for treatment-naïve subjects and 48 years (range 22 to 69 years) for treatment-experienced subjects.

For subjects in the treatment-naïve subgroup, the mean baseline log10 HIV-1 RNA value was 4.8 copies/mL, the mean baseline CD4+ cell count was 378x106 cells/L and 15.9% of subjects had a CD4+ cell count ≤ 200x106 cells/L. The majority of subjects (81.7%) had asymptomatic HIV-1 infection, 8.8% of subjects had symptomatic HIV 1 infection, and 9.5% were diagnosed with AIDS.

The baseline disease characteristics in the treatment-experienced subgroup reflected a more advanced stage of HIV 1 disease, the mean (SD) baseline log10 HIV-1 RNA value was 4.8 (0.76) copies/mL, the mean baseline CD4+ cell count was 198 (214)x106 cells/L and 66.7% of subjects had a CD4+ cell count ≤ 200x106 cells/L. The median number of years since HIV diagnosis was 8.5 years (range 2 to 24 years).

Table E3: Baseline Disease and Baseline Resistance Characteristics – GS-US-216-0130 Week-24 Analysis

	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Baseline Disease Characteristics			
HIV-1 RNA, log_{10} Copies/mL			
Mean (SD)	4.8 (0.76)	4.8 (1.04)	4.8 (0.78)
Median (Range)	4.8 (2.6 – 7.0)	5.0 (2.7 – 6.8)	4.8 (2.6 – 7.0)
HIV-1 RNA Category, n (%)			
≤100,000 Copies/mL	173 (58.6)	9 (50.0)	182 (58.1)
>100,000 Copies/mL	122 (41.4)	9 (50.0)	131 (41.9)
CD4+ Cell Count, $x10^6$ Cells/L			
Mean (SD)	378.2 (199.94)	197.8 (214.30)	367.8 (204.79)
Median (Range)	370.0 (6 – 1473)	107.0 (5 – 643)	361.0 (5 – 1473)
Subjects with CD4+ Cell Count, n (%			
≤200x10^6 Cells/L	47 (15.9)	12 (66.7)	59 (18.8)
201 to 500x10^6 Cells/L	179 (60.7)	3 (16.7)	182 (58.1)
>500x10^6 Cells/L	69 (23.4)	3 (16.7)	72 (23.0)
Years Since HIV Diagnosis			
Mean (SD)	NA	10.8 (7.13)	NA
Median (Range)	NA	8.5 (2.0 - 24.0)	NA
HIV Disease Status, n (%)			
Asymptomatic	241 (81.7)	10 (55.6)	251 (80.2)
Symptomatic	26 (8.8)	2 (11.1)	28 (8.9)
AIDS	28 (9.5)	6 (33.3)	34 (10.9)

Up to Week 24, the mean percentage adherence to the prescribed DRV 800 mg and COBI 150 mg pills was 99.2% in treatment-naïve subjects and 97.3% in treatment-experienced subjects.

In the treatment-naïve subgroup, virologic response at Week 24 was reached by 247 subjects (83.7%; 95% CI: 79.0% to 87.8%). There were 29 subjects (9.8%) with virologic failure. Of the 17 subjects with virologic failure due to HIV-1 RNA ≥50 copies/mL at Week 24, 14 were still receiving study medication at Week 36 with HIV-1 RNA levels available in 10 subjects. Of these 10 subjects, 6 had HIV-1 RNA levels <50 copies/mL.

Few treatment-experienced subjects were enrolled in the study (n=18), and virologic response at Week 24 in this subgroup was reached by 11 subjects (61.1%; 95% CI 35.7% to 82.7%).

Table E4: Proportion of Subjects With HIV-1 RNA Levels <50 Copies/mL (Snapshot Analysis) – GS-US-216-0130 Week-24 Analysis

HIV-1 RNA Category, Number of Subjects, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Virologic Response at Week 24			
HIV-1 RNA <50 Copies/mL	**247 (83.7)**	**11 (61.1)**	**258 (82.4)**
95% CIs[a]	79.0% to 87.8%	35.7% to 82.7%	77.8% to 86.5%
Virologic Failure at Week 24	**29 (9.8)**	**7 (38.9)**	**36 (11.5)**
HIV-1 RNA ≥50 Copies/mL	17 (5.8)	5 (27.8)	22 (7.0)
Discontinued due to Lack of Efficacy	0	0	0
Discontinued due to Other Reasons and Last Available HIV-1 RNA ≥50 Copies/mL	12 (4.1)	2 (11.1)	14 (4.5)
No Virologic Data in Week-24 Window[b]	**19 (6.4)**	**0**	**19 (6.1)**
Discontinued due to Adverse Event/Death	14 (4.7)	0	14 (4.5)
Discontinued due to Other Reasons and Last Available HIV-1 RNA <50 Copies/mL	3 (1.0)	0	3 (1.0)
Missing Data During Window but on Study Medication	2 (0.7)	0	2 (0.6)

In sensitivity analyses these results were confirmed:

Table E5: Sensitivity Analyses for the Proportion of Subjects With HIV-1 RNA Levels <50 Copies/mL at Week 24 – GS-US-216-0130 Week-24 Analysis

Analysis/Imputation Method Number (%) of Responders HIV-1 RNA Levels <50 Copies/mL	Treatment-naïve		Treatment-experienced		All Subjects	
TLOVR	N=295	232 (78.6)	N=18	8 (44.4)	N=313	240 (76.7)
Missing=Excluded	N=267	250 (93.6)	N=16	11 (68.8)	N=283	261 (92.2)
Missing=Failure	N=295	250 (84.7)	N=18	11 (61.1)	N=313	261 (83.4)
Last Observation Carried Forward	N=282	253 (89.7)	N=17	11 (64.7)	N=299	264 (88.3)

At Week 24, the mean (SD) increase from baseline in CD4+ cell count in the treatment-naïve subgroup was +145 (131.6)x 10^6 cells/L (M=E analysis), and 133 (135.4)x10^6 cells/L (LOCF analysis). In the treatment-experienced subgroup, the mean (SD) increase from baseline in CD4+ cell count was +99 (161.9)x 10^6 cells/L (M=E analysis), and 88 (155.4)x10^6 cells/L (LOCF analysis).

Comparison of DRV/RTV and DRV/COBI week 24 efficacy results

In treatment-naïve subjects, response rates in study GS-US-216-0130 were comparable to those in study TMC114-C211. In treatment-experienced subjects, response rates were 61.1% in study GS-US-216-0130 and 70.1% in study TMC114-C229.

Table E6: Virologic Responses and Change From Baseline in CD4+ Cell Count – Week-24 Analyses of Studies GS-US-216-0130, DRV/rtv 800/100 mg Once Daily Arm of TMC114-C211, and TMC114-C229

	Treatment–naïve Subjects		Treatment–experienced Subjects	
Efficacy Parameter	**TMC114-C211 DRV/rtv 800/100 mg qd N=343**	**GS-US-216-0130 DRV/COBI Single Agents 800/150 mg qd N=295**	**TMC114-C229 DRV/rtv 800/100 mg qd N=294**	**GS-US-216-0130 DRV/COBI Single Agents 800/150 mg qd N=18**
Virologic Response (Snapshot)				
HIV-1 RNA <50 Copies/mL, n (%)	280 (81.6)	247 (83.7)	206 (70.1)	11 (61.1)
Virologic Response (TLOVR)				
HIV-1 RNA <50 Copies/mL, n (%)	273 (79.6)	232 (78.6)	201 (68.4)	8 (44.4)
Log_{10} Viral Load (Copies/mL) [a]				
Mean (SD) Change From Baseline	-3.11 (0.67)	-3.00 (0.79)	-2.09 (1.08)	-2.56 (1.46)
CD4+ Cell Count ($x10^6$ cells/L) [a]				
Mean (SD) Change From Baseline	+142 (113)	+145 (131.6)	+83 (123)	+99 (161.9)

PK-PD relationship

In HIV-infected treatment-naïve subjects of study TMC114-C211 there was no apparent relationship between DRV exposure and virologic response. Similarly, in treatment-naïve subjects receiving DRV/COBI there was no apparent relationship between the decrease in log_{10} plasma viral load from baseline at Week 24 and DRV exposure.

In treatment experienced patients receiving DRV/RTV the virologic response was not related to DRV exposure, as well, although unexpectedly higher DRV exposures seemed to result in smaller decreases of viral load. In DRV-COBI the number of 18 patients was too limited to draw conclusions.

Resistance

In the Week-192 analysis of the TMC114-C211 study, the proportion of virologic failures (based on viral load ≥50 copies/mL; ITT – TLOVR non-virologic failure [non-VF] censored) in the group of subjects receiving DRV/rtv 800/100 mg once daily was 16.0%. None of the developing mutations in 4 subjects with PI RAMs were primary (ie, major) PI mutations. . In 4 virologic failures a maximum of 2 developing (IAS-USA) NRTI RAMs were observed.

In the Week-48 analysis of the TMC114-C229 study, the proportion of virologic failures (based on viral load ≥50 copies/mL; ITT – TLOVR non-VF censored) in the DRV/rtv 800/100 mg once daily group was 22.1%, from whom 7 subjects (12%) developed (IAS-USA) PI RAMs. One virologic failure developed primary (ie, major) PI mutations, which included 3 DRV RAMs, resulting in decreased susceptibility to DRV. Four (6.7%) virologic failures developed 1 or 2 (IAS-USA) NRTI RAMs with 3 from 4 acquiring decreased susceptibility to a NRTI included in the treatment regimen. Of the viruses isolated from subjects receiving DRV/rtv 800/100 mg once daily and experiencing virologic failure in the TMC114-C229 study, 98% remained susceptible to DRV after treatment.

DRV-COBI: Of the 313 subjects who received at least 1 dose of the study medication DRV/COBI 800/150 mg once daily, 10 met the criteria for post baseline resistance analysis: 5 treatment-naïve subjects (1 confirmed suboptimal virologic response, 2 virologic rebounds, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit) and 5 treatment-experienced subjects (1 confirmed suboptimal virologic response, 2 virologic rebounds, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit). No genotypic and phenotypic resistance development was seen in the ART-naïve subjects. One ART-experienced subject had developed a DRV RAM at position I84 as a mixture with WT (I84I/V) without consequences for phenotypic resistance testing. No other PI RAMs or NRTI RAMs were recorded.

2.3.1. Supplementary analyses

1. Treatment outcomes for treatment-naive subjects by baseline viral load category at W 24-48 (- 0130)

Treatment outcomes in study GS-US-216-0130 for treatment-naive subjects by baseline viral load category in the FDA-defined snapshot analysis, both at Week 24 and Week 48, are presented in next Table.

While in the Week-24 analysis, there was a 10% difference in the response rates between subjects with a baseline viral load ≤100,000 copies/mL (87.9%) versus subjects with a baseline viral load >100,000 copies/mL (77.9%), this difference was only 2.7% in the Week-48 analysis. The response rate increased in the subjects with baseline viral load >100,000 copies/mL from 77.9% to 81.1%, because additional subjects achieved virologic response between Week 24 and Week 48. Some subjects with a high viral load at baseline need a period longer than 24 weeks to reach undetectable levels, and therefore may still become a responder between Week 24 and Week 48.

Similar results were seen in study TMC114-C211 where at the Week-24 time point (Week-48 analysis), there was 18.3% difference in the response rates (time to loss of virologic response imputation method used) between subjects with a baseline viral load ≤100,000 copies/mL (85.8%) versus subjects with a baseline viral load >100,000 copies/mL (67.5%). This difference was only 6.3% at the Week-48 time point (Week-48 analysis) due to an increase in response rate from 67.5% at Week 24 to 79.5% at Week 48 in the subjects with baseline viral load >100,000 copies/mL.

