25 September 2014
EMA/664620/2014
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/0064

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. 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 4 February 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

Update of the SmPC (sections 4.1 [75/150/300/600 mg tablets)] 4.2, 4.4 and 5.2) with an extension of indication to use darunavir once daily in children aged 3 to 12 years ≥ 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance-associated mutations (DRV RAMs). This proposed change is based on the data from a 2 week once daily substudy of the Phase 2 study TMC114 C228 and results from model-based pharmacokinetic simulations. The Package Leaflet has been updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics 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 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 of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Greg Markey

Submission date:	4 February 2014
Start of procedure:	21 February 2014
Rapporteur's preliminary assessment report circulated on:	17 April 2014
Co-Rapporteur's preliminary assessment report circulated on:	14 April 2014
PRAC Rapporteur Assessment Report circulated on:	24 April 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	8 May 2014
Rapporteur's updated assessment report circulated on:	19 May 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2014
MAH's responses submitted to the CHMP on:	23 June 2014
PRAC Rapporteur Assessment Report circulated on:	25 August 2014
Joint Rapporteur's final assessment report on the MAH's responses circulated on:	2 September 2014
CHMP opinion:	25 September 2014

2. Scientific discussion

2.1. Introduction

Darunavir, administered twice daily (b.i.d.) in combination with low-dose ritonavir (rtv) and with other ARV agents, is currently indicated for the treatment of HIV-1 infection in treatment-experienced adults and treatment-experienced paediatric subjects aged ≥ 3 years and ≥ 15 kg body weight.

Darunavir, administered once daily (q.d.) in combination with low-dose rtv and with other ARV agents, is currently indicated for the treatment of HIV-1 infection in adults and paediatric subjects from the age of 12 years and at least 40 kg who are either treatment-naive or treatment-experienced with no darunavir resistance-associated mutations (RAMs)*, who have plasma HIV-1 RNA < 100,000 copies/ml, and CD4+ cell count ≥ 100 cells x 10^6/l.

With this type II variation, the MAH requests an extension of the indication to:

Darunavir administered q.d. in combination with low-dose rtv and with other ARV agents, in paediatric

subjects aged 3 to <12 years and weighing ≥ 15 kg who are 1) treatment-naive or 2) treatment experienced with no DRV RAMs, plasma HIV-I RNA <100,000 copies/ml, and CD4+ cell count >100x10^6 cells/l.

Similar to the development of DRV/rtv in adults, the paediatric clinical development program focused first on treatment-experienced HIV-1 infected children, and progressed from older to younger children: a weight based DRV/rtv twice daily (b.i.d.) regimen has been investigated in trial TMC114-C212 in treatment-experienced paediatric patients from 6 to < 18 years of age, followed by trial TMC114-TiDP29-C228 in treatment-experienced paediatric patients from 3 to < 6 years of age. In addition, after at least 32 weeks of treatment with the twice daily regimen, the pharmacokinetics of a DRV/rtv once daily (q.d.) regimen was evaluated in a subset of TMC114-C228 patients after a 2 week once daily treatment period. Finally, the use of DRV/rtv 800/100 mg once daily in treatment-naïve adolescents between 12 to < 18 years of age has been investigated in TMC114-TiDP29-C230.

The registration of the darunavir oral suspension in 2012 allows for dosing in the young age groups (EMEA/H/C/707/X/041/G).

In the present application, the proposed extension of the q.d. indication to subjects aged 3 to <12 years who are a) treatment-naïve or b) treatment-experienced with no DRV RAMs, plasma HIV-1 RNA <100,000 copies/mL, and CD4+ cell count ≥ 100x106 cells/L, is supported by data from:

the 2-week qd substudy of Phase 2 study TMC114-C228 in treatment-experienced subjects aged 3 to <6years, along with results from model-based pharmacokinetic simulations;

extrapolation of efficacy data from adults treated with DRV/rtv qd (Phase 3 study TMC114-C211 in treatment-naïve HIV-1 infected adults and study TMC114-TiDP31-C229 in treatment-experienced HIV-1 infected adults with no DRV RAMs), and data from pediatric subjects aged 12 to <18 years and weighing ≥ 40 kg treated with DRV/rtv qd (study TMC114-TiDP29-C230);

safety data from pediatric clinical studies and Compassionate Use (CU) and other programs up to a cut-off date of 31 October 2013.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

During the assessment procedure, the MAH was requested to address preclinical safety margins and in vitro affinity to off target receptors. It was re-itererated by the MAH that for the original submission of DRV for treatment of HIV-1 infection in adults, all preclinical safety margins were calculated assuming a DRV Cmax of 10,000 ng/mL. As such, those previously established preclinical margins for DRV could apply to this pediatric population as well. No further preclinical data are available for DRV on in vitro affinity to off-target receptors.

In the absence of clinical safety signals and PK/PD (safety) relationships for DRV, it is considered that the proposed dosing regimens for the pediatric population are justified.

2.2.1. Ecotoxicity / environmental risk assessment

For type II variations, the evaluation of the environmental impact should be made if there is an increase in the environmental exposure e.g. a new indication may result in a significant increase in the extent of the use (Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 corr 1).

Based on the current total Prezista sale volume, the naïve indication in children aged 3 to < 12 years of age is not expected to increase on the total environmental exposure. Hence, the MAH didn't submit an updated Environmental Risk Assessment with this application.

The justification by the MAH is considered acceptable by the CHMP. The CHMP agrees with the MAH that no increase in the environmental exposure is expected.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies (paediatric program)**

Study title	Study number TMC114-TiDP29-	Date of completion (LPLV)	Date of submission of final study report
A Phase I, open label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of darunavir (DRV) to that of the commercial 300 mg tablet formulation in the presence of low dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low dose ritonavir.	C169	18/08/2008	CSR included in application EMEA/H/C/000707/X41G, submitted to EMA May 4th 2011.
A Phase II, open label trial to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV in combination with low dose ritonavir (DRV/rtv) in treatment experienced HIV-1 infected children from 3 years to < 6 years of age. After at least 32 weeks of treatment with the twice daily regimen, the pharmacokinetics of a DRV/rtv once daily regimen was evaluated in a subset of patients after a 2 week once daily treatment period.	C228	28/02/2011	The 24 weeks and 48 weeks study reports for TMC114-TiDP29-C228 are included in the response to questions on EMEA/H/C/000707/X/41G (March 22nd, 2012).
A Phase II, open label trial, to investigate pharmacokinetics, safety, tolerability and antiviral activity of TMC114/rtv b.i.d. in treatment experienced HIV-1 infected children and adolescents	C212	08/10/2011 (main phase); 30/03/2011 (long term	24 weeks data of this study was the initial scope of application EMEA/H/C/000707/X/020, submitted to EMA June 27th 2008. 48 weeks data have

from 6 to <18 years and weighing ⩾20 kg.		extension)	been submitted in the Response to Questions of this same application, submitted to EMA February 18th 2009. The final study report has been submitted in an Article 46 submission on September 30th, 2011. The response to questions has been submitted on January 17th, 2012.
A Phase II, open label trial, to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV/rtv once daily in treatment-naïve HIV 1 infected adolescents aged between 12 and < 18 years.	C230	31/03/2011	Study report was submitted according to Article 46 of Regulation (EC) No1901/2006 (concluded in September 2012), and submitted as part of EMEA/H/C/000707/II/054.

2.3.2. Clinical pharmacology

A total of 10 HIV-1 infected paediatric subjects were treated with study medication in the once daily sub-study TMC114-C228.

