19 July 2012
EMA/CHMP/304651/2012

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prezista

darunavir

Procedure No.: EMEA/H/C/000707/X/0041/G

Note

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

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Product information

Name of the medicinal product:	Prezista
Applicant:	Janssen-Cilag International N V Turnhoutseweg 30 BE-2340 Beerse Belgium
Active substance:	darunavir
International Nonproprietary Name/Common Name:	darunavir
Pharmaco-therapeutic group (ATC Code):	Protease inhibitors (J05AE10)
Therapeutic indication:	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 patients as well as antiretroviral therapy (ART)-experienced 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.
Pharmaceutical form:	Oral Suspension
Strengths:	100 mg/ml
Route of administration:	Oral use
Packaging:	bottle (LDPE)
Package sizes:	1 bottle

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List of abbreviations

AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AUC	Area under the curve
b.i.d.	twice daily
CI	confidence interval
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
DRV	darunavir
ECG	electrocardiogram
FC	fold change in EC50
GCP	Good Clinical Practice
HIV-1	human immunodeficiency virus – type 1
ICH	International Conference on Harmonization
ITT	intent-to-treat
NNRTI	non-nucleoside analogue reverse transcriptase inhibitor
NRTI	nucleoside analogue reverse transcriptase inhibitor
OBR	optimized background regimen
PCR	polymerase chain reaction
PI	protease inhibitor
PK	pharmacokinetic(s)
RAM	resistance-associated mutation
RNA	ribonucleic acid
rtv	ritonavir (low-dose given as booster)
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	system organ class
TLOVR	time to loss of virologic response

1. Background information on the procedure

1.1. Submission of the dossier

The MAH Janssen-Cilag International N V submitted on 5 May 2011 an extension for a Marketing Authorisation to the European Medicines Agency (EMA) for Prezista, 100 mg/ml oral suspension, through the centralised procedure falling within Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2c and d).

The MAH applied for a new formulation (Oral Suspension 100mg/mL).

In addition, the MAH applied for the following indication: *"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 patients as well as antiretroviral therapy (ART)-experienced paediatric patients from the age of 3 years and at least 10 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."

Furthermore pursuant to Commission Regulation 1234/2008, art.7-2(b), this line extension application was grouped with a type II variation to update the section 4.1 of the SmPC for the existing 75mg, 150mg, 300mg, 600mg film coated tablets with the new paediatric indication (3 to 6 years weighing 10 to < 20 kg, HIV positive, treatment experienced patients) and introduce consequential changes to sections 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC for the existing 75mg, 150mg, 300mg, 400mg 600mg film coated tablets. The patient leaflet was updated accordingly.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on MAHs' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

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

At the time of submission of the application, the PIP (P/138/2010) was not yet completed as some measures were deferred.

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 MAH 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.

Janssen-Cilag International NV is already the Marketing Authorisation Holder for the Prezista 75 mg, 150 mg, 300 mg, 400 mg and 600 mg film-coated tablets.

Licensing status

Prezista has been given a Marketing Authorisation in European Union since 12 February 2007.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Barbara van Zwieten-Boot** Co-Rapporteur: **Ian Hudson**

- The application was received by the EMA on 5 May 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 August 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 08 August 2011 (Annex 2).
- During the meeting on 22 September 2011, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the MAH on 27 September 2011 (Annex 3).
- The MAH submitted the responses to the CHMP consolidated List of Questions on 22 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the MAH's responses to the List of Questions to all CHMP members on 7 May 2012 (Annex 4).
- During the CHMP meeting on 24 May 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the MAH (Annex 5).
- The MAH submitted the responses to the CHMP List of Outstanding Issues on 19 June 2012.
- The Rapporteurs circulated the Joint Assessment Report on the MAH's responses to the List of Outstanding Issues to all CHMP members on 4 July 2012 (Annex 6).
- During the meeting on 19 July 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Prezista 100 ml/mg oral suspension and the variation to the terms of the Marketing Authorisation on 19 July 2012.