Table E7

Table 1: Treatment Outcomes for Treatment-naïve Subjects at Weeks 24 and 48 by Baseline Viral Load Category (Snapshot Analysis) – GS-US-216-0130 Week-24 and Week-48 Analyses

	Week 24 (Week-24 Analysis)		Week 48 (Week-48 Analysis)	
	Treatment-naïve N=295		Treatment-naïve N=295	
HIV-1 RNA Category, Number of Subjects, n (%)	**HIV-1 RNA ≤100,000 copies/mL N=173**	**HIV-1 RNA >100,000 copies/mL N=122**	**HIV-1 RNA ≤100,000 copies/mL N=173**	**HIV-1 RNA >100,000 copies/mL N=122**
Virologic Response				
HIV-1 RNA <50 Copies/mL	**152 (87.9)**	**95 (77.9)**	**145 (83.8)**	**99 (81.1)**
95% CIs[a]	82.0 to 92.3	69.5 to 84.9	77.5 to 89.0	73.1 to 87.7
Virologic Failure	**6 (3.5)**	**23 (18.9)**	**8 (4.6)**	**16 (13.1)**
HIV-1 RNA ≥50 Copies/mL	1 (0.6)	16 (13.1)	2 (1.2)	7 (5.7)
Discontinued due to Lack of Efficacy	0	0	0	0
Discontinued due to Other Reasons and Last Available HIV-1 RNA ≥50 Copies/mL	5 (2.9)	7 (5.7)	6 (3.5)	9 (7.4)
No Virologic Data in Week 24 or 48 Window[b]	**15 (8.7)**	**4 (3.3)**	**20 (11.6)**	**7 (5.7)**

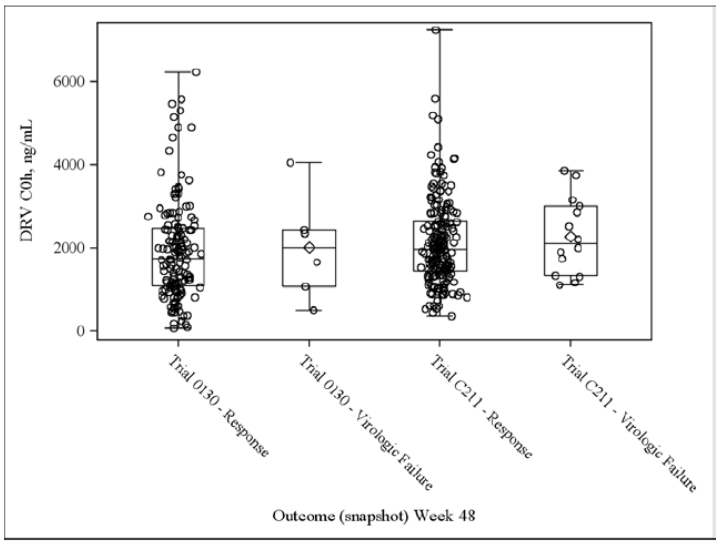
N=total number of subjects; n=number of observations.
[a] 95% CI is the 2-sided exact 95% CI for binomial proportions.
[b] Week-24 window: 20-30 weeks; Week 48 window: 42-54 weeks.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 4.2.1.1 and Module 5.3.5.2/GS-US-216-0130-Anal-W48-EFF/Table 4.2.1.4

When looking at the darunavir (DRV) predose plasma concentration (C0h) based on population pharmacokinetics, subjects with baseline viral load ≤ 100,000 copies/mL versus subjects with baseline viral load >100,000 copies/mL who were virologic failures at Week 48 had similar exposure (Figure 1 and Figure 2). Also in earlier studies with DRV boosted with low-dose ritonavir (rtv), there was no relevant relationship between DRV C0h and virologic outcome (see Week-48 results from studies TMC114-C211 and

TMC114-C229 in Module 5.3.5.1). Descriptive statistics for DRV C0h by response are provided in Appendix 1 and Appendix 2.

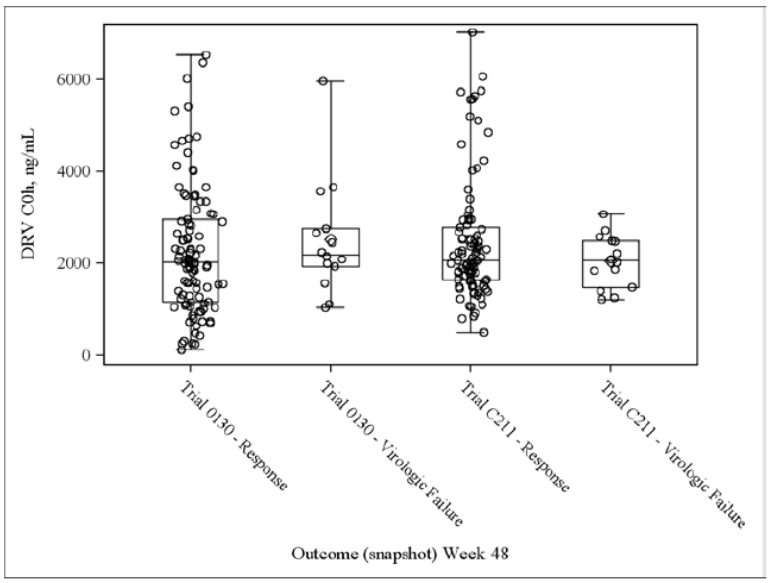
The Week-48 population pharmacokinetics of the treatment-naïve HIV-1 infected adults treated with DRV/rtv 800/100 mg once daily of the Phase 3b study TMC114-C211 showed that subjects both with baseline viral load ≤ 100,000 copies/mL and with baseline viral load >100,000 copies/mL who were virologic failures had similar C0h compared to subjects who responded (Figure 1 and Figure 2). Furthermore, DRV C0h was similar between subjects who failed virologically with baseline viral ≤ 100,000 copies/mL versus those who failed virologically with baseline viral load >100,000 copies/mL load (Figure 1 and Figure 2).

Figure 1: **Darunavir C_{0h} by Response (Snapshot) for Treatment-naïve Subjects With Baseline Viral Load ≤100,000 Copies/mL - GS-US-216-0130 and TMC114-C211 Week-48 Analysis**



The boxplots represent Q1, median, and Q3. The whiskers represent the minimum and maximum value. The diamond represents the mean.

Figure 2: **Darunavir C_{0h} by Response (Snapshot) for Treatment-naïve Subjects With Baseline Viral Load >100,000 Copies/mL - GS-US-216-0130 and TMC114-C211 Week-48 Analysis**



The boxplots represent Q1, median, and Q3. The whiskers represent the minimum and maximum value. The diamond represents the mean.

2. DRV trough levels will exceed its EC50 of both wild type virus or PI resistant HIV-1 strains in case of switch from EFV-containing regimens to DRV/COBI.

As indicated in Table below, overall, the DRV exposures (C0h, area under the plasma concentration time curve [AUC]) in human immunodeficiency virus type 1 (HIV-1) infected subjects are comparable when boosted by cobicistat (COBI) versus rtv, and the efficacy and safety findings from study GS-US-216-0130 were consistent with those from registration studies with rtv-boosted DRV (see Module 2.7.4/Summary of Clinical Safety dated 13 December 2013).

Table E8

Table 2: Darunavir Pharmacokinetic Parameters from GS-US-216-0130 (COBI-Boosted) Compared to Those From Other Registrational Studies With Ritonavir-Boosting

Pharmacokinetic Parameter		GS-US-216-0130 DRV/COBI 800/150 mg qd (N=298)	TMC114-C211[a] DRV/rtv 800/100 mg qd (N=335)	TMC114-C229[a] DRV/rtv 800/100 mg qd (N=280)
AUC_{24h} (ng.h/mL)	Mean (SD)	100,152 (32,043)	93,026 (27,050)	93,334 (28,626)
	Median (Range)	96,900 (34,500-224,000)	87,854 (45,000-219,240)	87,788 (45,456-236,920)
C_{0h} (ng/mL)	Mean (SD)	2,043 (1,257)	2,282 (1,168)	2,160 (1,201)
	Median (Range)	1,875 (70-6,890)	2,041 (368-7,242)	1,896 (184-7,881)

qd=once daily; rtv=low-dose ritonavir; SD=standard deviation

[a] From DRV registrational studies TMC114-C211 (ARTEMIS) and TMC114-C229 (ODIN), included in Module 5.3.5.1.

Furthermore, DRV plasma concentrations when boosted by COBI are anticipated to be on the plateau of the concentration-response curve and are far above the protein-binding corrected 50% effective concentration (EC50): the mean DRV C0h in HIV-infected subjects in study GS-US-216-0130 was >37-fold above the protein binding corrected EC50 for wild-type virus (55 ng/mL). The EC50 of protease inhibitor (PI) resistant virus is not considered relevant for the patient population treated with DRV/COBI as patients should be either treatment-naïve or treatment-experienced with no DRV resistance-associated mutations (ie, fully susceptible to DRV and all or almost all PIs). In none of the registrational studies, including study GS-US-216-0130 with boosted DRV, there has been any indication of a relevant exposure-response relationship for DRV pharmacokinetics.

In the clinical setting where patients would switch from an efavirenz (EFV)-based regimen to DRV/COBI, there will be residual inductive effects of EFV on cytochrome P450 (CYP) enzymes during the first weeks after the switch. For COBI, the impact on the exposure has been shown to be only modest: 10 to 20% lower COBI AUC was observed in 1 to 2 weeks following switch from Atripla (ATR) to STRIBILD® (STB) in Phase 1 study GS-US-236-0120.4

For DRV, any initial lower DRV exposure after a switch from an EFV-based regimen has not been quantitatively evaluated. It is anticipated to be no more than 15 to 30% during a limited time period, as the decrease in DRV exposure when DRV/rtv was given concomitantly with EFV was 31% for minimum plasma concentration (Cmin), and 13% for AUC. Overall, and despite the lack of data to allow for a detailed quantitative assessment of the effects, given that COBI boosted DRV concentrations are well above the wild-type EC50 as stated above (>37-fold), it is anticipated that DRV concentrations would still be well above this value even in the presence of some residual CYP3A inducing effect after a switch from an EFV-based regimen.

The antiviral activity of DRV during the switch period is also bolstered by the activity of the nucleoside/nucleotide reverse transcriptase inhibitor background regimen, which is not impacted by CYP3A induction. Furthermore, in subjects switching from EFV for reasons other than virologic failure, although initially after switch the DRV exposure could be somewhat lower than that in the absence of a preceding EFV treatment, an impact of this on antiviral activity would be expected to be offset by the activity of the remaining EFV concentrations during the first weeks after switch, as shown for other antivirals in a switch scenario,1 due to the long EFV elimination half-life of ~50 hours (mean EFV concentrations were above the 90% inhibitory concentration for 5 weeks following switch from ATR to STB in Phase 1 study GS-US-236-01204 and also in a switch study to Complera3).

In Table E9, the antiretroviral (ARV) use just before switching to DRV/COBI is shown for the 18 treatment-experienced subjects either failing or responding at Week 48 in study GS-US-216-0130. Of the 9 treatment-experienced subjects who failed at Week 48 (snapshot), 1 subject had stopped EFV 30 days prior to when DRV/COBI was started. As the CYP3A inducing effect of EFV is anticipated to have largely reverted within 30 days prior to the start of DRV/COBI treatment, this is therefore not considered a relevant case for discussion on a possible pharmacokinetic interaction.

An equal number of 3 subjects of responders (n=3/9) as well as failures (n=3/9) used EFV prior to switching to DRV/COBI. These data suggest that there is no clear effect of prior EFV use on outcome in the present study, but should be interpreted with caution as the sample size for the cases is very small.

Based on the above considerations, the Applicant is of the opinion that the clinical risk is limited in terms of efficacy in switching from an EFV-containing regimen to a DRV/COBI-containing regimen. The plasma concentrations of DRV in addition to remaining EFV plasma concentrations and/or those of the background ARVs are anticipated to provide sufficient antiviral activity throughout the switch period.