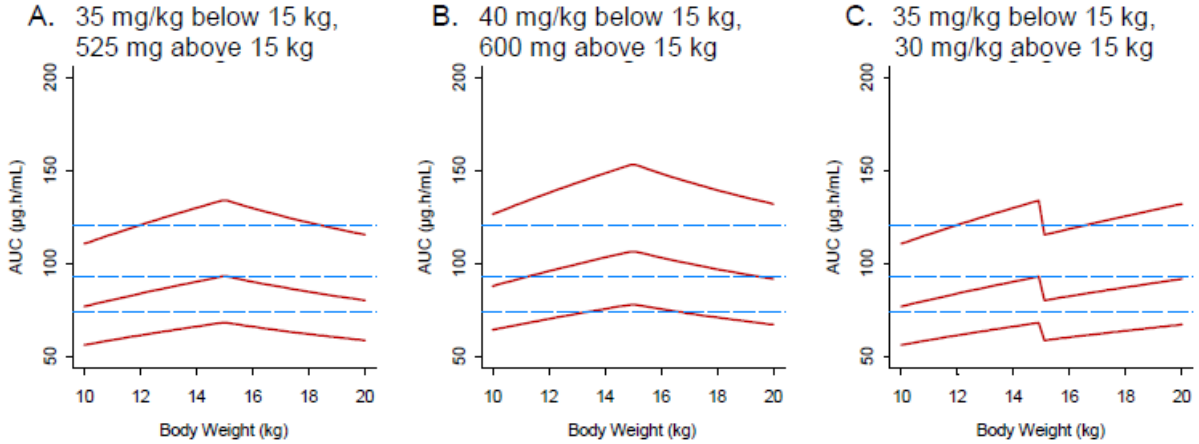
Treatment-experienced HIV-1 infected paediatric subjects from 3 to <6 years of age who participated in study TMC114-C228, and who had a confirmed viral load <50 HIV-1 RNA copies/ml after 24 weeks of treatment, could participate in the once-daily sub-study of this study. These subjects had their weight-based DRV/rtv twice-daily dosing regimen in the main study switched for 2 weeks to a target dose of DRV/rtv 40/7 mg/kg once daily for subjects weighing 10 to <15 kg and a dose of 600/100 mg once daily for subjects weighing ≥ 15 kg; their optimized background regimen (OBR) of antiretroviral (ARV) drugs from the main study was continued. After completion of the rich PK sampling of DRV and rtv in plasma at Week 2 of the once-daily sub-study, all subjects reverted back to their DRV/rtv twice-daily dosing regimen in the main study.

The population PK model for DRV, consisting of adult and paediatric (TMC114-C212, TMC114-C228, TMC125-C206, TMC125-C216) PK data, was updated with the results of the once-daily sub-study of TMC114-C228 and study TMC114-C230 (a study in treatment-naive paediatric subjects aged from 12 to <18 years). This model was then used to simulate dosing regimens to recommend a weight-based once-daily dose of DRV in combination with rtv for paediatric subjects from 3 to <12 years of age and weighing ≥15 kg. The objective of this model-based simulation was to achieve PK exposures (AUC24h) and plasma trough concentrations (C0h) in the HIV-1 infected paediatric population that were similar to those observed when DRV/rtv is administered at a dose of 800/100 mg once daily in HIV-1 infected adults (treatment-naive and treatment-experienced with no DRV RAMs). A target exposure (AUC24h) of 89.7 µh.h/ml was used, which represents the geometric mean DRV AUC24h observed in treatment-naive HIV-1 infected adults (study TMC114-C211). Darunavir AUC24h and C0h, when DRV is administered as DRV/rtv 800/100 mg once daily, is similar between treatment-naive HIV-1 infected adults and HIV-1 infected adults who are treatment-experienced with no DRV RAMs.

The DRV doses selected for use in the sub-study were based on simulations of DRV exposures using a previously developed population PK model for DRV updated to accommodate data from HIV-1 infected paediatric subjects from 3 to <18 years of age treated with a twice-daily regimen. Simulations for the expected DRV exposure according to the 5th, 50th (ie, median), and 95th percentile of α1 acid glycoprotein (AAG) in paediatric subjects from 3 to <6 years of age and weighing from 10 to <20 kg were performed for 3 different dosing strategies (see figure 1). The objective of this simulation was to determine a convenient

dose of DRV that would target the arithmetic mean exposure of DRV in adults when treated with DRV/rtv 800/100 mg once daily (ie, 93.0 µg.h/ml) while minimizing the risk of under-dosing.

Figure 1: Plots of Expected DRV Exposures (When Coadministered With rtv) in HIV-1 Infected Subjects From 3 to <6 Years of Age (Study TMC114-C228 Substudy)

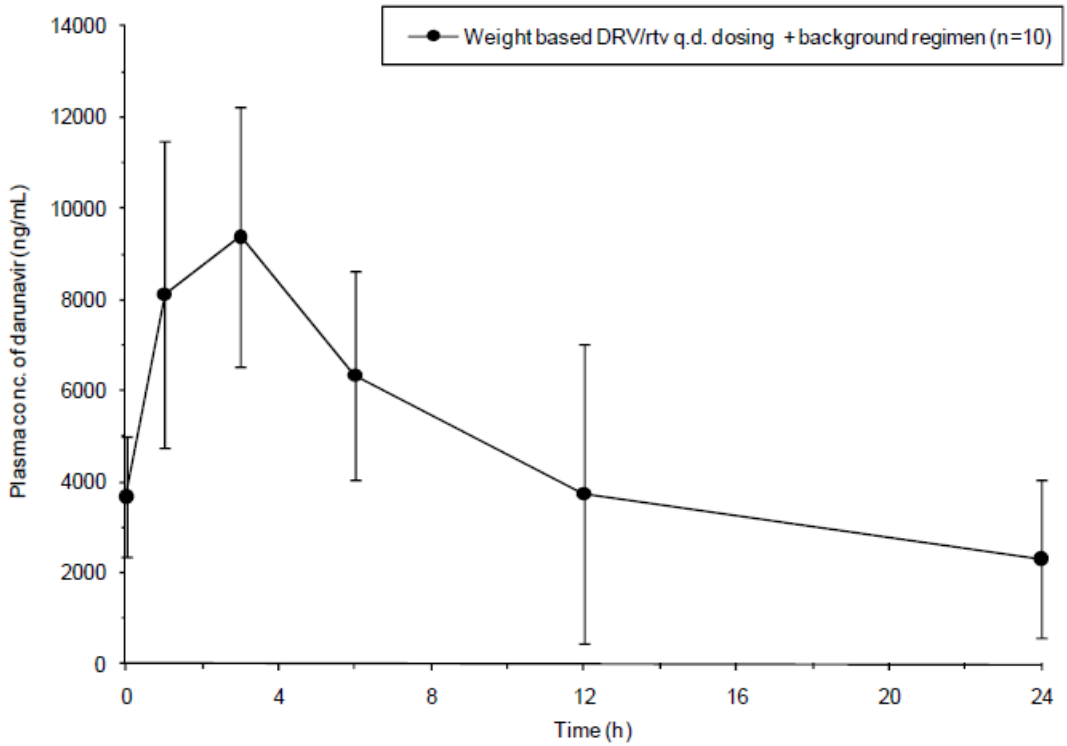


The expected DRV exposure is given for the 5th, 50th (ie, median), and 95th percentile of AAG concentrations (red lines), and compared with 80%, 100%, and 130% of the target exposure in adults (93.0 µg.h/mL, blue lines).
Source: Module 5.3.3.5/TMC114-C230-CPOP-W24-Err/Figure 0.5

The expected DRV exposure in dosing regimens A and C was considered insufficient, particularly for paediatric subjects with AAG below the median and with lower body weight. Dosing regimen B was implemented for the once-daily sub-study of TMC114-C228, i.e., 40 mg/kg once daily for subjects weighing less than 15 kg and 600 mg once daily for subjects weighing at least 15 kg (both co-administered with rtv), because this dosing strategy best fit the set objectives. This dosing strategy was endorsed by the Data Safety Monitoring Board for the study.