2. Scientific discussion

2.1. Introduction

PREZISTA (darunavir, DRV) is a protease inhibitor. DRV is currently licensed for use in treatment-experienced patients at a dose of 600mg twice daily (b.i.d.), with ritonavir 100mg b.i.d., in combination with other antiretroviral medicinal products. Treatment of ARV-naïve patients with DRV (800 mg once daily) in combination with ritonavir 100 mg qd and other antiretroviral medicinal products is also approved.

Furthermore, DRV is licensed for use in ART-experienced paediatric patients aged 6 to < 18 years and weighing at least 20 kg with a recommended dose of DRV based on body weight, that should not exceed the recommended adult dose (600/100 mg b.i.d.).

2.2. Quality aspects

2.2.1. Introduction

Prezista is currently presented as film coated tablets. The aim of this line extension is the addition of a new pharmaceutical form and a new strength of 100 mg/ml.

The finished product is presented as an oral suspension containing 100 mg/ml of darunavir (as ethanolate) as active substance. The other ingredients are hydroxypropyl cellulose, microcrystalline cellulose, carmellose sodium, sodium methylparahydroxybenzoate, citric acid monohydrate, sucralose, masking flavour, strawberry cream flavour, concentrated hydrochloric acid and purified water.

The oral suspension is presented in a glass bottle with a polypropylene (PP) closure with a LDPE liner and is packaged together with a dosing pipette. The bottle neck is filled with a low density polyethylene (LDPE) insert that accommodates the dosing pipette.

2.2.2. Active Substance

The quality information relating to the active substance Danuvir (as ethanolate) has already been evaluated in a previous centralised procedure leading the authorisation of Prezista film coated tablets and has been updated by means of approved variations.

The only change in the currently approved information is the addition of milling as the final step in the route of synthesis. Based on XRD, DSC, TGA and IR data and experimental designs, it has been demonstrated that the active substance is stable and no polymorphic changes are induced by the additional milling step.

Additional data of three commercial scale batches of the unmilled active substance packed LDPE bag from the manufacturer stored at long term (25°C/60%RH) for up 60 months, and accelerated (40°C/75%RH) for up 6 months under ICH conditions were presented. Photostability test following ICH guidelines Q1B was also performed on three batches. Results on stress conditions at 50°C for up to three months were also provide on three batches. The following parameters were tested: appearance, assay, chromatographic purity, water content, ethanol content, particle size and microbiological purity. Based on the result, the claimed retest period and storage conditions are considered justified.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The primary aim of the MAH was to develop a new pharmaceutical form that would provide a dosing flexibility by weight compared to the currently approved tablets

An oral suspension was selected as the formulation of choice due to the low solubility of the active substance.

All excipients chosen are well-known and comply with the relevant Ph Eur. monographs

Hydroxypropyl cellulose is used as a wetting agent. The commercially available mixture of microcrystalline cellulose and carmellose sodium, (MCC/NaCMC) is the suspending agent. Sodium methyl parahydroxybenzoate (sodium methylparaben) functions as the preservative of the aqueous system. The efficacy of the preservative system has been demonstrated according to the Ph.Eur. Sucralose is added as a non-cariogenic sweetening agent. Strawberry cream flavour and masking flavor are used to mask the bitter taste of the drug substance and to improve the acceptability of the taste. Citric acid monohydrate is selected as buffering agent and hydrochloric acid is added to adjust

the pH to the target value for optimum chemical stability. Purified water is employed as the vehicle for the formulation. For the flavouring agents, sufficient information has been provided and confirms the absence of any safety risk.

The compatibility between active substance and excipients was investigated during development. Stability studies on the oral suspension at accelerated conditions of 40°C/75% RH and long term at 25°C/60% RH support the use of all the excipients in the finished product formulation.