Table E9

Table 3: Listing of Previous ARVs Taken in Treatment-experienced Subjects at Week 48 (Snapshot Analysis) – Study GS-US-216-0130

Snapshot Response at Week 48	Unique Subject Identifier	Time to VF at Week 48	Reported Name of Drug, Med, or Therapy	Standardized Medication Name	Start Date/Time of Medication	Analysis Start Relative Day	End Date/Time of Medication	Analysis End Relative Day	Date of First Exposure to Treatment
Virologic Failure	0031-4106	1	NRTI/NNRTI: Atripla (EFV+FTC+TDF)	ATRIPLA	2007	.	2011-11-08	-30	2011-12-08
	0031-4109	1	NRTI: Truvada (FTC+TDF)	TRUVADA	2008-03	.	2011-12-07	-1	2011-12-08
			PI: Atazanavir (ATV)	ATAZANAVIR	2008-03	.	2011-12-07	-1	2011-12-08
			PI: Ritonavir (RTV)	RITONAVIR	2008-03	.	2011-12-07	-1	2011-12-08
	0031-4217	1	NRTI/NNRTI: Atripla (EFV+FTC+TDF)	ATRIPLA	2006	.	2012-01-29	-1	2012-01-30
	0310-4151	1	NNRTI: Nevirapine (NVP)	NEVIRAPINE	2010-06-16	-554	2011-12-21	-1	2011-12-22
			NRTI: Truvada (FTC+TDF)	TRUVADA	2010-06-16	-554	2011-12-21	-1	2011-12-22
	0550-4292	1	NRTI/NNRTI: Atripla (EFV+FTC+TDF)	ATRIPLA	2009-10-27	-853	2012-02-26	-1	2012-02-27
	0571-4301	1	NRTI/NNRTI: Atripla (EFV+FTC+TDF)	ATRIPLA	2011-08-15	-192	2012-02-22	-1	2012-02-23
	0661-4211	1	NRTI: Truvada (FTC+TDF)	TRUVADA	2009-01-14	-1106	2012-01-24	-1	2012-01-25
			PI: Atazanavir (ATV)	ATAZANAVIR	2009-01-14	-1106	2012-01-24	-1	2012-01-25
			PI: Ritonavir (RTV)	RITONAVIR	2009-01-14	-1106	2012-01-24	-1	2012-01-25
	1534-4274	254	NRTI: Truvada (FTC+TDF)	TRUVADA		.	2012-02-19	-1	2012-02-20
			PI: Ritonavir (RTV)	RITONAVIR	2004-08-10	-2750	2012-02-19	-1	2012-02-20
			PI: Saquinavir (SQV)	SAQUINAVIR		.	2012-02-19	-1	2012-02-20
	2154-4108	1	PI: Kaletra (LPV+RTV)	KALETRA	2011-03	.	2011-12-07	-1	2011-12-08
Virologic Success	0031-4277	NA	NRTI: Lamivudine (3TC)	LAMIVUDINE	2008-01	.	2012-01-24	-27	2012-02-20
			NRTI: Tenofovir DF (TDF)	TENOFOVIR DF	2008-01	.	2012-01-24	-27	2012-02-20
	0354-4135	NA	IN: Raltegravir (RAL)	RALTEGRAVIR	2010-09	.	2011-12-18	-1	2011-12-19
			NRTI: Truvada (FTC+TDF)	TRUVADA	2009-11	.	2011-12-18	-1	2011-12-19
	0571-4256	NA	NRTI/NNRTI: Atripla (EFV+FTC+TDF)	ATRIPLA	2011-10-25	-113	2012-02-13	-2	2012-02-15
	0754-4246	NA	Other	COMPLERA	2011-04-22	-293	2012-02-08	-1	2012-02-09
	0991-4306	NA	NRTI/NNRTI: Atripla (EFV+FTC+TDF)	ATRIPLA	2011-05-20	-280	2012-02-23	-1	2012-02-24
	1407-4009	NA	NRTI: Truvada (FTC+TDF)	TRUVADA	2007-04	.	2011-10-26	-1	2011-10-27
			PI: Kaletra (LPV+RTV)	KALETRA	2007-04	.	2011-10-26	-1	2011-10-27
	2843-4172	NA	NNRTI: Efavirenz (EFV)	EFAVIRENZ	2011-07-08	-181	2012-01-04	-1	2012-01-05
			NRTI: Epzicom/Kivexa (ABV+3TC)	EPZICOM	2011-07-08	-181	2012-01-04	-1	2012-01-05
	6046-4094	NA	NRTI: Truvada (FTC+TDF)	TRUVADA	2011-07-07	-151	2011-11-03	-32	2011-12-05
			PI: Atazanavir (ATV)	ATAZANAVIR	2011-07-07	-151	2011-11-03	-32	2011-12-05
			PI: Ritonavir (RTV)	RITONAVIR	2011-07-07	-151	2011-11-03	-32	2011-12-05

It should be noted that if the time to virologic failure at Week 48=1, this means the subject never responded.
Note that for Subject 4158 (virologic success) no previous ARV is available and therefore not included in this table.

[LPREVARV.rtf] [TMC114\GS-US-216-0130\DBR_WEEK48\RE_RTQ_DAY80\lprevarv.sas] 21MAR2014, 13:05

2.3.2. Discussion

Bioequivalence of DRV when boosted by either RTV or COBI has been demonstrated and as such COBI has been registered as a pharmaco-enhancer of DRV.

Furthermore, the application for a fixed dose combination of DRV/COBI has been submitted in 2013 based on the same PK studies and on study GS-US-216-0130.

When boosted by either ritonavir or COBI, DRV achieved viral suppression < 50 copies/ml in treatment naïve patients in either 81.6% (data ARTEMIS study) or 83.7% (data GS-US-216-0130) at week 24.

The efficacy data at week 24 of DRV/COBI 800/150 mg QD mostly in 295 treatment naïve patients do not show major concerns regarding virologic response, virologic failures, or development of RAMs. About the treatment experienced patients not much can be said since the included number was low (n=18).

The MAH has included a sufficient number of treatment naïve patients (almost 300 treatment-naïve patients) to determine safety of DRV when boosted by COBI (see below in the section of Safety), and also the efficacy can be deducted from this study. However, the follow up period of 24 weeks is relatively short for the evaluation of efficacy in patients with high baseline viral load (> 100,000 copies/ml). This may be relevant since COBI boosts DRV to a lesser extent than RTV (Ctau ~30% lower). Ctau of DRV was not considered relevant for antiviral activity in the total population in the studies that evaluated DRV in combination with RTV, but Ctau of DRV was not presented separately for the subjects with high baseline viral load who failed versus those with low baseline viral load who experienced virologic failure in the pivotal studies of DRV/RTV. The MAH was requested to clarify. From the additional analyses provided, there seems a clear difference in response between subjects with baseline viral load ≤ 100,000 copies/mL versus subjects with baseline viral load >100,000 copies/mL at 24 weeks, which could indicate reduced efficacy. Based on the response of the MAH it is concluded that this is not explained by lower DRV concentrations in these patients. Considering the Week 48 response, the difference in response between with baseline viral load ≤ 100,000 copies/mL versus subjects with baseline viral load >100,000 copies/mL is smaller as the number of virological failures has decreased in those with baseline viral load > 100,000 copies (i.e. the number of subjects with HIV-1 RNA ≥50 copies/mL). Similar results were seen in study TMC114-C211, in which the difference also decreased with time. These results indicate that patients with higher viral loads at start therapy possibly respond slower. The provided C0h data for the different subgroups (<100k, >100k, with or without failure) do not differ substantially between subgroups. As such, no evidence for a reduced activity of DRV in combination with COBI in higher baseline viral loads was found, which may be due to a lower C0h if DRV is boosted by COBI versus when boosted by RTV. Therefore, no limitation or restriction in 4.1 based on baseline viral load in the SmPC needs to be incorporated.

This lower exposure of DRV may also be relevant in treatment experienced patients switching from EFV to DRV when EFV concentrations are decreasing and DRV exposures are not fully achieved due to CYP3A4 induction by EFV in the first weeks after cessation of EFV and also COBI exposures are lower due to CYP3A4 induction. This may result in lack of antiviral activity after switch or only activity of the remaining backbone (e.g. tenofovir and emtricitabine). The MAH was requested to comment whether DRV trough levels will exceed its EC50 of both wild type virus or PI resistant HIV-1 strains in case of switch from EFV-containing regimens to DRV/COBI.

In their response they highlighted that the mean DRV C0h in HIV-infected subjects in study GS-US-216-0130 was >37-fold above the protein binding corrected EC50 for wild-type virus (55 ng/mL); as it is anticipated that the DRV exposure will be lowered no more than 15-30% the EC50 is still likely to be exceeded.

GS-US-216-0130 included 18 treatment experienced subjects. Of these, 6 patients used EFV prior to switching to DRV/COBI of whom 3 (out of 9) achieved virological response, and 3 patients did not. It cannot be concluded whether prior exposure to EFV did affect the outcome in this study based upon these small number; as half of patients who used EFV prior to switching to DRV/cobi achieved virological response is reassuring – however two patients did not which could be due to the CYP3A effect.

Two categories of patients who will switch from efavirenz to DRV/COBI based regimens must be considered: 1) patients intolerant to efavirenz but with virologic suppression, and 2) patients failing on efavirenz without virologic suppression. For the first category the concentration of DRV is far above the EC50 regardless of waning induction by EFV. In combination with the effect of the backbone ARVs DRV concentration will be sufficient to maintain virologic suppression. The second patient category has been studied in the ODIN study with convincing results if no DRV-associated mutations are present and viral load < 100,000 copies/ml. Although the MAH did not provide data from this particular subgroup of virologic failures on EFV the efficacy in the once daily DRV arm in the ODIN study is comforting. As mentioned by the MAH, the DRV concentration above the EC50 is probably sufficient in patients with treatment failure on EFV, with the known caveats (specific DRV mutations and viral load restriction) that are now stated in the SmPC for this patient category.

2.4. Clinical Safety aspects

The safety profile of DRV/RTV has been established in the two pivotal studies TMC114-C211 up to 192 weeks and TMC114-C229 up to 48 weeks and through post-marketing experience. The most recent periodic safety update report for DRV, covering the period 24 December 2011 to 23 December 2012, concluded that DRV continues to have a favorable benefit-risk profile for the registered indications and that no further changes to the Company Core Data Sheet and Risk Management Plan are recommended.

The safety profile of DRV/COBI is based on the data from the Phase 3b study GS US 216 0130 in HIV-1 infected subjects and on the safety profiles of the individual agents, DRV (in combination with rtv) and COBI up to 48 weeks.

The overall number of subjects exposed to DRV/COBI once daily in clinical studies included in this application is 313 from study GS US-216 0130 and 33 from study GS-US-216-0115. The overall number of subjects exposed to DRV/COBI once daily in clinical studies conducted by Gilead and not included in this application is 24 (study GS-US-216-0119 during 10 days) and 33 healthy subjects from study GS US 216-0115 who were exposed during 10 days.

Cobicistat

During the development of COBI adverse reactions for COBI-boosted atazanavir (ATV) were consistent with the safety profile of rtv-boosted ATV in HIV patients. No comparative safety data of DRV/RTV vs DRV/COBI in HIV patients is available, because DRV/COBI has only been evaluated in a single arm study in HIV patients (GS US 216 0130).

Cobicistat has been shown to decrease the estimated glomerular filtration rate (eGFR) calculated by Cockcroft-Gault method (eGFRCG) due to inhibition of tubular secretion of creatinine. An increase in serum creatinine due to COBI's inhibitory effect generally does not exceed 0.4 mg/dL from baseline.