The mean plasma concentration-time curve for DRV obtained in the sub-study is shown in figure 2. The maximum mean plasma concentrations were reached at 3 hours after intake of DRV/rtv.

Figure 2: **Mean (SD) Plasma Concentration-Time Profile of DRV at Week 2 After Administration of DRV/rtv 40/7 mg/kg Once Daily (Subjects <15 kg) or 600/100 mg Once Daily (Subjects ≥ 15kg) in HIV-1 Infected Subjects From 3 to <6 Years of Age (Study TMC114-C228 Substudy)**



The PK parameters for DRV are summarized in table 1. Based on the coefficient of variation (CV), the inter-individual variabilities of the minimum plasma concentration (Cmin), the maximum plasma concentration (Cmax), and AUC24h were 59%, 27%, and 38%, respectively.

When compared with historical data for DRV administered as DRV/rtv 800/100 mg once daily in treatment-naïve HIV-1 infected adults (sub-study of TMC114-C211), the Cmin, Cmax, and AUC24h values for DRV in treatment-experienced HIV-1 infected pediatric subjects from 3 to <6 years of age were 1.33-, 1.81-, and 1.62-fold higher, respectively, than in the adults (table 1).

Table 1: Pharmacokinetics of DRV After administration of DRV/rtv 40/7 mg/kg once daily (subjects <15 kg) or 600/100 mg once daily (subjects ⩾15 kg) in HIV-1 infected subjects from 3 to <6 years of age (study TMC114-C228 sub-study) and after administration of DRV/rtv 800/100 mg once daily in HIV-1 infected adults (study TMC114-C211 sub-study)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test Mean (SD)	Reference Mean (SD)	
	TMC114-C228 Substudy: DRV/rtv qd in Treatment-Experienced HIV-1 Infected Pediatric Subjects, Week 2	TMC114-C211 Substudy: DRV/rtv 800/100 mg qd in Treatment-Naïve HIV-1 Infected Adults, Week 4	
n	10	9	-
t_{max}, h	2.92 (0.93-11.6)	3.0 (1.0-4.1)	-
C_{0h}, ng/mL	3,670 (1,313)	1,826 (1,003)	-
C_{min}, ng/mL	2,063 (1,226)	1,189 (410)	1.33 (0.76; 2.32)
C_{max}, ng/mL	10,640 (2,881)	5,471 (1,320)	1.81 (1.44; 2.28)
AUC_{24h}, ng.h/mL	113,900 (43,540)	64,230 (18,210)	1.62 (1.21; 2.17)
CL/F, L/h	5.7 (1.8)	-	-

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

The PK parameters for rtv are summarized in table 2. Based on the CV, the inter-individual variabilities of Cmin, Cmax, and AUC24h were 47%, 62%, and 47%, respectively.

When compared with historical data for rtv administered as DRV/rtv 800/100 mg once daily in treatment-naïve HIV-1 infected adults (sub-study of TMC114-C211), rtv Cmin, Cmax, and AUC24h values in treatment-experienced HIV-1 infected paediatric subjects from 3 to <6 years of age were 1.31-, 3.45-, and 3.40-fold higher, respectively, than in the adults (table 2).

Table 2: Pharmacokinetics of rtv after administration of DRV/rtv 40/7 mg/kg once daily (subjects <15 kg) or 600/100 mg once daily (subjects ⩾15 kg) in HIV 1 infected subjects from 3 to <6 years of age (study TMC114 C228 sub-study) and after administration of DRV/rtv 800/100 mg once daily in HIV-1 infected adults (study TMC114-C211 sub-study).

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test Mean (SD)	Reference Mean (SD)	
	TMC114-C228 Substudy: DRV/rtv qd in Treatment-Experienced HIV-1 Infected Pediatric Subjects, Week 2	TMC114-C211 Substudy: DRV/rtv 800/100 mg qd in Treatment-Naïve HIV-1 Infected Adults, Week 4	
n	10	9	-
t_{max}, h	2.92 (0.93-11.6)	4.0 (0.0-6.0)	-
C_{0h}, ng/mL	318 (223)	141 (156)	-
C_{min}, ng/mL	102 (48.3)	84.1 (71.4)	1.31 (0.73-2.35)
C_{max}, ng/mL	2,356 (1,455)	603 (320)	3.45 (2.21-5.37)
AUC_{24h}, ng.h/mL	21,220 (10,010)	5,891 (3,152)	3.40 (2.26-5.12)
CL/F, L/h	5.4 (2.4)	-	-

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

As indicated, the population pharmacokinetic model is updated after inclusion of the data after once daily intake in the TMC114-C228 sub-study and in the TMC114-C230 trial, which was implemented by pooling the richly sampled data from the children aged 3 to <6 years in TMC114-C228 and from the children aged 12 to <18 years in TMC114-C230 together with the data that were used for the previous model adjustment accounting for DRV/rtv b.i.d. intake in children aged 3 to <18 years.

The dataset for the TMC114-C228 q.d. sub-study consisted of 10 individuals, with 59 observations after two weeks of treatment. The dataset for TMC114-C230 consisted of 12 individuals, with 71 observations after two weeks of treatment. The overall dataset for the parameter estimation, including the data from the ARIEL, DELPHI and DUET studies, consisted of 659 observations from 102 subjects (72 children and 30 adults).

The pharmacokinetic parameter values for darunavir were estimated in NONMEM using the paediatric population PK model, i.e. a two-compartment model with a first-order absorption (parameterized as KA and fixed to the previously obtained value). The distribution compartment was parameterized in terms of apparent volume (V3/F) and apparent inter-compartmental clearance (Q/F). Both V3/F and Q/F values were fixed. Equation 1 is used to describe the apparent clearance of darunavir as was determined previously.

Equation 1:

$$CL/F_i = \frac{CL_{int}/F \cdot \left(\frac{1}{1+K_{AFF} \cdot AAG_i}\right) \cdot \left(\frac{WT_i}{70}\right)^{\theta} \cdot e^{\eta_i}}{F_{rel}}$$

Where CL/F_i is the apparent oral clearance of an individual, CL_{int}/F the population estimate of apparent intrinsic clearance, K_{AFF} is the population estimate for the affinity of darunavir to alpha1-acid glycoprotein (AAG) and was fixed to its previously obtained value, θ is the influence of the individual weight (WTi) on apparent clearance and ηi is the individual random effect. Frel is the population estimate of the relative bioavailability correction for the commercial tablet formulation (Frel=1.18, fixed value) compared to the previously used clinical trial tablet formulation as determined in the original model in adults.

For V2/F, the model was adjusted as follows:

$$V2/F_i = \frac{V2/F \cdot \left(\frac{WT_i}{70}\right)^{\theta} \cdot e^{\eta_i}}{F_{rel}}$$

The model parameters are shown in the table 3 below.

Table 3: Darunavir parameter estimates for the original pediatric population pharmacokinetic model.

Parameter	Parameter Estimate	Parameter SEE (CV%)	IIV Estimate (CV%)	IIV SEE (CV%)
CL_{int}/F (L/h)	51.2	5.0	29	20
Influence of WT[a] on CL/F	0.512	11		
K_{AFF} of AAG (dL/mg)	0.0304	---		
V2/F (L)	127	11	47[b]	124
Influence of WT[a] on V2/F	0.769	19		
Q/F (L/h)	15.0	---	65	---
V3/F (L)	84.3	---	56	---
KA (1/h)	0.455	---	80[b]	32
F_{rel}	1.18	---		
Multplicative residual error	0.0597	12		

a : Change in parameter based on body weight (WT)

b : Correlation between the variance estimates of apparent central volume and absorption rate constant estimated at 0.69.