The proposed primary packaging for commercial distribution is 230-mL amber glass bottle with a child resistant, tamper evident (CR/TE), white polypropylene (PP) closure with a LDPE liner. A dosing pipette (LDPE/PS) complying with the EU directives and regulations for materials to be in contact with foodstuffs or drug (CE marked), is included. Functionality of the dosing pipette has been adequately demonstrated (dosing accuracy and uniformity of dosing of the product with use of the dosing system). The primary components of the packaging comply with the applicable EU directives and regulations for materials to be in contact with foodstuffs or drugs.

Adventitious agents

Satisfactory BSE/TSE statement is provided for the drug product, confirming that no materials of human or ruminant origin are used in the manufacturing process. This is in line with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)

Manufacture of the product

The manufacturing process is commonly used for oral suspensions and comprises of the following steps: compounding, mixing of the materials, and filling of the suspension into the primary packaging. It has been demonstrated that acceptable finished product is produced when the manufacturing process operates within the proven ranges. Critical process parameters have been identified and are controlled by adequate in-process controls

A summary of the process validation protocol that will be used to validate the process at commercial scale in the commercial site as listed in the dossier has been provided.

Product specification

The specifications include tests for: appearance, resuspendability, identification of drug substance (HPLC, HPLC-UV-Diode Array), identification of preservative (HPLC), assay (HPLC), preservative content (HPLC), contents of degradation products (HPLC), pH (Ph. Eur.), dissolution, microbiological purity (Ph.Eur.) and are appropriate for this type of pharmaceutical form and are in line with ICH Q6A 'Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances'. All tests included in the specification have been satisfactorily described and validated.

Batch analysis data on fourteen (7 production batches and 7 scale batches) batches demonstrate that the manufacturing process is consistent and produces a finished product within the proposed specifications.

Stability of the product

Stability data were provided for three batches of finished product packaged in the intended commercial container-closure system stored up to 12 months at long term conditions (25 °C/40% RH, 30°C/35% RH and 5°C) and up to 6 months in accelerated conditions (40°C/≤25% RH). The choice of stability conditions based on semi-permeable container-closure system is justified and supported by water loss studies in line with ICH Q1A (R2). Photostability studies in line with ICH requirements have been

carried out for up to 8 hours in light and also stress conditions stability studies (50°C, 5°C/40°C and -15°C/30°C) have been carried out

Eleven months and 21 months of closed-bottle storage in-use stability data have been provided. No significant changes in appearance/resuspendability, assay, content of preservative, impurities content (no degradation), dissolution or pH were observed. This was considered adequate to -support the in-use stability till the end of the shelf-life.

The stability batches were tested according to the release finished product specification. Stability testing parameters included: appearance/ resuspendability, assay for darunavir, assay for methylparaben, chromatographic purity, dissolution, pH, microbial purity and preservative efficacy.

Stability data under long term conditions (25°C/40% RH and 30°C/35% RH) and accelerated conditions (40°C/≤25% RH) showed that the product was stable and no significant change could be observed. All the results remained within the specifications.

However the results of the storage for 12months at 5°C has resulted in the proposed storage labelling 'do not refrigerate or freeze' due to the crystallisation of methylparaben

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance manufacture and controls are essentially the same as for the currently authorised film coated tablets. Information on development, manufacture and control of the proposed 100 mg/ml oral suspension has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this Prezista oral suspension 100 mg/ml is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Since DRV is already approved by oral route, as film-coated tablets, no additional non-clinical studies have been performed to support this application. This was acceptable to the CHMP. The discussions below are based on non clinical data submitted as part of the previous applications for DRV.

2.3.2. Pharmacology

Not applicable.

2.3.3. Pharmacokinetics

The exposure to DRV is higher in juvenile rats than in adult rats with exposure up to 3 times the adult exposure at age 5-11 days and with exposure approaching adult values at age 23-50 days. The higher exposure at 5-11 days is attributed to the limited metabolic capacity of the juvenile animals.

2.3.4. Toxicology

Data in juvenile rats show that the exposure in animals aged 5-11 days is higher than in adult animals. The high exposure at young age and the subsequent decrease in exposure from postnatal day 8 onwards is probably related to the maturation of the liver metabolising enzymes. In animals aged 23-50 days, toxicity is not higher than in adult animals. These results suggest that in rats, roughly after 3 weeks, the exposure in juvenile animals is comparable to that in adults.