DRV in combination with COBI

In healthy volunteers treatment with DRV/COBI 600/100 mg twice daily was not associated with increased adverse safety findings versus rtv-boosted DRV (GS-US-216-0119). In the other study in healthy volunteers (GS-US_216-0115) one subject from 33 discontinued DRV/COBI on Day 8 due to maculopapular rash (drug-related, grade 2); the rash resolved by Day 15.

GS US 216 0130

The number of subjects treated in the study (313 subjects in total) allows detecting adverse events (AEs) of reasonable frequency (in the range of 1 to 5%) during a 6-month treatment.

The review did not identify new ADRs associated with DRV/COBI compared to the well documented ADR safety profile of DRV, and that of COBI in HIV-1 infected subjects.

Exposure

The median duration of exposure to study medication through the cut-off date for the Week-24 analysis was 31.4 weeks (range 0.1 to 42.4 weeks), with a median exposure of 31.9 weeks in the treatment-naïve subjects and a median exposure of 26.6 weeks in treatment-experienced subjects. A total of 281 subjects (89.8%) had received the study medication for at least 24 weeks at the time of the cut-off date for this analysis, 89.8% of the treatment-naïve subjects and 88.9% of the treatment experienced subjects.

Adverse events

The primary endpoint were AEs: 5.8% of subjects experienced at least 1 grade 3 (5.1%) or grade 4 (0.6%) AE.

Five subjects (1.6%) experienced at least 1 grade 3 AE that was considered study drug-related by the investigator: neuropathy peripheral and immune reconstitution syndrome (both reported in the same subject), hypersensitivity, allergic dermatitis, maculopapular rash, and vesicular rash (reported in 1 subject each). There were 2 grade 4 AEs in 1 subject each, idiopathic thrombocytopenic purpura and hypersensitivity, neither were assessed as drug-related.

In total, 39.3% of subjects experienced at least 1 AE that was considered by the investigator as related to DRV/COBI. Diarrhea (14.7%) and nausea (14.4%) were the only AEs considered to be study drug-related in more than 5% of subjects, most drug related AEs were recorded in 1 or 2 subjects.

The other reported AEs were consistent with those expected in the subject population and the known safety profiles of the study medications: diarrhea (24.9%), nausea (21.4%), upper respiratory tract infection (9.9%), headache (9.3%), rash (preferred term, 8.6%), vomiting (8.3%), fatigue (6.4%), flatulence (6.1%), nasopharyngitis (5.8%) and sinusitis (5.4%).

Adverse drug reactions:

Overall, 62.6% of subjects experienced at least 1 ADR in the Week-24 analysis of the study. Individual ADRs with an incidence >10% were diarrhea (25.2%), nausea (21.4%), and rash (grouped term, 16.0%)

Deaths, SAEs and discontinuations

There were no deaths in the Week-24 analysis, 15 subjects (4.8%) experienced one or more SAEs, including 3 subjects (1.0%) who each had one SAE considered as drug-related by the investigator (immune reconstitution syndrome, rash, and maculopapular rash).

Treatment was permanently discontinued in 15 subjects (4.8%) because of 1 or more AEs. The most common AEs that led to discontinuation were rash (preferred term) and maculopapular rash, both of which were experienced by 3 subjects (1.0%). Nausea and hypersensitivity each resulted in discontinuation of 2 subjects (0.6%). All but 2 AEs that led to discontinuation were considered by the investigators to be study drug-related.

Specific concern: special interest

Overall, 23.6% of subjects experienced at least 1 AE of interest. Adverse events of interest to DRV/COBI were most prevalent in the AE groupings of Rash (grouped term, 16.3%), Lipid Abnormalities (2.9%) and Severe Skin Reactions (2.6%). None of the AEs of interest were grade 4 and few were grade 3 (rash, grouped term, reported in 2 [0.6%] subjects, hepatotoxicity in 2 [0.6%] subjects and immune reconstitution syndrome in 1 [0.3%] subject).

Seven subjects (2.2%) discontinued treatment for an AE of interest, all rash-related.

Laboratory: no major laboratory related AEs were reported, including no other renal dysfunction other than the known increase in serum creatinine due to COBI and mean change of eGFR -11.5 ml/min at week 24. An increase in creatinine was observed in 17.7% of subjects, the increase was grade 1 in 14.5% of subjects and grade 2 in 3.2% of subjects.

No apparent pharmacokinetic/pharmacodynamic relationships were observed between DRV AUC24h and the occurrence of rash, diarrhea, nausea, or vomiting, or between DRV AUC24h and the worst toxicity grade in alkaline phosphatase, ALT, AST, amylase, lipase, glucose, total cholesterol, LDL, HDL, or triglycerides. COBI exposures were not recorded.

Special populations

The dose of COBI to be used with DRV in children less than 18 years of age has not been established. DRV/COBI should not be used in children below 3 years of age in view of toxicity observed in juvenile rats dosed with DRV.

Limited information is available with DRV or COBI in patients 65 years of age and older.

Darunavir/COBI has not been investigated in patients with hepatic impairment. Limited information is available on the use of DRV/COBI in patients coinfected with hepatitis B or C. Darunavir/COBI has not been investigated in patients with renal impairment.

Comparison with historical controls DRV/RTV vs. DRV/COBI

The incidence of individual ADRs (any grade) in the Week-24 analyses of study GS US 216 0130 and of the historical studies was similar. The incidence of the ADR rash (any severity grade) was higher in study GS-US-216-0130, (16.0%), than in studies TMC114- C211 (8.2%) and TMC114 C229 (5.8%). The higher incidence of rash, along with a higher proportion of rash events leading to discontinuation in GS-US-216-0130 was due to grade 1 and grade 2 events. There were no noticeable differences in the incidence of grade 3 rashes and there were no cases of grade 4 rash. Rash was mostly mild to moderate, often occurring within the first 4 weeks of treatment and resolving with continued dosing.

Additional week 48 data GS_US-216-0130

An interim safety analysis was done of the ongoing study GS-US-216-0130 at Week 48, when all subjects had been treated for 48 weeks or discontinued earlier (cut-off date 08 February 2013).

The overall safety profile of DRV/COBI 800/150 mg once daily is similar in the Week-48 analysis as in the Week-24 analysis of study GS-US-216-0130, taking into account the increase in exposure duration.

No new pattern or safety signal was observed.

Overall, 91.4% of subjects experienced at least 1 AE, compared to 87.9% in the Week-24 analysis. The incidence of SAEs was 4.8% in the Week 24 analysis and 8.3% in the Week-48 analysis; none of the new SAEs were considered to be related to the study medication.

There was 1 new AE leading to treatment discontinuation in the Week-48 analysis: renal tubular disorder (verbatim: proximal tubulopathy, grade 1, not related, not serious).

Overall, there were 5 new subjects with AEs reported by the investigator as possibly related to the study medication (diarrhea, flatulence, gastroesophageal reflux disease, oropharyngeal pain, influenza, obesity, depression, abnormal dreams, and insomnia), none were serious, of grade 4, or led to treatment discontinuation.

There were no new grade 4 AEs in the Week-48 analysis. None of the new grade 3 AEs reported were considered related to the study medication.

AEs of interest: Overall, there was no increase over time in the occurrence of AEs of interest: 27.2% of subjects experienced at least 1 AE of interest in the Week-48 analysis, compared to 23.6% in the Week 24 analysis. The newly reported preferred terms under the AEs of interest were hyperlipidemia, ocular icterus, diabetes mellitus, impaired fasting glucose, ECG ST-T segment abnormal, amylase increased, and lipase increased.

No new safety signals were identified in the Week-48 analysis. The overall ADR profile of DRV/COBI 800/150 mg once daily at Week 48 is consistent with the Week-24 profile. At Week 48, 66.5% of subjects experienced at least 1 ADR, compared to 62.6% of subjects in the Week-24 analysis. Since the Week-24 analysis, 12 additional subjects (3.8%) reported at least 1 ADR; 2 additional subjects (0.6%) had at least 1 serious ADR and none had an ADR that led to treatment discontinuation.

Laboratory: There were no clinically relevant changes from baseline through Week 48 in mean values for the hematology parameters or clinical chemistry parameters, for the lipid parameters (fasting HDL cholesterol, fasting LDL cholesterol, fasting total cholesterol to HDL cholesterol ratio, or fasting glucose), or for the liver-related laboratory tests (AST, ALT, bilirubin [direct, indirect and total]).

Renal function: The increase from baseline in serum creatinine from Week 2 onwards (mean change 0.09 mg/dL) remained stable during DRV/COBI treatment. In the Week-48 analysis, 7 subjects (2.2%, ie, 1 subject more than in the Week-24 analysis) had a confirmed creatinine increase from baseline $\geq$ 0.4 mg/dL at 1 or more consecutive visits. In these 7 subjects, the maximum observed increases from baseline at any visit ranged between +0.41 and +0.69 mg/dL. Four of these subjects had last recorded creatinine value <0.4mg/dL. Except for one subject (CRF ID 1236-4051, who discontinued, renal AE not related to study medication), none of the 7 subjects presented laboratory abnormalities suggestive of renal proximal tubulopathy or signs of subclinical kidney disease.

Table S1: DRV/COBI Adverse Drug Reactions - GS-US-216-0130 Week-48 Analysis

ADR System Organ Class	Frequency category	Adverse Drug Reactions
Immune System Disorders	Common	(Drug) Hypersensitivity
	Uncommon	Immune Reconstitution **I**nflammatory Syndrome
Metabolism and Nutrition Disorders	Common	Anorexia, Diabetes Mellitus, Hypercholesterolaemia, Hypertriglyceridaemia
	Uncommon	Hyperlipidaemia
Psychiatric Disorders	Common	Abnormal Dreams
Nervous System Disorders	Very Common	Headache
Gastrointestinal Disorders	Very Common	Diarrhoea, Nausea
	Common	Abdominal Distension, Abdominal Pain, Dyspepsia, Flatulence, Vomiting
	Uncommon	Pancreatic Enzymes Increased, Pancreatitis Acute
Hepatobiliary Disorders	Common	Hepatic Enzyme Increased
Skin and Subcutaneous Tissue Disorders	Very Common	Rash
	Common	Angioedema, Pruritus, Urticaria
Musculoskeletal and Connective tissue Disorders	Common	Myalgia
General Disorders and Administration site Conditions	Common	Fatigue
	Uncommon	Asthenia
Investigations	Common	Increased Blood Creatinine

Frequency categories are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

The Adverse Drug Reactions that are known from DRV and COBI as separate components are also noticed in study US-GS-216-0130; no new safety data emerged.

However, the incidence of rash and nausea of DRV when combined with COBI is higher than in other studies when DRV was combined with RTV: the incidence of the ADR rash (any severity grade) was higher in study GS-US-216-0130 (16.0%), than in studies TMC114- C211 (8.2%) and TMC114-C229 (5.8%).

Adverse drug reaction of rash was reported in 16% (from which 5.8% with grade 2 or more), plus in 5 subjects (1.6%) drug hypersensitivity was reported. Rash resulted in discontinuation in 7 (2.2%) patients, and SAE was reported in 3 patients: 2 with rash and 1 with hypersensitivity.

2.4.1. Discussion

The Adverse Drug Reactions that are known from DRV and COBI as separate components are also noticed in study US-GS-216-0130; no new safety data emerged.

However, the incidence of rash and nausea of DRV when combined with COBI is higher than in other studies when DRV was combined with RTV: the incidence of the ADR rash (any severity grade) was higher in study GS-US-216-0130 (16.0%), than in studies TMC114- C211 (8.2%) and TMC114-C229 (5.8%).

Adverse drug reaction of rash was reported in 16% (from which 5.8% with grade 2 or more), plus in 5 subjects (1.6%) drug hypersensitivity was reported. Rash resulted in discontinuation in 7 (2.2%) patients, and SAE was reported in 3 patients: 2 with rash and 1 with hypersensitivity.

Appropriate labelling proposals have been made.