The parameter estimates obtained from the model update are shown in table 4. Only slight changes in the parameter estimates are observed for CL/F and V2/F, compared to the model developed for children from 3 to ≤ 18 years old after b.i.d administration. The influence of body weight on CL/F and V2/F was unchanged. The major impact of the model adjustment was the increase of V3/F and Q/F. Due to the once daily dosing, more information was gathered on these parameters, allowing their estimation. IIV on V2/F and V3/F on the other hand were too small to be properly estimated compared to the previous model. The goodness-of-fit plots for the adjusted model showed that the bias in the individual prediction versus the observation is minimal.

Table 4: Darunavir population PK parameters after update.

Parameter	Parameter Estimate	Parameter SEE (CV%)	IIV Estimate (CV%)	IIV SEE (CV%)
CL_{inf}/F (L/h)	51.0	4.7	28	20
Influence of WT[a] on CL/F	0.504	11		
K_{AFF} of AAG (dL/mg)	0.0304	---		
V2/F (L)	137	21		
Influence of WT[a] on V2/F	0.774	18		
Q/F (L/h)	19.1	16	64	59
V3/F (L)	254	41		
KA (1/h)	0.528	17	50	66
F_{rel}	1.18	---		
Multiplicative residual error	0.0717	12		

a : Change in parameter based on body weight (WT)

The arithmetic mean darunavir exposure is 120 µg.h/ml (see table 5) which represents 129% of the target (exposure arithmetic mean of 93.0 µg.h/ml in ARTEMIS study). The geometric mean darunavir exposure is 115 µg.h/ml which represents 128% of the target geometric mean (exposure geometric mean of 89.7 µg.h/ml in ARTEMIS study).

Table 5. Summary statistics of the median individual pharmacokinetic parameters in the TMC114-C228 q.d. sub-study.

Parameter	AUC_{tau} (µg.h/mL)	C_{0h} (ng/mL)	CL/F (L/h)	$C_{ss, ave}$ (ng/mL)
N	10	10	10	10
Mean	120	3371	5.39	5014
Geometric mean	115	3029	5.12	4783
SD	40.6	1715	1.69	1690
SE	12.8	542	0.53	534
95% CI	95.2 - 145	2309 - 4434	4.34 – 6.43	3967 - 6062
Min	76.3	1570	2.90	3178
5^{th} percentile	81.5	1641	2.99	3397
25^{th} percentile	90.5	2277	4.08	3772
Median	107	2981	5.66	4455
75^{th} percentile	141	3678	6.63	5887
95^{th} percentile	187	6340	7.40	7800
Max	193	6416	7.87	8033

The fact that the mean exposure is on the upper side of the target may be explained by two individuals having a high exposure. These two subjects exhibited high AAG values and low body weight, as illustrated in figure 3, therefore, low clearances and high exposures were expected.

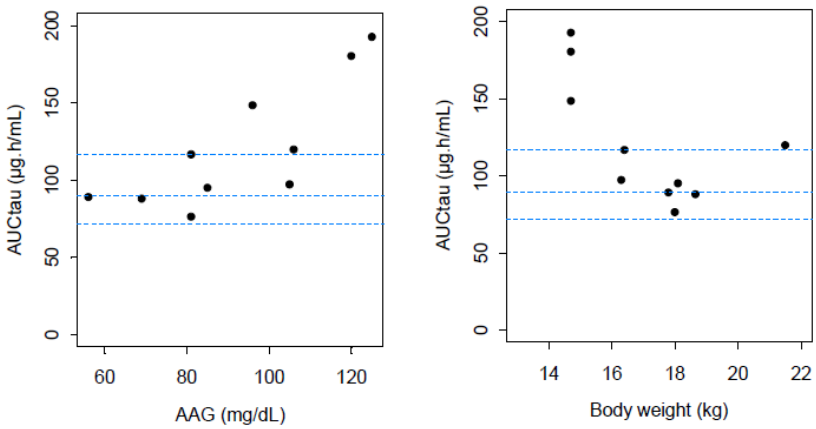


Figure 3: Correlation of the model-estimated AUCtau with AAG (left) and body weight (right). The blue dotted lines represent the target adult exposure (geometric mean) and its 80-130% associated interval.

The results of the population PK analysis of DRV at Week 2 of the sub-study were consistent with the non-compartmental PK analysis.

The arithmetic mean AUC24h for DRV was 120 µg.h/mL, which was 1.29-fold higher than the arithmetic mean of the target adult exposure in study TMC114-C211 (93.0 µg.h/ml). The geometric mean AUC24h for DRV was 115 µg.h/ml, which was 1.28-fold higher than the geometric mean of the target DRV exposure in treatment-naïve HIV-1 infected adults in study TMC114-C211 (89.7 µg.h/ml).

Simulated dosing regimens were investigated for their ability to achieve DRV exposures that were close to the target adult exposure while minimizing the pill burden and permitting a switch from the DRV oral suspension to a DRV tablet formulation at the earliest opportunity. While clinical studies were conducted with DRV/rtv once-daily treatment in children from 3 to <6 years of age (10 to 20 kg) and from 12 to <18 years of age (40 to 65 kg), the adjusted population PK model was used to bridge data to cover also children 6 to <12 years of age (20 to 40 kg) for DRV/rtv once-daily dosing.

Because AAG concentrations were shown to be important determinants for DRV exposure in the population PK analysis, simulations were performed using the 5th, 50th (i.e., median) and 95th percentile of AAG concentrations observed in TMC114-C228 and TMC114-C230. Based on the typical value of the clearance parameter obtained in the updated popPK analysis (see table 4), the expected DRV exposures (AUC24h) for different dosing regimens were simulated over a weight range of 10 to 65 kg.

The investigated weight range was divided into 5 weight bands: 10 to 15 kg, 15 to 20 kg, 20 to 30 kg, 30 to 40 kg, and ≥ 40 kg. For each of these weight bands, various dosing regimens were simulated, taking the available DRV tablet strengths (75-, 400-, and 600-mg tablets) and the DRV oral suspension (100-mg/ml suspension) into consideration. The following once-daily regimens were explored for DRV:

- 30, 35, and 40 mg/kg for the 10 to 15 kg weight band
- 30 and 35 mg/kg, and 600 mg for the 15 to 20 kg weight band
- 600 and 675 mg for the 20 to 30 kg weight band
- 675 and 800 mg for the 30 to 40 kg weight band
- 800 mg for the ⩾40 kg weight band

The simulations assumed the presence of rtv (7 mg/kg or 100 mg q.d.).