2.3.5. Ecotoxicity/environmental risk assessment

The results are included in table 1.

Table 1. Summary of Main Studies

CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	study report missing	2.47	not B (tentative)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.47	PM
Persistence	ready biodegradability	not ready	potentially P
	DT50		PM
Toxicity	NOEC or CMR	aquatic toxicity: not T, but CMR not investigated	not investigated
PBT-statement:	Darunavir is considered not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	6	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)	not reported		
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	0.192 g/L at pH 4 and 20°C	
		0.163 g/L at pH 7 and 20°C	
		0.179 g/L at pH 9 and 20°C	
Hydrolysis	OECD 111	t½ = 316 d at pH 4 and at 30°C and 40°C	
		hydrolytically stable at pH 7	
		t½ = 161 d at pH 9 and 30°C t½ = 39.9 d at pH 9 and 40°C	
Adsorption-Desorption	OECD 106	K_d = 75.3 L/kg; K_{oc} = 345 L/kg	activated sludge
		K_d = 42.0 L/kg; K_{oc} = 993 L/kg	sandy loam
		K_d = 4.12 L/kg; K_{oc} = 389 L/kg	loam
		K_d = 18.1 L/kg; K_{oc} = 933 L/kg	loamy sand
		K_d = 9.50 L/kg; K_{oc} = 265 L/kg	sandy clay loam
		K_d = 8.18 L/kg; K_{oc} = 732 L/kg	clay
Ready Biodegradability Test	OECD 301	not readily biodegradable	no primary degradation
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = PM $DT_{50, sediment}$ = PM $DT_{50, whole\ system}$ = PM % shifting to sediment = PM	PM

CAS-number (if available):					
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	≥ 43	mg/L	*P. subcapitata*
D. magna Acute toxicity test	OECD 202	EC50	> 44	mg/L	*D. magna*
Daphnia sp. Reproduction Test	OECD 211	NOEC	19	mg/L	*D. magna*
Fish, acute toxicity test	OECD 203	EC50	> 38	mg/L	*O. mykiss*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	≥ 9.4	mg/L	*P. Promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 1000	mg/L	activated sludge
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	≥ 80	mg/kg	*C. riparius*

2.3.6. Discussion on non-clinical aspects

The available data suggest that in very young children, who do not have mature drug-metabolising enzymes yet, it may be expected that comparable doses cause a higher exposure compared to adults. The activity of drug metabolising enzymes increases from birth and approaches adult values by 1-3 years of age. Juvenile rats of 3 weeks correspond to human infants of 2 years. Rats of 23 days old, the age from which exposure was shown to be comparable to that in adult rats, correspond to children slightly older than 2 years old. Hence, it can be concluded that from 3 years of age, an increased exposure compared to adult is no longer expected.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical perspective, there were no specific concerns.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical studys were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical studiess conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The following studies were submitted:

- a relative bioavailability study TMC114-C169 in healthy subjects, comparing the 100 mg/ml suspension versus the 300 mg tablet;
- a Phase II study TMC114-TiDP29-C228 (TMC114-C228 or C228 or ARIEL) in treatment-experienced HIV-1 infected paediatric subjects between 3 and < 6 years of age and weighing between 10 and < 20 kg. DRV was administered orally as oral suspension, together with low dose ritonavir (80 mg/ml oral solution, or capsule 100 mg).

GCP inspection of the study C228 has been performed by EMA from 20 August 2011 till 3 September 2011. Three sites were inspected (1 in Kenya, 2 in South Africa).

- Critical GCP issues have been detected in the Kenyan site: multiple findings demonstrated a lack of study/site oversight and a therefore a deficiency in the quality control system of the sponsor/CRO.

These findings resulted in the exclusion of data from this site (6 children out the 27 enrolled in the study).