2.5. Risk management plan

The updated RMP (version 21.0) (23/07/2014) was submitted pertaining variations: II/63, II/64 and II/67.

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table Ph 1 Summary of the Safety Concerns

Important Identified Risks	Severe Skin Reactions
	Hepatotoxicity
	Hyperglycaemia
	Lipid Abnormalities
	Pancreatitis
	Fat Redistribution
	Immune Reconstitution Inflammatory Syndrome
	Development of Drug Resistance
	Overdose due to Medication Error
	Drug-Drug Interactions
Important Potential Risks	Coronary Artery Events
	Cardiac Conduction Abnormalities
	Convulsions
	Growth Abnormalities in the Paediatric Population
	Off-Label Use of DRV/COBI in the Paediatric Population
Missing Information	Older People (65 years and above)
	Pregnant and breast-feeding women
	DRV/rtv
	Long-term safety data in children from 3 to 17 years of age

Impact of palatability of the oral suspension on adherence and efficacy in treatment-experienced children > 15 kg

DRV/COBI

Children <18 years of age

Long-term safety of DRV/COBI in adults

Subjects with severe hepatic impairment (Child-Pugh C)

Subjects with renal impairment

The PRAC agreed on that summary of the safety concerns.

Pharmacovigilance plans

Table 2.2: Ongoing and planned studies in the PhV development plan

Study / activity type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned / started)**	**Date for submission of interim or final reports (planned or actual)**
TMC114HIV3015, a single arm, open-label trial to assess the pharmacokinetics of darunavir/ritonavir, etravirine, and rilpivirine in HIV-1-infected pregnant women (This study will be amended to include an evaluation of the pharmacokinetics of DRV/COBI during pregnancy as well.) Category 3	To assess the PK of DRV/rtv and DRV/COBI in HIV-1-infected pregnant women	Pregnant and breast-feeding women (Missing Information)	Started	Interim data: PREZISTA/rtv twice daily group: IA for internal use only was performed (this treatment arm is still enrolling) PREZISTA/rtv qd group: 4Q2014 Final data: PBRER following finalisation of the trial. 2Q2017
TMC114-EPPICC, Pharmacovigilance study on use of PREZISTA in HIV-1-infected children and adolescents in Europe, Category 3	To monitor PREZISTA use in children and adolescents with HIV infection in a “real world” setting within EPPICC.	Long-term safety data in children from 3 to 17 years of age, and growth abnormalities in the paediatric population.	Started	First annual report submitted September 2011 Second annual report: submitted September 2012 Third annual report submitted

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports (planned or actual)
				September 2013 Submission fourth annual report: September 2014 Submission fifth annual report: September 2015
A planned study to assess growth abnormalities (height) in children using PREZISTA in which data will be compared with data from EPPICC or other data in children on other ARV.1 No study name is available at this time, Category 3	To assess growth abnormalities (height) in children using PREZISTA.	Growth abnormalities in the paediatric population	Planned	Submission of the protocol: March 2014. Final study results are expected by August 2015.
TMC114-TiDP29-C232, Continued access to darunavir/ritonavir (DRV/rtv) in HIV-1-infected children and adolescents aged 3 years and above, Category 3	To continue the provision of PREZISTA for paediatric subjects who have completed treatment with PREZISTA in the clinical trials TMC114-C212, TMC114-TiDP29-C228 or TMC114-TiDP29-TMC114-TiDP29-C230, and who continue to benefit from using it. In addition, information on the safety of	Long-term safety of DRV/rtv in children from 3 to 17 years of age	Started	Final data: June 2015

[1] This title represents the draft title of the protocol and will be updated upon availability of the final protocol planned for December 2013.

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports (planned or actual)
	PREZISTA/rtv in combination with other ARVs will be assessed.			
GS-US-216-0130 A Phase 3b, single-arm trial to evaluate the safety and efficacy of COBI-boosted DRV plus two fully active NRTIs in HIV-1 infected, ART-naïve and –experienced adults with no DRV-RAMs. Category 3	To evaluate the safety and tolerability of DRV+COBI plus 2 fully active NRTIs through 48 weeks of treatment and beyond. After 48 weeks of treatment, subjects were given the option to participate in an open-label extension of the study to receive COBI until it becomes commercially available, or until termination of COBI development for any reason.	Missing information: Long-term safety of DRV/COBI in adults	Started	3Q 2015 (Final report)
GS-US-216-0128 (conducted by Gilead) An open-label trial to confirm the dose of COBI-boosted ATV or COBI-boosted DRV in pediatrics aged 3 to < 18 years. Category 3	To evaluate PK, safety, and efficacy of ATV/COBI and DRV/COBI in children and adolescents	Missing information: Safety of DRV/COBI in children <18 years of age	Planned	February 2018 (Week 48 report) February 2022 (Final report)
GS-US-236-0118 (conducted by Gilead) A Phase 3 open-label safety trial of	To evaluate the effect (including long-term effects), safety, and	Missing information: Safety of DRV/COBI in subjects with renal	Started	3Q 2015 (Final report)

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned / started)	Date for submission of interim or final reports (planned or actual)
COBI-containing highly active ARV regimens in HIV-1 infected patients with mild to moderate renal impairment. Category 3	tolerability of COBI-containing regimens (STB, ATV/COBI or DRV/COBI) on renal parameters through 48 weeks of treatment and beyond	impairment		

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table Ph 2: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks:		
Severe Skin Reactions	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Hepatotoxicity	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties) of the SmPC.	None
Hyperglycaemia	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Lipid Abnormalities	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Pancreatitis	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Fat Redistribution	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Immune Reconstitution Inflammatory Syndrome	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Development of Drug Resistance	Adequate information and guidance to help the prescriber is provided in Sections 4.1 (Therapeutic indications) and 4.4 (Special warnings and precautions for use) of the SmPC.	None
Overdose due to Medication Error	Adequate information and guidance to help the prescriber is provided in Sections 4.1 (Therapeutic indications) and 4.2 (Posology and method of administration) of the SmPC, and in the PIL.	None
Drug-Drug Interactions	Adequate information and guidance to help the prescriber is provided in Sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and 4.8 (Undesirable effects) of the SmPC, and in the PIL.	None
Important Potential Risks:		
Coronary Artery Events	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Cardiac Conduction Abnormalities	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Convulsions	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Growth Abnormalities in the Paediatric Population	None proposed.	None
Off-Label Use of DRV/COBI in the Paediatric Population	Adequate information and guidance to help the prescriber is provided in Sections 4.1 (Therapeutic indications) and 4.2 (Posology and method of administration) of the SmPC.	None
Missing Information:		
<u>DRV/rtv and DRV/COBI</u>		
Older People (65 years and above)	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), and 5.2 (Pharmacokinetic properties) of the SmPC.	None
Pregnant and breast-feeding women	Adequate information and guidance to help the prescriber is provided in Sections 4.6 (Fertility, pregnancy and lactation) of the SmPC.	None
<u>DRV/rtv</u>		
Long-term safety data in children from 3 to 17 years of age	Adequate information and guidance to help the prescriber is provided in Sections 4.8 (Undesirable effects, subsection Paediatric population) and 5.1 (Pharmacodynamic properties, subsection Clinical results) of the SmPC.	None
Impact of palatability of the oral suspension on adherence and efficacy in treatment-experienced children > 15 kg	Adequate information and guidance to help the prescriber is provided in Section 4.2 (Posology and method of administration) of the SmPC.	None
<u>DRV/COBI</u>		
Children <18 years of age	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration).	None
Long-Term safety of DRV/COBI in adults	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Subjects with severe hepatic impairment	Adequate information and guidance to help the prescriber is provided in Sections 4.2	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
(Child-Pugh C)	(Posology and method of administration), 4.3 (Contraindications), and 5.2 (Pharmacokinetic properties) of the SmPC.	
Subjects with renal impairment	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), and 4.4 (Special warnings and precautions for use).	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice without changes.

2.6. Changes to the Product Information

During the procedure, the CHMP requested that:

1. Specific safety concerns when DRV is used in combination with COBI to be included in the SmPC.
2. Week 48 data of study GS-US-216-0130 to be incorporated in the SmPC.
3. Since there is a difference in interaction potential of Prezista when boosted with ritonavir or cobicistat, the information on these interactions to be described more clearly in the SmPC.

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

SmPC

4.1 Therapeutic indications

PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight (see section 4.2).

PREZISTA, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients (see section 4.2).
In deciding to initiate treatment with PREZISTA co-administered with cobicistat or low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of PREZISTA.

4.2 Posology and method of administration

[...]

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different contraindications and recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat (see sections 4.3, 4.4 and 4.5).

Posology
PREZISTA must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with PREZISTA. Cobicistat is not indicated for use in twice daily regimens or for use in the pediatric population.

ART-naïve adult patients
The recommended dose regimen is 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food.

ART-experienced adult patients
The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food.

A dose regimen of 800 mg once daily with cobicistat 150 mg once daily or ritonavir 100 mg once daily taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir 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.
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

[...]

ART-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kilograms)
PREZISTA twice daily taken with ritonavir taken with food is usually recommended.

A once daily dose regimen of PREZISTA taken with ritonavir taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir 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.
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

The weight-based dose of PREZISTA and ritonavir in paediatric patients is provided in the table below. The recommended dose of PREZISTA with low dose ritonavir should not exceed the recommended adult dose (600/100 mg twice daily or 800/100 mg once daily). The dose of cobicistat to be used with PREZISTA in children less than 18 years of age has not been established.

Recommended dose for treatment-experienced paediatric patients with PREZISTA and ritonavir[a]		
Body weight (kg)	**Dose (once daily with food)**	**Dose (twice daily with food)**
≥ 15 kg to < 30 kg	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily	380 mg (3.8 ml) PREZISTA/50 mg (0.6 ml) ritonavir twice daily
≥ 30 kg to < 40 kg	675 mg (6.8 ml)[b] PREZISTA/100 mg (1.2 ml) ritonavir once daily	460 mg (4.6 ml) PREZISTA/60 mg (0.8 ml) ritonavir twice daily
≥ 40 kg	800 mg (8 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir twice daily

[a] ritonavir oral solution: 80 mg/ml
[b] rounded up for suspension dosing convenience

For ART-experienced paediatric patients HIV genotypic testing is recommended. However, when HIV genotypic testing is not feasible, the PREZISTA/ritonavir once daily dosing regimen is recommended in HIV protease inhibitor-naïve paediatric patients and the twice daily dosing regimen is recommended in HIV protease inhibitor-experienced patients.

PREZISTA oral suspension can be used in patients unable to swallow PREZISTA tablets. PREZISTA is also available as 75 mg, 150 mg, 300 mg, 400 mg, 600 mg and 800 mg film-coated tablets.

Advice on missed doses
The following guidance is based on the half-life of darunavir in the presence of cobicistat or ritonavir and the recommended dosing interval of approximately 12 hours (twice daily regimen) or approximately 24 hours (once daily regimen).

- If using the twice daily regimen: in case a dose of PREZISTA and/or ritonavir was missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and ritonavir with food as soon as possible. If this was noticed later than 6 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.
- If using the once daily regimen: in case a dose of PREZISTA and/or cobicistat or ritonavir was missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and cobicistat or ritonavir with food as soon as possible. If this was noticed later than 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

Special populations

[...]

Renal impairment
No dose adjustment is required for darunavir/ritonavir in patients with renal impairment (see sections 4.4 and 5.2). Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients.

Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with creatine clearance less than 70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir dipovoxil.

For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Paediatric patients
PREZISTA should not be used in children.
- below 3 years of age, because of safety concerns (see sections 4.4 and 5.3), or,
- less than 15 kg body weight, as the dose for this population has not been established in a sufficient number of patients (see section 5.1)

Administration of PREZISTA 800 mg once daily with low dose ritonavir in treatment-naïve adolescents 12 to 17 years weighing at least 40 kg leads to darunavir exposures within the therapeutic range as established in adults receiving the same dosing regimen. Since PREZISTA once daily has also been registered for use in treatment-experienced adults without darunavir 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, the same indication of PREZISTA once daily applies to treatment-experienced children 3 to 17 years weighing at least 15 kg.
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Method of administration
Patients should be instructed to take PREZISTA with cobicistat or low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir (see sections 4.4, 4.5 and 5.2).