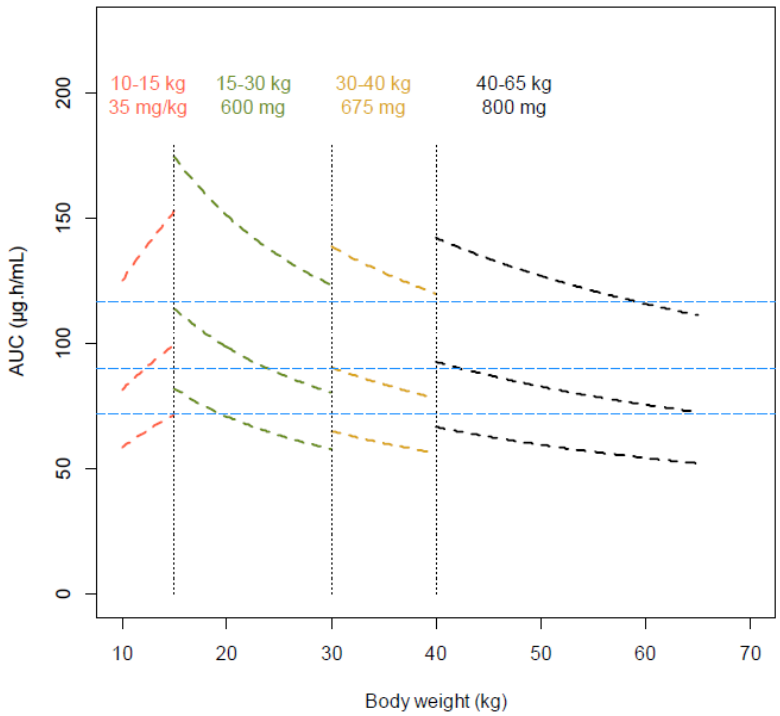
The result summary for DRV AUC and C0h obtained with the NONMEM simulations for the different q.d. dosing regimen per weight band together with observed values in adults in TMC114-C211 are displayed in table 6.

Table 6. Summary statistics of the simulated DRV AUC and C0h parameters for once daily regimen.

Weight Category	QD DRV Dose	C_{0h} Median (ng/mL) (5^{th}-95^{th} percentile)	AUC Median (µg.h/mL) (5^{th}-95^{th} percentile)
10-15 kg	30 mg/kg	2203 (1337 - 4002)	77.2 (52.0 – 125)
10-15 kg	35 mg/kg	2570 (1560 - 4669)	90.0 (60.6 – 146)
10-15 kg	40 mg/kg	2937 (1782 - 5336)	103 (69.3 – 167)
15-20 kg	30 mg/kg	2495 (1514 - 4537)	91.5 (62.9 – 146)
15-20 kg	35 mg/kg	2911 (1767 - 5293)	107 (73.3 – 171)
15-20 kg	600 mg	2893 (1708 - 5372)	106 (73.1 – 170)
20-30 kg	600 mg	2298 (1301 - 4461)	88.4 (59.7 – 146)
20-30 kg	675 mg	2585 (1463 - 5019)	99.5 (67.2 – 164)
30-40 kg	675 mg	2084 (1190 - 4000)	83.8 (57.6 – 135)
30-40 kg	800 mg	2470 (1410 - 4741)	99.3 (68.3 – 160)
40-65 kg	800 mg	1920 (1031 - 3948)	81.1 (53.8 – 137)
Adult (TMC114-C211)	800 mg	2041 (911 – 4632)	87.9 (60.5 – 143)

The expected exposures (AUC24h) for DRV/rtv once-daily dosing regimens of 35 mg/kg for subjects weighing 10 to <15 kg, 600/100 mg for subjects weighing 15 to <30 kg, 675/100 mg for subjects weighing 30 to <40 kg, and 800/100 mg for subjects weighing ≥ 40 to 65 kg are shown in Figure 4.

Figure 4: Plots of the expected DRV AUC24h when co-administered with rtv in HIV-1 infected subjects from 3 to <18 years of age in weight bands across the weight range of 10 to 65 kg.



Red curve = 35 mg/kg once daily in subjects weighing 10 to 15 kg. Green curve = 600 mg once daily in subjects weighing 15 to 30 kg. Yellow curve = 675 mg once daily in subjects weighing 30 to 40 kg. Black curve = 800 mg once daily in subjects weighing 40 to 65 kg. The expected exposure is given for the 5th, 50th (ie, median), and 95th percentile of AAG concentrations, and compared with 80%, 100%, and 130% of the target exposure in adults (89.7 µg.h/ml, blue lines).

The mean exposure of DRV achieved with the dosing regimens shown in figure 9 is expected to be within 80% to 130% of the target DRV exposure in treatment-naïve HIV-1 infected adults in study TMC114-C211 when AAG concentration is average. This regimen limits the risk of overexposure without compromising efficacy, as the lower range of exposure (AUC and C0h) is within observed adult ranges. There is a greater chance of achieving a higher DRV exposure in children with higher AAG concentrations. However, no association was observed between the exposure of DRV and the development of AEs or laboratory abnormalities in DRV studies conducted to date.

Based on DRV exposure, these proposed dosing regimens could be considered for treatment naïve

HIV-1 infected paediatric subjects as well as treatment-experienced HIV-1 infected paediatric subjects without DRV RAMs because DRV exposure is comparable to that observed in treatment-naïve HIV-1 infected adults and treatment-experienced HIV-1 infected adults with no DRV RAMs when treated with DRV/rtv 800/100 mg once daily (table 7).

Table 7. Population PK estimates for DRV following administration of DRV/rtv 800/100 mg once daily in treatment-naïve and treatment-experienced HIV-1 infected adults (studies TMC114-C211 and TMC114-C229).

	Geometric Mean; Median (Range)	
	Treatment-Naïve HIV-1 Infected Adults	Treatment-Experienced HIV-1 Infected Subjects Without DRV RAMs
Parameter	TMC114-C211	TMC114-C229
N	335	280
AUC_{24h}, ng.h/mL	89,706	89,471
	87,854	87,788
	(45,000-219,240)	(45,456-236,920)
C_{0h}, ng/mL	2,027	1,856
	2,041	1,896
	(368-7,242)	(184-7,881)

N = maximum number of subjects with data.

2.3.3. Discussion

A population pharmacokinetic model for darunavir in adults was already available. This model was adjusted as follows:

- adjustment to accommodate the difference in exposure after administration of the clinical trial and the commercial tablet formulation.

-adjustment to accommodate the data from children between the ages of 3 to <18 years old treated b.i.d. This model was based on richly sampled plasma concentration profiles obtained in studies TMC114-C228, TMC114-C212, TMC125-C206 and TMC125-C216 (studies submitted with the original marketing authorisation application).

- update of the model by inclusion of the data obtained after once daily intake (TMC114-C228 sub-study and in the TMC114-C230 trial), which was implemented by pooling the richly sampled data from the children aged 3 to <6 years in TMC114-C228 and from the children aged 12 to <18 years in TMC114-C230 together with the data that were used for the previous model adjustment accounting for DRV/rtv b.i.d. intake in children aged 3 to <18 years.

- This model was then used to simulate once-daily dosing regimens in HIV-1 infected pediatric subjects from 3 to <12 years of age and weighing ⩾15 kg that would achieve similar levels of darunavir exposure to those observed in HIV-1 infected adults.

Individual darunavir pharmacokinetic parameters for subjects involved in the TMC114-C228 q.d. sub-study were derived during the population pharmacokinetic analysis as described before. Simulation records were added to the dataset to obtain an estimation of the through darunavir plasma concentrations.

The goodness-of-fit plots from the adjusted model, containing only the data from the TMC114-C228 q.d. sub-study subjects, indicate that the model predictions appear to be accurate, with no detectable bias present for individual predictions.
The results of the population PK analysis of DRV at Week 2 of the sub-study were consistent with the non-compartmental PK analysis.