- In the two sites in South Africa, some areas of GCP non compliance were noted. However, the overall clinical study performance of the respective sites was assessed as GCP compliant and the data were considered trustworthy and acceptable.

2.4.2. Pharmacokinetics

Study TMC 114-C169

This was a an open-label, randomised, crossover trial in healthy subjects that compared the bioavailability of an oral suspension formulation of DRV to that of the registered 300 mg tablet formulation of DRV when a single dose of 600 mg DRV with 100 mg rtv was administered under fasted and fed conditions. The study also assessed multiple dose pharmacokinetics of DRV formulated as the suspension in the presence of low-dose rtv. Hence, the study was divided into two sequential parts.

In Part 1 during 3 sessions each subject received:

- Treatment A: DRV 600 mg single dose (2 × 300 mg tablet) under fed conditions on day 3, and rtv 100 mg twice daily (b.i.d.) on days 1 to 5;
- Treatment B: DRV 600 mg single dose (6 ml 100 mg/ml suspension) under fasted conditions on day 3, and rtv 100 mg b.i.d. on days 1 to 5;
- Treatment C: DRV 600 mg single dose (6 ml 100 mg/ml suspension) under fed conditions on day 3, and rtv 100 mg b.i.d. on days 1 to 5.

In Part 2 each subject received:

- Treatment D: DRV 600 mg b.i.d. (6 ml 100 mg/ml suspension) on days 1 to 6 and a morning dose on day 7 under fed conditions, and rtv 100 mg b.i.d. on days 1 to 9.

Treatment A, B and C were separated with a washout period of 7 days. Part 2 was started after the results were available of Part 1. In the fed conditions, DRV/rtv were administered 10 min after completion of a standard breakfast consisting of 3 to 5 slices of bread, 2 slices of ham or cheese, butter, jelly, and 2 cups of decaffeinated coffee or tea with milk and/or sugar.

The design of study C169 was considered acceptable to compare the bioavailability of DRV/rtv. The selected 600 mg dose is in the linear dose range.

The results of this study showed that after single dose, AUC and C_{max} were bioequivalent for DRV suspension under fed and fasting conditions and DRV tablet under fed condition. After administration of the suspension under fasting conditions, t_{max} was clearly earlier reached than under fed conditions.

For rtv, C_{0h} and C_{min} were comparable between the first 3 arms. Under fed conditions, C_{max} and AUC were comparable after administration of the tablet and the suspension. Under fasting conditions, AUC and C_{max} were clearly higher compared to administration under fed conditions of the tablet and suspension. This has been observed in previous studies and is probably due to DRV affecting the absorption phase of rtv.

The results from Part 2 (multiple dose arm) showed that the pharmacokinetics for DRV and rtv were comparable with data already available in adults and children.

Study TMC114-C228

This was an open-label, Phase II study to evaluate the pharmacokinetics, safety and antiviral activity to support dose recommendations by body weight of DRV/rtv, in combination with other ARVs, in treatment-experienced HIV-1 infected children aged from 3 to < 6 years and weighing between 10 and < 20 kg. In addition, efficacy, safety and tolerability of DRV/rtv were evaluated in combination with other ARVs over a 48-week treatment period (see Section 2.5).

The first 2 weeks of the study were designed to support dose recommendations of DRV/rtv in children aged from 3 to < 6 years and weighing between 10 and < 20 kg.

Selection of the dose

A dose similar to the highest DRV/rtv doses tested in the paediatric study TMC114-C212 (EMEA/H/C/000707/X/20&21, opinion issued on 23 April 2009, extension of indication in the treatment of HIV-1 infection in ARV treatment experienced adolescents and children of 6 years and above and with a body weight of more than 20 kg) was selected based on the favourable pharmacokinetic, safety, tolerability and efficacy observed in this study and to avoid the risk of under-dosing due to an increase in apparent clearance of DRV in young children (due to maturation of the liver by which DRV is metabolised).