[...]

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use in patients with severe (Child-Pugh Class C) hepatic impairment.

Concomitant treatment with any of the following medicinal products is contraindicated given the expected decrease in plasma concentrations of darunavir, ritonavir and cobicistat and the potential for loss of therapeutic effect (see sections 4.4 and 4.5).

Applicable to darunavir boosted with either ritonavir or cobicistat:
- The combination product lopinavir/ritonavir (see section 4.5).

- The strong CYP3A inducers rifampicin and herbal preparations containing St John's wort (*Hypericum perforatum*). Co-administration is expected to reduce plasma concentrations of darunavir, ritonavir and cobicistat, which could lead to loss of therapeutic effect and possible development of resistance (see sections 4.4 and 4.5).

Applicable to darunavir boosted with cobicistat, not when boosted with ritonavir:
- Darunavir boosted with cobicistat is more sensitive for CYP3A induction than darunavir boosted with ritonavir. Concomitant use with strong CYP3A inducers is contraindicated, since these may reduce the exposure to cobicistat and darunavir leading to loss of therapeutic effect. Strong CYP3A inducers include e.g. carbamazepine, phenobarbital and phenytoin (see sections 4.4 and 4.5).

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co-administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:
- alfuzosin (alpha 1-adrenoreceptor antagonist
- amiodarone, bepridil, dronedarone, quinidine, ranolazine, systemic lidocaine (antiarrhythmics/antianginals)
- astemizole, terfenadine (antihistamines)
- colchicine when used in patients with renal and/or hepatic impairment (antigout) (see section 4.5)
- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- cisapride (gastrointestinal motility agents)
- pimozide, quetiapine, sertindole (antipsychotics/neuroleptics) (see section 4.5)
- triazolam, midazolam administered orally (sedatives/hypnotics) (for caution on parenterally administered midazolam, see section 4.5)
- sildenafil - when used for the treatment of pulmonary arterial hypertension, avanafil (PDE-5 inhibitors)
- simvastatin and lovastatin (HMG-CoA reductase inhibitors) (see section 4.5)
- ticagrelor (antiplatelets) (see section 4.5).

4.4 Special warnings and precautions for use

[…]

PREZISTA must always be given orally with cobicistat or low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products (see section 5.2). The Summary of Product Characteristics of cobicistat or ritonavir as appropriate, must therefore be consulted prior to initiation of therapy with PREZISTA.

Increasing the dose of ritonavir from that recommended in section 4.2 did not significantly affect darunavir concentrations. It is not recommended to alter the dose of cobicistat or ritonavir.

[…]

<u>ART-experienced patients – once daily dosing</u>
PREZISTA used in combination with cobicistat or low dose ritonavir once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/l (see section 4.2). Combinations with optimised background regimen (OBRs) other than ≥ 2 NRTIs have not been studied in this population. Limited data are available in patients with HIV-1 clades other than B (see section 5.1).

[…]

<u>Severe skin reactions</u>
During the darunavir/ritonavir clinical development program (N=3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and Stevens-Johnson Syndrome has been rarely (< 0.1%) reported, and during post-marketing experience toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported. PREZISTA should be discontinued immediately if signs or symptoms of severe skin reactions develop. These can include, but are not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing PREZISTA/ritonavir + raltegravir compared to patients receiving PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA (see section 4.8).

Darunavir contains a sulphonamide moiety. PREZISTA should be used with caution in patients with a known sulphonamide allergy.

Hepatotoxicity
Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA. During the darunavir/ritonavir clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination antiretroviral therapy with PREZISTA/ritonavir. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these medicinal products.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA used in combination with cobicistat or low dose ritonavir and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of PREZISTA used in combination with cobicistat or low dose ritonavir treatment.

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients using PREZISTA used in combination with cobicistat or low dose ritonavir, interruption or discontinuation of treatment should be considered promptly.

Patients with coexisting conditions

[...]

Renal impairment
No special precautions or dose adjustments for darunavir/ritonavir are required in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis. Therefore, no special precautions or dose adjustments are required in these patients (see sections 4.2 and 5.2). Cobicistat has not been studied in patients receiving dialysis, therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients (see section 4.2).

Cobicistat decreases the estimated creatinine clearance due to inhibition of tubular secretion of creatinine. This should be taken into consideration if darunavir with cobicistat is administered to patients in whom the estimated creatinine clearance is used to adjust doses of co-administered medicinal products (see section 4.2 and cobicistat SmPC).

There are currently inadequate data to determine whether co-administration of tenofovir disoproxil fumarate and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil fumarate without cobicistat.

[...]

Immune reconstitution inflammatory syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical studies with PREZISTA co-administered with low dose ritonavir.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8).

Interactions with medicinal products

Pharmacokinetic enhancer and concomitant medications

Darunavir has different interaction profiles depending on whether the compound is boosted with ritonavir or cobicistat:

- Darunavir boosted with cobicistat is more sensitive for CYP3A induction: concomitant use of darunavir/cobicistat and strong CYP3A inducers is therefore contraindicated (see section 4.3), and concomitant use with weak to moderate CYP3A inducers is not recommended (see section 4.5). Concomitant use of darunavir/ritonavir and darunavir/cobicistat with lopinavir/ritonavir, rifampicin and herbal products containing St John's wort, *Hypericum perforatum*, is contraindicated (see section 4.5).
- Unlike ritonavir, cobicistat does not have inducing effects on enzymes or transport proteins (see section 4.5). If switching the pharmacoenhancer from ritonavir to cobicistat, caution is required during the first two weeks of treatment with darunavir/cobicistat, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of ritonavir as a pharmacoenhancer. A dose reduction of the co-administered drug may be needed in these cases.

Efavirenz in combination with PREZISTA/ritonavir 800/100 mg once daily may result in sub-optimal darunavir C_{min}. If efavirenz is to be used in combination with PREZISTA/ritonavir, the PREZISTA/ritonavir 600/100 mg twice daily regimen should be used. See the Summary of Product Characteristics for PREZISTA 75 mg, 150 mg, 300 mg or 600 mg tablets (see section 4.5).

[…]

4.5 Interaction with other medicinal products and other forms of interaction

The interaction profile of darunavir may differ depending on whether ritonavir or cobicistat is used as pharmacoenhancer. The recommendations given for concomitant use of darunavir and other medicinal products may therefore differ depending on whether darunavir is boosted with ritonavir or cobicistat (see sections 4.3 and 4.4), and caution is also required during the first time of treatment if switching the pharmacoenhancer from ritonavir to cobicistat (see section 4.4).

Medicinal products that affect darunavir exposure (ritonavir as pharmacoenhancer)

Darunavir and ritonavir are metabolised by CYP3A. Medicinal products that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of these compounds and consequently that of darunavir, leading to loss of therapeutic effect and possible development of resistance (see sections 4.3 and 4.4). CYP3A inducers that are contraindicated include rifampicin, St John's wort and lopinavir.

Co-administration of darunavir and ritonavir with other medicinal products that inhibit CYP3A may decrease the clearance of darunavir and ritonavir, which may result in increased plasma concentrations of darunavir and ritonavir. Co-administration with strong CYP3A4 inhibitors is not recommended and caution is warranted, these interactions are described in the interaction table below (e.g. indinavir, systemic azoles like ketoconazole and clotrimazole).

Medicinal products that affect darunavir exposure (cobicistat as pharmacoenhancer)

Darunavir and cobicistat are metabolised by CYP3A, and co-administration with CYP3A inducers may therefore result in subtherapeutic plasma exposure to darunavir. Darunavir boosted with cobicistat is more sensitive to CYP3A induction than ritonavir-boosted darunavir: co-administration of darunavir/cobicistat with medicinal products that are strong inducers of CYP3A (e.g. St John's wort, rifampicin, carbamazepine, phenobarbital, and phenytoin) is contraindicated (see section 4.3). Co-administration of darunavir/cobicistat with weak to moderate CYP3A inducers (e.g. efavirenz, etravirine, nevirapine, boceprevir, telaprevir, fluticasone, and bosentan) is not recommended (see interaction table below).

For co-administration with strong CYP3A4 inhibitors, the same recommendations apply independent of whether darunavir is boosted with ritonavir or with cobicistat (see section above).

Medicinal products that may be affected by darunavir boosted with ritonavir

Darunavir and ritonavir are inhibitors of CYP3A, CYP2D6 and P-gp. Co-administration of darunavir/ritonavir with medicinal products primarily metabolised by CYP3A and/or CYP2D6 or transported by P-gp may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

Darunavir co-administered with low dose ritonavir must not be combined with medicinal products that are highly dependent on CYP3A for clearance and for which increased systemic exposure is associated with serious and/or life-threatening events (narrow therapeutic index) (see section 4.3).

The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily. Therefore, darunavir must only be used in combination with a pharmacokinetic enhancer (see section 5.2).

A clinical study utilising a cocktail of medicinal products that are metabolised by cytochromes CYP2C9, CYP2C19 and CYP2D6 demonstrated an increase in CYP2C9 and CYP2C19 activity and inhibition of CYP2D6 activity in the presence of darunavir/ritonavir, which may be attributed to the presence of low dose ritonavir. Co-administration of darunavir and ritonavir with medicinal products which are primarily metabolised by CYP2D6 (such as flecainide, propafenone, metoprolol) may result in increased plasma concentrations of these medicinal products, which could increase or prolong their therapeutic effect and adverse reactions. Co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C9 (such as warfarin) and CYP2C19 (such as methadone) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Although the effect on CYP2C8 has only been studied *in vitro*, co-administration of darunavir and ritonavir and medicinal products primarily metabolised by CYP2C8 (such as paclitaxel, rosiglitazone, repaglinide) may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Ritonavir inhibits the transporters P-glycoprotein, OATP1B1 and OATP1B3, and co-administration with substrates of these transporters can result in increased plasma concentrations of these compounds (e.g. dabigatran etexilate, digoxin, statins and bosentan; see the Interaction table below).

Medicinal products that may be affected by darunavir boosted with cobicistat

The recommendations for darunavir boosted with ritonavir are adequate also for darunavir boosted with cobicistat with regard to substrates of CYP3A4, CYP2D6, P-glycoprotein, OATP1B1 and OATP1B3 (see contraindications and recommendations presented in the section above). Cobicistat 150 mg given with darunavir 800 mg once daily enhances darunavir pharmacokinetic parameters in a comparable way to ritonavir (see section 5.2).

Unlike ritonavir, cobicistat does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Interaction table

Interaction studies have only been performed in adults.

Several of the interaction studies (indicated by # in the table below) have been performed at lower than recommended doses of darunavir or with a different dosing regimen (see section 4.2 Posology). The effects on co-administered medicinal products may thus be underestimated and clinical monitoring of safety may be indicated.

The interaction profile of darunavir depends on whether ritonavir or cobicistat is used as pharmacokinetic enhancer. Darunavir may therefore have different recommendations for concomitant medications depending on whether the compound is boosted with ritonavir or cobicistat. No interaction studies presented in the table have been performed with darunavir boosted with cobicistat. The same recommendations apply, unless specifically indicated. For further information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Interactions between darunavir/ritonavir and antiretroviral and non-antiretroviral medicinal products are listed in the table below (not determined as “ND”). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125% range.

In the table below the specific pharmacokinetic enhancer is specified when recommendeations differ. When the recommendation is the same for PREZISTA when co-administered with a low dose ritonavir or cobicistat, the term “boosted PREZISTA” is used.