Simulated dosing regimens were investigated for their ability to achieve DRV exposures that were close to the target adult exposure while minimizing the pill burden and permitting a switch from the DRV oral suspension to a DRV tablet formulation at the earliest opportunity. While clinical studies were conducted with DRV/rtv once-daily treatment in children from 3 to <6 years of age (10 to 20 kg) and from 12 to <18 years of age (40 to 65 kg), the adjusted population PK model was used to bridge data to cover also children 6 to <12 years of age (20 to 40 kg) for DRV/rtv once-daily dosing, which is considered acceptable.
Different dosing regimens were simulated over a weight range of 10 to 65 kg. For children with a weight of 10 to <15 kg, a regimen of 35 mg/kg resulted in a similar exposure compared to adult. This also account for a DRV q.d. regimen of 600 mg in children of 15 to < 30 kg, although for the 15 – 20 kg exposure was at the higher end, it is considered not to be a safety problem and it offers the opportunity of the use of the tablet formulation instead of the suspension for the whole group.
A DRV q.d. regimen of 675 mg is expected to provide comparable exposure to adult in the 30 to <40 kg group. From 40 kg and above, the adult DRV/rtv regimen (800/100 mg q.d.) can be used from 40 kg onward and leads to similar DRV exposure compared to adult.
Nonetheless, exposures seen for both darunavir and ritonavir in the phase II study (TMC114- 228) in 3- 6 years old seem high and are higher than that seen in any adult studies involving chronic dosing. This is particularly true of the Cmax values for both components, with mean values of 10.6 and 2.4 µg/ml for darunavir and ritonavir respectively. Although safety events in this study appear acceptable it is considered that the data being in only 10 individuals are too limited to allow a thorough assessment of safety. Further data to support safety with exposures with these Cmax values is required. In addition a mechanistic PKPD discussion of the importance of Cmax for safety based on all data should be provided.

In addition to this, although the population PK model seems well developed and validated, it seems to be less accurate for prediction of higher plasma concentrations regarding Cmax (see diagnostic plots). A similar divergence is seen for the plots for the study in the 3-6 year olds. This is often the case for these models where Cmax is less well defined due to sparse sampling. In general it appears that the model will under predict the Cmax. Further diagnostic plots are therefore required to show the accuracy of prediction of the plasma concentration profiles in the children for which PK data are available. However it is accepted that if sufficient data are provided from previous studies to support safety at the exposures seen in the clinical study for 3 - 6 year olds then the model is probably judged sufficient to bridge to simulate similar exposures in the other age categories.

Based on DRV exposure, these proposed dosing regimens could be considered for treatment naïve HIV-1 infected paediatric subjects as well as treatment-experienced HIV-1 infected paediatric subjects without DRV RAMs because DRV exposure is comparable to that observed in treatment-naïve HIV-1 infected adults and treatment-experienced HIV-1 infected adults with no DRV RAMs when treated with DRV/rtv 800/100 mg once daily.

Based upon these data, the SmPC proposes the following dose regimens:

ART naïve paediatric patients (3 to 17 years of age and weighing at least 15 kilograms).

The weight based dose of PREZISTA and ritonavir in paediatric patients is provided in the table below.

Table 8

Recommended dose for treatment-naïve paediatric patients with PREZISTA and ritonavir[a]	
Body weight (kg)	Dose (once daily with food)
≥ 15 kg to < 30 kg	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily
≥ 30 kg to < 40 kg	675 mg (6.8 ml)[b] PREZISTA/100 mg (1.2 ml) ritonavir once daily
≥ 40 kg	800 mg (8 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily

[a] ritonavir oral solution: 80 mg/ml

[b] rounded up for suspension dosing convenience

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).

Table 9

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

With regard to the recommended doses, in the POPPK model weight is a covariate with an exponent of 0.502 (i.e., somewhat lower than the value of 0.75 normally expected), although it is accepted that AAG is also a covariate in the model which can also influence the relationship. The relationship with weight would suggest lower doses in each of the age categories would achieve the target drug exposure as defined in the adult population (see table below for comparison of MAH's proposal and assessor's calculation of dose required in children by scaling the adult dose with body weight with the exponent 0.502.

In the TMC114-C228 once daily substudy, a darunavir/low-dose ritonavir (DRV/rtv) dosing regimen of 40/7 mg/kg once daily was evaluated for subjects <15 kg, and a dosing regimen of 600/100 mg once daily for

subjects ≥15 kg. Table 10 displays the individual maximum plasma concentration (Cmax) values observed with their DRV/rtv allocated treatment. Table 11 presents summary statistics of Cmax per DRV/rtv dosing regimen.

Tables 10 & 11

Table 1: Individual Doses and C_{max} Values Observed in the TMC114-C228 Once Daily Substudy

Subject ID	DRV/rtv Once Daily Dose	Observed C_{max} (ng/mL)
TMC114-C228-0001	600/100 mg	12,800
TMC114-C228-0003	600/100 mg	7,020
TMC114-C228-0007	600/100 mg	10,100
TMC114-C228-0009	600/100 mg	6,000
TMC114-C228-0015	600/100 mg	11,700
TMC114-C228-0020	600/100 mg	7,940
TMC114-C228-0021	40/7 mg/kg	13,000
TMC114-C228-0027	600/100 mg	10,700
TMC114-C228-0029	40/7 mg/kg	15,000
TMC114-C228-0040	40/7 mg/kg	12,100

Table 2: Summary Statistics of C_{max} Values in TMC114-C228 Once Daily Substudy per DRV/rtv Dose Regimen

DRV/rtv Dose	C_{max} (ng/mL)			
	N	Mean	SD	Max
40/7 mg/kg[a]	3	13,367	1,484	15,000
600/100 mg	7	9,466	2,528	12,800

SD=standard deviation.

[a] This dose regimen was evaluated in children <15kg, which is not subject of this application.

It is acknowledged that the DRV/rtv 40/7 mg once daily dose in pediatric subjects weighing less than 15 kg could lead to higher Cmax values than those typically observed in adults, as also shown in Table 15. Simulations indicated that a DRV/rtv 35/7 mg/kg once daily dose regimen would be more appropriate for the pediatric subpopulation of 10 to <15kg. However, this specific pediatric population (<15 kg) is not subject of this application.

For children ≥15 to <30 kg, a DRV/rtv 600/100 mg once daily dosing regimen is proposed, as also evaluated in the once daily substudy of TMC114-C228. All children dosed with 600/100 mg once daily in TMC114-C228 weighed between 16 and 21 kg. As such, it is not unexpected that the observed individual and mean C-max for this particular subset of subjects are on the higher end of those anticipated for the full pediatric cohort of ≥15 to <30 kg. However, the observed Cmax values were still within the range of those observed in other studies for children and adults**.**

Furthermore, the anticipated DRV exposures with the proposed once daily dosing regimen were also compared with the approved twice daily dosing regimen for this pediatric population. This comparison showed that the range of anticipated exposures, including Cmax, is similar for the once daily and twice daily regimens. It is acknowledged that there may be some bias in the estimation of Cmax with the population pharmacokinetic (popPK) model (which has been further validated), but this bias is anticipated to be minimal, and similar for both the once daily and twice daily dosing regimens.

Conclusions on clinical pharmacology

The proposed dosing regimens could be considered for treatment naïve HIV-1 infected paediatric subjects as well as treatment-experienced HIV-1 infected paediatric subjects without DRV RAMs as the population pharmacokinetic analysis indicate that DRV exposure is comparable to that observed in treatment-naïve HIV-1 infected adults and treatment-experienced HIV-1 infected adults with no DRV RAMs when treated with DRV/rtv 800/100 mg once daily. However, in the PK substudy higher Cmax levels were observed, which may trigger safety concerns. Moreover, although the population pharmacokinetic model predicted a comparable exposure, there was uncertainty with regard to the prediction of Cmax and the recommended dose. This aspect was however further clarified by the MAH during the variation procedure. The MAH presented additional data indicating that although with the limitations of the model, Cmax values were within the range of once daily dosing. As shown in PK figures, the predicted 95th percentile are comparable for recommended once and the approved twice daily dosing regimens.