The rtv dose was selected on the dosing tables provided by the WHO for enhancing lopinavir (LPV). Rtv is used as booster for LPV and the recommended doses are 3.0 mg/kg b.i.d. for children weighing 7 to 15 kg, and 2.5 mg/kg b.i.d. for children weighing 15 to 40 kg. A dose of 3.0 mg/kg b.i.d. of rtv (oral solution) was selected for study TMC114-C228, with the aim not to exceed a dose of 50 mg b.i.d..

Subjects were initially to be given a dose of DRV/rtv 20/3 mg/kg b.i.d., together with an OBR consisting of ≥ 2 active ARVs with available pediatric dose recommendations. The doses were administered within 30 min after completion of a meal.

Dose adjustment at 2 weeks

The first 2 weeks of the trial were designed to support dose recommendations of DRV/rtv in the studied patient population. At Week 2, pharmacokinetic assessments were performed: sampling occurred at 5 different time points on Day 14.

At Week 2, 42 subjects were screened. Fifteen subjects did not fulfil all inclusion/exclusion criteria, and were not treated. Twenty-seven children, on a stable ARV treatment for ≥ 12 weeks, but who needed to change their ARV regimen because it was currently failing (plasma viral load > 1000 copies/mL), and who had < 3 DRV resistance-associated mutations (RAMs), were included in the study with 14 (51.9%) children in the 10 to < 15 kg weight band and 13 (48.1%) in the 15 to < 20 kg weight band. Blood samples were obtained up to 12h after administration for analysis of DRV and rtv. Data for 24 subjects were available as 3 subjects were excluded having concentration below the limit of quantification (BLQ).

Population pharmacokinetic analysis was applied at Week-2. An independent Data Safety Monitoring Board (DSMB) reviewed all available pharmacokinetic, safety and antiviral activity data, in order to support the DRV/rtv pediatric dose recommendations. The absolute pediatric DRV/rtv dose was not to exceed the recommended dose for treatment-experienced HIV-1 infected adults. From the pharmacokinetic data of previous studies, a reference steady-state exposure (AUC_{12h}) was identified as the mean steady-state exposure in adults (62.3 µg.h/mL). If the geometric mean of the AUC_{12h} in children was < 80% or > 130% of the reference AUC_{12h}, or when a trend in AUC_{12h} with the body weight was observed, a dose adjustment would have to be considered.

Based on the week 2 PK results, the DRV/rtv dose was adjusted from 20/3 mg/kg b.i.d. to 25 mg/kg combined with rtv 3 mg/kg for subjects between 10 to < 15 kg (i.e. dose based on their body weight), and DRV/rtv 375/50 mg for subjects between 15 to < 20 kg (i.e. fixed dose). It was felt that this dose adjustment would reduce the risk of underdosing at lower body weights, while for children weighing between 15 to < 20 kg, the change in exposure with body weight would become continuous and the new dose would facilitate a potential switch to the tablet formulations.

Subjects in trial TMC114-C228 continued treatment with DRV/rtv in combination with an OBR up to 48 weeks to evaluate safety, tolerability, and efficacy of DRV/rtv in this population.

PK revision based on GCP inspection findings and weight errors

During the course of this application, the MAH informed the CHMP that an incorrect registration of the weight of the children was applied during the study. Consequently, a limited number of subjects were incorrectly categorized to a body weight subgroup. This resulted in incorrect PK values in the low weight group < 15 kg. The individual estimates of the DRV AUC_{12h}, the pre dose plasma concentration (C_{0h}), the apparent total clearance (CL/F), and the average plasma concentration at steady-state ($C_{ss,ave}$) were influenced by this error.

In parallel, the outcome of the EMA GCP inspection was known and the data from the Kenyan site was excluded from the study (6 patients out of 27 i.e. 22%).

A new population pharmacokinetic analysis was applied as a result of these findings (see table 2).

Table 2. Comparison of the mean of median individual AUC_{tau} to the target adult value at week 24, excluding data from site KE00004 and correcting the data for bodyweight.