Table: INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS

(Detailed table not shown)

4.6 Fertility, pregnancy and lactation

Pregnancy

[...]

PREZISTA co-administered with cobicistat or low dose ritonavir should be used during pregnancy only if the potential benefit justifies the potential risk.

4.7 Effects on ability to drive and use machines

PREZISTA in combination with cobicistat or ritonavir has no or negligible influence on the ability to drive and use machines. However, dizziness has been reported in some patients during treatment with regimens containing PREZISTA co-administered with cobicistat or low dose ritonavir and should be borne in mind when considering a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

During the clinical development program (N=2,613 treatment-experienced subjects who initiated therapy with PREZISTA/ritonavir 600/100 mg twice daily), 51.3% of subjects experienced at least one adverse reaction. The total mean treatment duration for subjects was 95.3 weeks. The most frequent adverse reactions reported in clinical trials and as spontaneous reports are diarrhoea, nausea, rash, headache and vomiting. The most frequent serious reactions are acute renal failure, myocardial infarction, immune reconstitution inflammatory syndrome, thrombocytopenia, osteonecrosis, diarrhoea, hepatitis and pyrexia.

In the 96 week analysis, the safety profile of PREZISTA/ritonavir 800/100 mg once daily in treatment-naïve subjects was similar to that seen with PREZISTA/ritonavir 600/100 mg twice daily in treatment-experienced subjects except for nausea which was observed more frequently in treatment-naïve subjects. This was driven by mild intensity nausea. No new safety findings were identified in the 192 week analysis of the treatment- naïve subjects in which the mean treatment duration of PREZISTA/ritonavir 800/100 mg once daily was 162.5 weeks.

During the Phase III clinical trial GS-US-216-130 with darunavir/cobicistat (N=313 treatment-naïve and treatment-experienced subjects), 66.5% of subjects experienced at least one adverse reaction. The mean treatment duration was 58.4 weeks. The most frequent adverse reactions reported were diarrhoea (28%), nausea (23%), and rash (16%). Serious adverse reactions are diabetes mellitus, (drug) hypersensitivity, immune reconstitution inflammatory syndrome, rash and vomiting.

For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Tabulated list of adverse reactions

[...]

Adverse reactions observed with darunavir/ritonavir in clinical trials and post-marketing

[table not shown]

Adverse reactions with darunavir/cobicistat in adult patients

MedDRA system organ class Frequency category	Adverse reaction
Immune system disorders	
common	(drug) hypersensitivity
uncommon	immune reconstitution inflammatory syndrome
Metabolism and nutrition disorders	
common	lipodystrophy (including lipohypertrophy, lipodystrophy, lipoatrophy)*, anorexia, diabetes mellitus, hypercholesterolaemia, hypertriglyceridaemia, hyperlipidaemia
Psychiatric disorders	
common	abnormal dreams
Nervous system disorders	
very common	headache
Gastrointestinal disorders	
very common	diarrhoea, nausea
common	vomiting, abdominal pain, abdominal distension, dyspepsia, flatulence, pancreatic enzymes increased
uncommon	pancreatitis acute
Hepatobiliary disorders	
common	hepatic enzyme increased
uncommon	hepatitis*, cytolytic hepatitis*
Skin and subcutaneous tissue disorders	
very common	rash (including macular, maculopapular, papular, erythematous, pruritic rash, generalised rash, and allergic dermatitis)
common	angioedema, pruritus, urticaria
rare	drug reaction with eosinophilia and systemic symptoms*, Stevens-Johnson syndrome*
not known	toxic epidermal necrolysis*, acute generalised exanthematous pustulosis*
Musculoskeletal and connective tissue disorders	
common	myalgia, osteonecrosis*
Reproductive system and breast disorders	
uncommon	gynaecomastia*
General disorders and administration site conditions	
common	fatigue
uncommon	asthenia
Investigations	
common	increased blood creatinine

* these adverse drug reactions have not been reported in clinical trial experience with darunavir/cobicistat but have been noted with darunavir/ritonavir treatment and could be expected with darunavir/cobicistat too.

Description of selected adverse reactions

Rash
In clinical trials, rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In cases of severe skin reaction see the warning in section 4.4. In a

single arm trial investigating darunavir 800 mg once daily in combination with cobicistat 150 mg once daily and other antiretrovirals 2.2% of patients discontinued treatment due to rash.

During the clinical development program of raltegravir in treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing PREZISTA/ritonavir + raltegravir compared to those containing PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA/ritonavir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

[…]

Immune reconstitution inflammatory syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

[…]

5.1 Pharmacodynamic properties

[…]

Resistance

[…]

Viruses isolated from patients on PREZISTA/ritonavir 600/100 mg twice daily experiencing virologic failure by rebound that were susceptible to tipranavir at baseline remained susceptible to tipranavir after treatment in the vast majority of cases.

The lowest rates of developing resistant HIV virus are observed in ART-naïve patients who are treated for the first time with darunavir in combination with other ART.

The table below shows the development of HIV-1 protease mutations and loss of susceptibility to PIs in virologic failures at endpoint in the *ARTEMIS*, *ODIN* and *TITAN* trials.

	ARTEMIS Week 192	ODIN Week 48		TITAN Week 48
	PREZISTA/ ritonavir 800/100 mg once daily N=343	PREZISTA/ ritonavir 800/100 mg once daily N=294	PREZISTA/ ritonavir 600/100 mg twice daily N=296	PREZISTA/ ritonavir 600/100 mg twice daily N=298
Total number of virologic failures[a], n (%)	55 (16.0%)	65 (22.1%)	54 (18.2%)	31 (10.4%)
Rebounders	39 (11.4%)	11 (3.7%)	11 (3.7%)	16 (5.4%)
Never suppressed subjects	16 (4.7%)	54 (18.4%)	43 (14.5%)	15 (5.0%)
Number of subjects with virologic failure and paired baseline/endpoint genotypes, developing mutations[b] at endpoint, n/N				
Primary (major) PI mutations	0/43	1/60	0/42	6/28
PI RAMs	4/43	7/60	4/42	10/28

Number of subjects with virologic failure and paired baseline/endpoint phenotypes, showing loss of susceptibility to PIs at endpoint compared to baseline, n/N				
PI				
darunavir	0/39	1/58	0/41	3/26
amprenavir	0/39	1/58	0/40	0/22
atazanavir	0/39	2/56	0/40	0/22
indinavir	0/39	2/57	0/40	1/24
lopinavir	0/39	1/58	0/40	0/23
saquinavir	0/39	0/56	0/40	0/22
tipranavir	0/39	0/58	0/41	1/25

[a] TLOVR non-VF censored algorithm based on HIV-1 RNA < 50 copies/ml, except for *TITAN* (HIV-1 RNA < 400 copies/ml)

[b] IAS-USA lists

Low rates of developing resistant HIV-1 virus were observed in ART-naïve patients who are treated for the first time with darunavir/cobicistat once daily in combination with other ART, and in ART-experienced patients with no darunavir RAMs receiving darunavir/cobicistat in combination with other ART. The table below shows the development of HIV-1 protease mutations and resistance to PIs in virologic failures at endpoint in the GS-US-216-130 trial.

	GS-US-216-130 Week 48	
	Treatment-naïve darunavir/cobicistat 800/150 mg once daily N=295	Treatment-experienced darunavir/cobicistat 800/150 mg once daily N=18
Number of subjects with virologic failure[a] and genotype data that develop mutations[b] at endpoint, n/N		
Primary (major) PI mutations	0/8	1/7
PI RAMs	2/8	1/7
Number of subjects with virologic failure[a] and phenotype data that show resistance to PIs at endpoint[c], n/N		
HIV PI		
darunavir	0/8	0/7
amprenavir	0/8	0/7
atazanavir	0/8	0/7
indinavir	0/8	0/7
lopinavir	0/8	0/7
saquinavir	0/8	0/7
tipranavir	0/8	0/7

[a] Virogic failures were defined as: never suppressed: confirmed HIV-1 RNA < 1 $\log_{10}$ reduction from baseline and ≥ 50 copies/ml at the week-8; rebound: HIV-1 RNA < 50 copies/ml followed by confirmed HIV-1 RNA to ≥ 400 copies/ml or confirmed > 1 $\log_{10}$ HIV-1 RNA increase from the nadir; discontinuations with HIV-1 RNA ≥ 400 copies/ml at last visit

[b] IAS-USA lists

[c] In GS-US216-130 baseline phenotype was not available

Cross-resistance

Darunavir FC was less than 10 for 90% of 3,309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to most PIs remain susceptible to darunavir.

In the virologic failures of the *ARTEMIS* trial no cross-resistance with other PIs was observed.
In the virologic failures of the GS-US-216-130 trial no cross-resistance with other HIV PIs was observed.

Clinical results

All clinical trials were performed with PREZISTA co-administered with low dose ritonavir.

The pharmacokinetic enhancing effect of cobicistat on darunavir was evaluated in a Phase I study in healthy subjects that were administered darunavir 800 mg with either cobicistat at 150 mg or ritonavir at 100 mg once daily. The steady-state pharmacokinetic parameters of darunavir were comparable when boosted with cobicistat versus ritonavir. For information on cobicistat, consult the cobicistat Summary of Product Characteristics.

Adult patients

Efficacy of darunavir 800 mg once daily co-administered with 150 mg cobicistat once daily in ART-naïve and ART-experienced patients

GS-US-216-130 is a single arm, open-label, Phase III trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with cobicistat in 313 HIV-1 infected adult patients (295 treatment-naïve and 18 treatment-experienced). These patients received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily with an investigator selected background regimen consisting of 2 active NRTIs.

HIV-1 infected patients who were eligible for this trial had a screening genotype showing no darunavir RAMs and plasma HIV-1 RNA ≥ 1000 copies/ml. The table below shows the efficacy data of the 48 week analyses from the GS-US-216-130 trial:

	GS-US-216-130		
Outcomes at Week 48	Treatment-naïve darunavir/cobicistat 800/150 mg once daily+ OBR N=295	Treatment-experienced darunavir/cobicistat 800/150 mg once daily + OBR N=18	All subjects darunavir/cobicistat 800/150 mg once daily + OBR N=313
HIV-1 RNA < 50 copies/ml[a]	245 (83.1%)	8 (44.4%)	253 (80.8%)
mean HIV-1 RNA log change from baseline (log_{10} copies/ml)	-3.01	-2.39	-2.97
CD4+ cell count mean change from baseline[b]	+174	+102	+170

[a] Imputations according to the TLOVR algorithm

[b] Last Observation Carried Forward imputation

[...]

Efficacy of PREZISTA 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-naïve patients

The evidence of efficacy of PREZISTA/ritonavir 800/100 mg once daily is based on the analyses of 192 week data from the randomised, controlled, open-label Phase III trial *ARTEMIS* in antiretroviral treatment-naïve HIV-1 infected patients comparing PREZISTA/ritonavir 800/100 mg once daily with lopinavir/ritonavir 800/200 mg per day (given as a twice-daily or as a once-daily regimen). Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg once daily and emtricitabine 200 mg once daily.