2.4. Clinical Efficacy

2.4.1. Main study

Once Daily Substudy of TMC114-C228 in Treatment-experienced Pediatric Subjects Aged 3 to <6 Years

Study TMC114-C228 has been submitted and assessed within procedure X-41-G. The present 2-week pharmacokinetic substudy of TMC114-C228 was performed between Weeks 32 and 40 to evaluate the pharmacokinetics of DRV/rtv q.d. dosing. Dosing recommendations for the DRV/rtv q.d. substudy were based on the updated pharmacokinetic model of DRV with the rich pharmacokinetic data obtained at Week 2 with the b.i.d. dosing regimen of DRV/rtv in the main study TMC114-C228.

Ten treatment-experienced HIV-1 infected children aged 3 to <6 years and weighing between 10 and <20 kg were treated with DRV/rtv qd for 2 weeks. Seven subjects received DRV/rtv 600/96 mg qd, and 3 subjects were to receive DRV/rtv 560/92 mg (40/7 mg/kg) qd. However, due to the accuracy constraints of the rtv pipette, the actual rtv dose for the latter 3 subjects was also 96 mg qd.

The main objective of the q.d. dosing TMC114-C228 substudy was to evaluate the pharmacokinetics of DRV/rtv at steady-state after q.d. dosing in HIV-1 infected children, aged from 3 to < 6 years at screening and weighing between 10 and < 20 kg at screening, with a confirmed undetectable plasma viral load (< 50 HIV-1 RNA copies/mL) at Week 32. See section 2.3 on details. The secondary objective was to evaluate the short-term safety and tolerability. AEs were monitored, as part of the main study, on an ongoing basis from signing the ICF onwards until the last study-related visit.

No formal sample size calculation was performed. There was no randomisation. The study was open label.

All subjects participating in the substudy remained undetectable (< 50 HIV-1 RNA copies/mL) after 2 weeks of DRV/rtv q.d. dosing.

2.4.2. Discussion on clinical efficacy

This small 2-week pharmacokinetic substudy of TMC114-C228 was intended to collect data on pharmacokinetics. There is very limited data on efficacy, all 10 subjects maintained undetectable plasma viral load (< 50 HIV-1 RNA copies/mL). However, efficacy of the once daily dose regimen in treatment naïve children can be extrapolated from adults.

2.4.3. Conclusions on the clinical efficacy

In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (Doc. Ref. EMEA/CPMP/EWP/633/02), based on the identification of suitable dose regimens and the expectation that PK/PD relationships are the same in children as in adults, an extrapolation of efficacy data obtained in adults to children may be accepted.

As DRV exposure in treatment naïve HIV-1 infected paediatric subjects as well as treatment-experienced HIV-1 infected paediatric subjects without DRV RAMs was found to be comparable to that observed in treatment-naïve HIV-1 infected adults and treatment-experienced HIV-1 infected adults with no DRV RAMs when treated with DRV/rtv 800/100 mg once daily, efficacy of 800/100 mg once daily DRV/rtv can be assumed.

2.5. Clinical Safety aspects

2.5.1. Studies

Once Daily Substudy of TMC114-C228 in Treatment-experienced Pediatric Subjects Aged 3 to <6 Years

The secondary objective of this substudy was to evaluate the short-term safety and tolerability. AEs were monitored, as part of the main study, on an ongoing basis from signing the ICF onwards until the last study-related visit.

Four AEs occurred in 2 subjects: cough and rhinorrhea in 1 subject, and ear pain and oropharyngeal pain in 1 subject. Each of these AEs were grade 1 in severity, and none were considered by the investigator related to DRV. There were no grade 2 to 4 AEs, no serious adverse events (SAEs), no deaths, and no AEs led to discontinuation. There were no AEs related to physical of neurologic examinations, weight, or laboratory assessment.

The safety results of the qd substudy of TMC114-C228 are in line with those of the main part of the study. There were no new clinically relevant safety findings compared with the known safety profile of DRV/rtv in HIV-1 infected adults and in treatment-experienced HIV-1 infected pediatric subjects aged 6 to <18 years.

Safety in Other Clinical Studies and Programs

In total 180 HIV-1 infected pediatric subjects <18 years of age have been treated with DRV/rtv in the ongoing CU program (or exceptionally EAPs or PAA programs) up to the cut-off date of 31 October 2013. Sixty-six of these subjects were <12 years of age. Each of the 180 treated subjects had limited treatment options due to virologic failure or intolerance to multiple ARV regimens. Between 1 August 2012 and 31 October 2013, 2 new SAEs were reported in 1 subject <12 years of age. Both SAEs (viral load increased and diarrhea) were considered by the reporting physician as at least possibly related to DRV/rtv.

Nine new SAEs were reported in 6 subjects <18 years of age and treated with DRV/rtv in the ongoing continued-access study TMC114-C232. Two of these SAEs (pneumonia and asthma) occurred in 1 subject who was <12 years of age. Follow-up information was received for 6 pediatric subjects with 10 SAEs that started prior to 1 August 2012. Seven of these SAEs (appendicitis, tuberculosis, intestinal obstruction, asthma, pneumonia, road traffic accident, and femur fraction) occurred in 4 subjects <12 years of age. All events (new and follow-up cases) were assessed as not related to DRV/rtv by the investigator.

None of the SAEs reported between 1 August 2012 and 31 October 2013 had a fatal outcome. No new ADRs were identified and no new safety concerns emerged from these data that would affect the benefit/risk assessment for the use of DRV/rtv in HIV-1 infected pediatric subjects.

2.5.2. Discussion on clinical safety

There were no new clinically relevant safety findings compared with the known safety profile of DRV/rtv in HIV-1 infected adults and in treatment-experienced HIV-1 infected paediatric subjects aged 6 to <18 years.

2.5.3. Conclusions on the clinical safety

There were no new clinically relevant safety findings compared with the known safety profile of DRV/rtv in HIV-1 infected adults and in treatment-experienced HIV-1 infected pediatric subjects aged 6 to <18 years.

2.6. Risk management plan

An initial submitted RMP (version 18.0) was deemed approvable if updated and satisfactory responses provided to outstanding questions (separate RMP Assessment Report as endorsed by PRAC on 8 May 2014).

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 12. 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 13. 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 September 2013 Submission fourth annual report: September 2014 Submission fifth annual report: September 2015
A planned study to assess growth abnormalities (height)	To assess growth abnormalities (height) in children	Growth abnormalities in the	Planned	Submission of the protocol:

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)
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	using PREZISTA.	paediatric population		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 PREZISTA/rtv in combination with other ARVs will be assessed.	Long-term safety of DRV/rtv in children from 3 to 17 years of age	Started	Final data: June 2015
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	To evaluate the safety and tolerability of DRV+COBI plus 2 fully active NRTIs through 48 weeks of treatment and beyond. After 48	Missing information: Long-term safety of DRV/COBI in adults	Started	3Q 2015 (Final report)

[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)
infected, ART-naïve and –experienced adults with no DRV-RAMs. Category 3	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.			
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 COBI-containing highly active ARV regimens in HIV-1 infected patients with mild to moderate renal impairment. Category 3	To evaluate the effect (including long-term effects), safety, and tolerability of COBI-containing regimens (STB, ATV/COBI or DRV/COBI) on renal parameters through 48 weeks of treatment and beyond	Missing information: Safety of DRV/COBI in subjects with renal impairment	Started	3Q 2015 (Final report)

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations

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 14: 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
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	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	
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
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	None

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

2.7. Changes to the Product Information

As a consequence of this new indication, sections 4.1 (75/150/300/600 mg tablets), 4.2, 4.4 and 5.2 of the SmPCs of Prezista have been updated. The package Leaflet has been updated accordingly.