	Before Dose Adjustment			After Dose Adjustment		
	Overall	10 to < 15 kg	15 to < 20 kg	Overall	10 to < 15 kg	15 to < 20 kg
Original analysis[a]	107%	111%[d]	104%	128%	140%	122%
Reanalysis[b]	107%	110%[d]	104%	129%	153%	113%
Repeated reanalysis[c]	107%	110%[d]	104%	136%	153%	127%

[a] Original Week-24 analysis, including Site KE00004.
[b] Revised Week-24 analysis with correction of body weight data and including Site KE00004.
[c] Repeated Week-24 reanalysis with correction of body weight data and excluding Site KE00004.
[d] Difference in the percentages lies in the rounding of the values (the difference between the 2 values is 0.3%).

The revised week-24 analyses showed that the DRV AUC_{12h} increased from 110% to 153% of the adult target exposure for the lower weight group (10 to < 15 kg), and from 104% to 127% of the adult target exposure for the higher weight group (15 to < 20 kg). This increase was confirmed with week 48 data (see table 3).

Table 3. Comparison of the mean of median individual AUC_{tau} to the target adult value at week 48, excluding data from the Kenyan site but not correcting the data for bodyweight.

Before dose adjustment			After dose adjustment		
Overall	10 to <15 kg	15 to <20 kg	Overall	10 to <15 kg	15 to <20 kg
110%	111%	109%	131%	146%	126%

The mean DRV AUC_{12h} of 153% (revised Week-24 analyses) and 146% (Week-48 analyses) for the lower weight group (i.e., deviations of 23% and 16% from the upper boundary of the adult target exposure range) were outside the limit of extrapolation for safety data. Hence, the MAH revised its dosing proposal during the course of this application. They recommended the pre-Week 2 adjustment dose of DRV/RTV 20/3 mg/kg twice daily for children weighting 10 to < 15 kg. The proposed dose for the children weighing 15 to < 20 kg remained similar to the post-week 2 analysis i.e. DRV/RTV 375/50 mg twice daily.

2.4.3. Pharmacodynamics

Not applicable.

2.4.4. Discussion on clinical pharmacology

Study C228 was an open-label, Phase II study to evaluate the pharmacokinetics, safety and antiviral activity to support dose recommendations by body weight of DRV/rtv, in combination with other ARVs, in treatment-experienced HIV-1 infected children aged from 3 to < 6 years and weighing between 10 and < 20 kg. The first 2 weeks of the study were designed to support dose recommendations of DRV/rtv in children aged from 3 to < 6 years and weighing between 10 and < 20 kg.

Subjects were initially to be given a dose of DRV/rtv 20/3 mg/kg b.i.d., together with an OBR consisting of ≥ 2 active ARVs with available pediatric dose recommendations.

Twenty-seven children were included in the study with 14 (51.9%) children in the 10 to < 15 kg weight band and 13 (48.1%) in the 15 to < 20 kg weight band.

At Week 2, pharmacokinetic assessments were performed. Once these data were available, an independent DSMB reviewed all available pharmacokinetic, safety and antiviral activity data. Based on the Week 2-results, the DRV/rtv dose was adjusted from 20/3 mg/kg b.i.d. to 25 mg/kg combined with rtv 3 mg/kg for subjects between 10 to < 15 kg (i.e. dose based on their body weight), and DRV/rtv 375/50 mg for subjects between 15 to < 20 kg (i.e. fixed dose).

During the course of the application, the findings of the EMA inspection have resulted in the exclusion of the data from 6 of the initial 27 children enrolled in the study (22%). In addition, the MAH informed the CHMP of a new finding during the review of the application: incorrect registration of the children's weight and subsequent increases of dose resulted in incorrect PK values in the low weight group < 15 kg. As a result of these findings, a re-analysis of the PK data was performed by the MAH which led them to propose a revised dosing for children weighting 10 to < 15 kg (DRV/RTV 20/3 mg/kg twice daily).

Table 4 summarise the data presented data of Phase II study TMC114-C228 in treatment-experienced HIV-1 infected paediatric subjects.