The table below shows the efficacy data of the 48 week and 96 week analyses from the *ARTEMIS* trial:

ARTEMIS						
	Week 48[a]			Week 96[b]		
Outcomes	PREZISTA / ritonavir 800/100 mg once daily N=343	Lopinavir/ ritonavir 800/200 mg per day N=346	Treatment difference (95% CI of difference)	PREZISTA / ritonavir 800/100 mg once daily N=343	Lopinavir / ritonavir 800/200 mg per day N=346	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[c]	83.7% (287)	78.3% (271)	5.3% (-0.5; 11.2)[d]	79.0% (271)	70.8% (245)	8.2% (1.7; 14.7)[d]
All patients						
With baseline HIV-RNA < 100,000	85.8% (194/226)	84.5% (191/226)	1.3% (-5.2; 7.9)[d]	80.5% (182/226)	75.2% (170/226)	5.3% (-2.3; 13.0)[d]
With baseline HIV-RNA ≥ 100,000	79.5% (93/117)	66.7% (80/120)	12.8% (1.6; 24.1)[d]	76.1% (89/117)	62.5% (75/120)	13.6% (1.9; 25.3)[d]
With baseline CD4+ cell count < 200	79.4% (112/141)	70.3% (104/148)	9.2% (-0.8; 19.2)[d]	78.7% (111/141)	64.9% (96/148)	13.9% (3.5; 24.2)[d]
With baseline CD4+ cell count ≥ 200	86.6% (175/202)	84.3% (167/198)	2.3% (-4.6; 9.2)[d]	79.2% (160/202)	75.3% (149/198)	4.0% (-4.3; 12.2)[d]
median CD4+ cell count change from baseline (x 10^6/l)[e]	137	141		171	188	

[a] Data based on analyses at week 48

[b] Data based on analyses at week 96

[c] Imputations according to the TLOVR algorithm

[d] Based on normal approximation to the difference in % response

[e] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0

[…]

Efficacy of PREZISTA 600 mg twice daily co-administered with 100 mg ritonavir twice daily in ART-experienced patients

[…]

The table below shows the efficacy data of the 48 week analysis from the *TITAN* trial.

TITAN			
Outcomes	PREZISTA/ritonavir 600/100 mg twice daily + OBR N=298	Lopinavir/ritonavir 400/100 mg twice daily + OBR N=297	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a]	70.8% (211)	60.3% (179)	10.5% (2.9; 18.1)[b]
median CD4+ cell count change from baseline ($x\ 10^6$/l)[c]	88	81	

[a] Imputations according to the TLOVR algorithm

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

[c] NC=F

At 48 weeks non-inferiority in virologic response to the PREZISTA/ritonavir treatment, defined as the percentage of patients with plasma HIV-1 RNA level < 400 and < 50 copies/ml, was demonstrated (at the pre-defined 12% non-inferiority margin) for both ITT and OP populations. These results were confirmed in the analysis of data at 96 weeks of treatment in the *TITAN* trial, with 60.4% of patients in the PREZISTA/ritonavir arm having HIV-1 RNA < 50 copies/ml at week 96 compared to 55.2% in the lopinavir/ritonavir arm [difference: 5.2%, 95% CI (-2.8; 13.1)].

ODIN is a Phase III, randomised, open-label trial comparing PREZISTA/ritonavir 800/100 mg once daily versus PREZISTA/ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/ml. Efficacy analysis is based on 48 weeks of treatment (see table below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

ODIN			
Outcomes	PREZISTA/ritonavir 800/100 mg once daily + OBR N=294	PREZISTA/ritonavir 600/100 mg twice daily + OBR N=296	Treatment difference (95% CI of difference)
HIV-1 RNA < 50 copies/ml[a]	72.1% (212)	70.9% (210)	1.2% (-6.1; 8.5)[b]
With Baseline HIV-1 RNA (copies/ml)	77.6% (198/255)	73.2% (194/265)	4.4% (-3.0; 11.9)
< 100,000	35.9% (14/39)	51.6% (16/31)	-15.7% (-39.2; 7.7)
≥ 100,000			
With Baseline CD4+ cell count ($x\ 10^6$/l)	75.1% (184/245)	72.5% (187/258)	2.6% (-5.1; 10.3)
≥ 100	57.1% (28/49)	60.5% (23/38)	-3.4% (-24.5; 17.8)
< 100			
With HIV-1 clade			
Type B	70.4% (126/179)	64.3% (128/199)	6.1% (-3.4; 15.6)
Type AE	90.5% (38/42)	91.2% (31/34)	-0.7% (-14.0; 12.6)
Type C	72.7% (32/44)	78.8% (26/33)	-6.1% (-2.6; 13.7)
Other[c]	55.2% (16/29)	83.3% (25/30)	-28.2% (-51.0; -5.3)
mean CD4+ cell count change from baseline ($x\ 10^6$/l)[e]	108	112	-5[d] (-25; 16)

[a] Imputations according to the TLOVR algorithm
[b] Based on a normal approximation of the difference in % response
[c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX
[d] Difference in means
[e] Last Observation Carried Forward imputation

At 48 weeks, virologic response, defined as the percentage of patients with plasma HIV-1 RNA level < 50 copies/ml, with PREZISTA/ritonavir 800/100 mg once daily treatment was demonstrated to be non-inferior (at the pre-defined 12% non-inferiority margin) compared to PREZISTA/ritonavir 600/100 mg twice daily for both ITT and OP populations.

PREZISTA/ritonavir 800/100 mg once daily in ART-experienced patients should not be used in patients with one or more darunavir resistance associated mutations (DRV-RAMs) or HIV-1 RNA ≥ 100,000 copies/ml or CD4+ cell count < 100 cells x 10^6/l (see section 4.2 and 4.4). Limited data is available in patients with HIV-1 clades other than B.

POWER 1 *and* ***POWER 2*** are randomised, controlled trials comparing PREZISTA co-administered with ritonavir (600/100 mg twice daily) with a control group receiving an investigator-selected PI(s) regimen in HIV-1 infected patients who had previously failed more than 1 PI containing regimen. An OBR consisting of at least 2 NRTIs with or without enfuvirtide (ENF) was used in both trials.

The table below shows the efficacy data of the 48-week and 96-week analyses from the pooled *POWER* 1 and *POWER* 2 trials.

POWER 1 and POWER 2 pooled data						
	Week 48			Week 96		
Outcomes	PREZISTA/ ritonavir 600/100 mg twice daily n=131	Control n=124	Treatment difference	PREZISTA/ ritonavir 600/100 mg twice daily n=131	Control n=124	Treatment difference
HIV RNA < 50 copies/ml [a]	45.0% (59)	11.3% (14)	33.7% (23.4%; 44.1%)[c]	38.9% (51)	8.9% (11)	30.1% (20.1; 40.0)[c]
CD4+ cell count mean change from baseline (x 10^6/l)[b]	103	17	86 (57; 114)[c]	133	15	118 (83.9; 153.4)[c]

[a] Imputations according to the TLOVR algorithm
[b] Last Observation Carried Forward imputation
[c] 95% confidence intervals.

[...]

Paediatric patients

ART-experienced paediatric patients from the age of 3 to < 6 years
The pharmacokinetics, safety, tolerability and efficacy of PREZISTA/ritonavir b.i.d. in combination with other antiretroviral agents in 21 ART-experienced HIV-1 infected paediatric patients aged 3 to < 6 years and weighing 10 kg to < 20 kg was evaluated in an open-label, Phase II trial, ***ARIEL***. Patients received a weight-based twice daily treatment regimen, patients weighing 10 kg to < 15 kg received darunavir/ritonavir 25/3 mg/kg b.i.d, and patients weighing 15 kg to < 20 kg received darunavir/ritonavir 375/50 mg b.i.d. At week 48, the virologic response, defined as the percentage of patients with confirmed plasma viral load < 50 HIV-1 RNA copies/ml, was evaluated in 16 paediatric patients 15 kg to < 20 kg and 5 paediatric patients 10 kg to < 15 kg receiving PREZISTA/ritonavir in combination with other antiretroviral agents (see section 4.2 for dosage recommendations per body weight).

ARIEL		
Outcomes at week 48	PREZISTA/ritonavir	
	10 kg to < 15 kg N=5	15 kg to < 20 kg N=16
HIV-1 RNA < 50 copies/ml[a]	80.0% (4)	81.3% (13)
CD4+ percent change from baseline[b]	4	4
CD4+ cell count mean change from baseline[b]	16	241

[a] Imputations according to the TLOVR algorithm.
[b] NC=F

[...]

5.2 Pharmacokinetic properties

The pharmacokinetic properties of darunavir, co-administered with cobicistat or ritonavir, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to darunavir was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to darunavir in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of α_1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG and, therefore, higher plasma concentrations.

Darunavir is primarily metabolised by CYP3A. Cobicistat and ritonavir inhibit CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

For information on cobicistat pharmacokinetic properties, consult the cobicistat Summary of Product Characteristics.

Absorption
Darunavir was rapidly absorbed following oral administration. Maximum plasma concentration of darunavir in the presence of low dose ritonavir is generally achieved within 2.5-4.0 hours.

The absolute oral bioavailability of a single 600 mg dose of darunavir alone was approximately 37% and increased to approximately 82% in the presence of 100 mg twice daily ritonavir. The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg twice daily (see section 4.4).

When administered without food, the relative bioavailability of darunavir in the presence of cobicistat or low dose ritonavir is lower as compared to intake with food. Therefore, PREZISTA tablets should be taken with cobicistat or ritonavir and with food. The type of food does not affect exposure to darunavir.

[...]

Special populations

Paediatric population

[...]

The pharmacokinetics of darunavir in combination with ritonavir taken twice daily in 14 treatment-experienced paediatric patients, aged 3 to < 6 years and weighing at least 15 kg to < 20 kg, showed that weight-based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 600/100 mg twice daily (see section 4.2).

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 12 ART-naïve paediatric patients, aged 12 to < 18 years and weighing at least 40 kg, showed that PREZISTA/ritonavir 800/100 mg once daily results in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 800/100 mg once daily. Therefore the same once daily dosage may be used in treatment-experienced adolescents aged 12 to < 18 years and weighing at least 40 kg without darunavir 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 (see section 4.2).
* DRV-RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

[…]

Annex II was also updated with a correction to the address of one of the manufacturers responsible for batch release

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of France, Romania, Ireland and Cyprus.

3. Overall conclusion and impact on the benefit/risk balance

The type II variation to update the darunavir (DRV; Prezista) product information concerns the inclusion of use of Tybost (cobicistat, COBI) 150 mg once daily as a pharmacokinetic enhancer next to ritonavir. COBI has been approved as a pharmaco-enhancer of Atazanavir and DRV in 2013.

Consequently, the SmPC of COBI was used by the MAH to update the SmPC of DRV using the data of an open-label, randomized, 2-period crossover Phase 1 study in 33 healthy subjects bioequivalence study, GS-US-216-0115. This demonstrated overall similar PK parameters of DRV apart from Ctau, that was ~30% lower. The MAH has already demonstrated that virologic suppression was not influenced by Ctau and as a consequence registration of COBI 150 mg qd as a booster of DRV 800 mg qd has been approved.

In addition, data from a single arm Phase III study GS-US-216-0130 in 295 treatment naive and 18 treatment experienced patients is now submitted to support efficacy and safety (48 week data).

The indications of DRV 800 mg qd boosted by RTV 100 mg qd will also apply to DRV 800 mg qd boosted by COBI 150 mg qd, but only in adults since in patients < 18 years COBI has not been studied.

For treatment experienced patients the same limitations will apply that are incorporated in the use of DRV 800 mg qd when boosted by RTV : without darunavir 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 other patient categories DRV 600 mg twice daily should be administered with RTV 100 mg twice daily, but COBI twice daily cannot be administered because this has never been studied.

The substantiation of the claim of adequate pharmaco-enhancement of DRV by COBI can be derived from study GS-US-216-0130: similar efficacy at week 24 was reported in treatment naive patients when DRV was boosted by COBI compared to efficacy rates from historical studies of DRV in combination with RTV. Efficacy at week 48 was in line with findings at week 24. The week 48 results have been included in section 5.1 of the SmPC.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1 and 5.2 of the SmPC for the 100mg/ml oral suspension and the 400mg, 800mg film-coated tablets with information on the use of darunavir with cobicistat as pharmacokinetic enhancer. Consequential changes have been introduced in the SmPC of all formulations and also in the Package Leaflet (for 100mg/ml, 400 mg and 800 mg film-coated tablets).

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. The manufacturer's address is also corrected in the PL.

Furthermore, there is an update of the Annex II with a correction to the address of one of the manufacturers responsible for batch release.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.