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

(Prezista 75 mg Tables SmPC shown as example)

4.1 Therapeutic indications

PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

PREZISTA 75 mg tablets may be used to provide suitable dose regimens (see section 4.2):

- For the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those that have been highly pre-treated.
- For the treatment of HIV-1 infection in paediatric patients from the age of 3 years and at least 15 kg body weight.

In deciding to initiate treatment with PREZISTA co-administered with 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.

Section 4.2 Posology and method of administration *(oral suspension)*

...

ART-naïve paediatric patients (3 to 17 years of age and weighing at least 15 kg)
The weight-based dose of PREZISTA and ritonavir in paediatric patients is provided in the table below.

Recommended dose for treatment-naïve paediatric patients (3 to 17 years) with PREZISTA tablets and ritonavir[a]	
Body weight (kg)	**Dose (once daily with food)**
≥ 15 kg to < 30 kg	600 mg PREZISTA/100 mg ritonavir once daily
≥ 30 kg to < 40 kg	675 mg PREZISTA/100 mg ritonavir once daily
≥ 40 kg	800 mg PREZISTA/100 mg ritonavir once daily

[a] ritonavir oral solution: 80 mg/ml

ART-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kg)
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).

Recommended dose for treatment-experienced paediatric patients (3 to 17 years of age) for PREZISTA tablets and ritonavir[a]		
Body weight (kg)	**Dose (once daily with food)**	**Dose (twice daily with food)**
≥ 15 kg–< 30 kg	600 mg PREZISTA/100 mg ritonavir once daily	375 mg PREZISTA/50 mg ritonavir twice daily
≥ 30 kg–< 40 kg	675 mg PREZISTA/100 mg ritonavir once daily	450 mg PREZISTA/60 mg ritonavir twice daily
≥ 40 kg	800 mg PREZISTA/100 mg ritonavir once daily	600 mg PREZISTA/100 mg ritonavir twice daily

[a] with ritonavir oral solution: 80 mg/ml

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.

[...]

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

Darunavir exposures in treatment-naïve adolescents 12 to 17 years weighing at least 40 kg receiving PREZISTA 800 mg once daily have been determined and were found to be within the therapeutic range as has been established in adults receiving PREZISTA 800 mg once daily. As a consequence, 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

Section 4.4 Special warnings and precautions for use

[...]

ART-experienced patients – once daily dosing
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).

Section 5.2 Pharmacokinetic properties

[...]

Paediatric population

[...]

The pharmacokinetics of darunavir in combination with ritonavir taken once daily in 10 treatment experienced paediatric patients, aged 3 to < 6 years and weighing at least 14 kg to < 20 kg, showed that weight based dosages resulted in darunavir exposure that was comparable to that achieved in adults receiving PREZISTA/ritonavir 800/100 mg once daily (see section 4.2). In addition, pharmacokinetic modeling and simulation of darunavir exposures in paediatric patients across the ages of 3 to < 18 years confirmed the darunavir exposures as observed in the clinical studies and allowed the identification of weight based PREZISTA/ritonavir once daily dosing regimens for paediatric patients weighing at least 15 kg that are

either ART naïve or treatment experienced paediatric patients without 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 L89

2.8. Significance of paediatric studies

Not applicable

3. Overall conclusion

Benefits

Beneficial effects

In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (Doc. Ref. EMEA/CPMP/EWP/633/02), based on the identification of suitable dose regimens and the expectation that PK/PD relationships are the same in children as in adults, the extrapolation of efficacy data obtained in adults to children may be accepted. The efficacy of DRV/rtv 800/100 mg qd in treatment-naïve HIV-1 infected adults was established in Phase 3 study TMC114-C211 and in treatment-experienced HIV-1 infected adults with no DRV RAMs in the Phase 3 study TMC114-C229. The use of the DRV/rtv qd regimen in paediatric subjects aged 12 to <18 years and weighing ≥40 kg was established in study TMC114-TiDP29-C230 (assessed II/54).

As DRV exposure in treatment naïve HIV-1 infected paediatric subjects as well as treatment-experienced HIV-1 infected paediatric subjects without DRV RAMs was found to be comparable to that observed in treatment-naïve HIV-1 infected adults and treatment-experienced HIV-1 infected adults with no DRV RAMs when treated with DRV/rtv 800/100 mg once daily, efficacy of 800/100 mg once daily DRV/rtv can be assumed.

In a small 2-week pharmacokinetic substudy of TMC114-C228 ten treatment-experienced HIV-1 infected children aged 3 to <6 years and weighing between 10 and <20 kg were treated with DRV/rtv qd for 2 weeks. Seven subjects received DRV/rtv 600/96 mg qd, and 3 subjects received DRV/rtv 560/96 mg (40/7 mg/kg) qd. All subjects maintained undetectable plasma viral load (< 50 HIV-1 RNA copies/mL) after 2 weeks.

Uncertainty in the knowledge about the beneficial effects

The only data on efficacy for the present extension of indication stems from the substudy of TMC114-C228 in treatment experienced children. This is very limited data. However, efficacy of the once daily dose regimen in treatment naïve children can be extrapolated from adults when exposure is comparable. However, in the PK substudy higher Cmax levels were observed, which may trigger safety concerns. Moreover, although the population pharmacokinetic model predicted a comparable exposure, there could be uncertainty with regard to the prediction of Cmax and the recommended dose. This has been further clarified though, with no indication that higher exposures (i.e. ≥ 10,000 to <15,000 ng/mL, or ≥ 15,000 ng/mL) would result in an increase in AEs, increased toxicity.

Risks

Unfavourable effects

There were no new clinically relevant safety findings compared with the known safety profile of DRV/rtv in HIV-1 infected adults and in treatment-experienced HIV-1 infected paediatric subjects aged 6 to <18 years.

Uncertainty in the knowledge about the unfavourable effects

Larger studies are required to assess the long-term effects of DRV on lipid and growth parameters. The on-going PASS study "Pharmacovigilance study on the safety and use of DRV in HIV infected children and adolescents in Europe" will provide this information. Annual reports from the on-going PASS study are being submitted to the CHMP. In addition, the MAH will initiate a study to compare of the data on growth from children treated with darunavir and other ART products. A study protocol has been submitted by the MAH in March 2014 and is currently under assessment (EMEA/H/C/000707/MEA069).

Benefit-risk balance

As stated in the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (Doc. Ref. EMEA/CPMP/EWP/633/02), provided that reliable pharmacokinetic data support robust dose recommendations, an extrapolation of efficacy data obtained in adults to children may be accepted.

Exposures with the once daily dose of 600/100 mg DRV/rtv as recommended for treatment-naïve children weighing ≥15kg and <30kg are similar to the once daily regimen of 800/100 mg DRV/rtv in adults and comparable to exposures with twice daily dosing as recommended in paediatric and adult patients. As such, safety and efficacy can be extrapolated. There seems no indication that higher exposures (i.e. ≥ 10,000 to <15,000 ng/mL, or ≥ 15,000 ng/mL) would result in an increase in AEs, increased toxicity.

The safety data in the claimed paediatric indication do not give rise to any new clinically relevant findings compared with the known DRV/rtv safety profile in HIV-1 infected adults. Lipid abnormalities and growth impairment were identified as potential risks related to the use of darunavir in treatment-naïve HIV-1 infected adolescents and adequate measures have been put in place to monitor those.

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 the SmPC (sections 4.1 [75/150/300/600 mg tablets)] 4.2, 4.4 and 5.2) with an extension of indication to use darunavir once daily in children aged 3 to 12 years ≥ 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance-associated mutations (DRV RAMs). This proposed change is based on the data from a 2 week once daily substudy of the Phase 2 study TMC114 C228 and results from model-based pharmacokinetic simulations. The Package Leaflet has been updated accordingly.

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