Table 4. Phase II study TMC114-C228 in treatment-experienced HIV-1 infected paediatric subjects

Week	Dose DRV/rtv (mg) twice daily	Number of subjects	Reasons for exclusion in PK analysis#	Number of subjects for PK analysis	Number of subjects <15kg in PK analysis[$]	Number of subjects for efficacy & safety analysis
0	20 / 3 for subjects weighting 10 to < 15 kg 375/50 for subjects 15 to < 20 kg	27	-		14	27
2	Dose adjustment: 25/3 for subjects weighting 10 to < 15 kg 375/50 for subjects 15 to < 20 kg	21	6: AAG data unreliable (Kenyan site) 1: no rtv conc = non compliant	27 – 8 = 19	9	27 – 6 (Kenyan site) – 1 (discontinua-tion) = 20* (11 children <15 kg)

Week	Dose DRV/rtv (mg) twice daily	Number of subjects	Reasons for exclusion in PK analysis#	Number of subjects for PK analysis	Number of subjects <15kg in PK analysis$	Number of subjects for efficacy & safety analysis
			1: no PK data			
24	Unchanged: 25/3 for subjects weighting 10 to < 15 kg 375/50 for subjects 15 to < 20 kg	21	6: AAG data unreliable (Kenyan site) 2: no rtv conc 1: no PK data	27 – 9 = 18	6	20
48	Unchanged: 25/3 for subjects weighting 10 to < 15 kg 375/50 for subjects 15 to < 20 kg	21	6: AAG data unreliable (Kenyan site) 1: no rtv conc 1: disconti-nuation	27 – 8 = 19	5**	20

# EMA inspection report after visit to 3 from 11 sites: GCP issues in Kenyan site (6 subjects): MAH decision to exclude these subjects from PK analysis and from efficacy/safety analysis. Concerns about the reliability of AAG measurements in this Kenyan site was reason to exclude these subjects from PK analysis at week 2.
$ subjects with very low body weights of 10 to < 12 kg were not enrolled in the study
* incorrect weight categorization of 2 subjects
** in 5 subjects with weight <15 kg: AUC_{tau} 146%

The EU guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004) states that, provided that data from adults are considered relevant, pharmacokinetic information can be used to extrapolate efficacy to the paediatric population. If similar exposure in adult and paediatric patients can be assumed to produce similar efficacy, pharmacokinetic data alone can be used to extrapolate efficacy.

The pharmacokinetic data available with the dose of DRV/rtv 375/50 mg/kg b.i.d. in children weighting 15 to < 20 kg have shown an exposure that is within the range of the reference dose in adults. However, a major objection was raised by the CHMP regarding the dose recommendation for children weighting 10 to < 15 kg since the pharmacokinetic data available with the dose of DRV/rtv 20/3 mg/kg b.i.d. are limited to the Week 2 data.

The MAH provided data from various studies in adults that demonstrate that the distribution and range of DRV AUC_{12h} and C_{0h} after administration of DRV/rtv 20/3 mg/kg b.i.d. in the first 2 weeks of study TMC114-C228 is within the range of DRV exposures in treatment-experienced adults treated with DRV/rtv 600/100 mg b.i.d. (see table 5).

Table 5. Summary Statistics of the DRV Pharmacokinetic Parameter Estimates in Adults[a] Treated with DRV/rtv 600/100 mg b.i.d. and Pediatric Subjects[b] Treated With DRV/rtv 20/3 mg/kg b.i.d.

	Mean (SD)							
	TMC114-C202/C213	TMC114-C215/C208	TMC114-C214	TMC125-C206	TMC125-C216	Pooled Analysis[a]	TMC114-C228	
Parameter							10 - < 15 kg	15 - < 20 kg
N	119	292	285	575	574	1845	10	9
C_{0h}, ng/mL	3578 (1151)	4119 (1645)	3490 (1401)	3760 (1468)	3614 (1392)	3718 (1458)	4510 (2031)	4191 (2288)
AUC_{12h}, µg.h/mL	62.3 (16.1)	65.1 (20.4)	58.4 (16.8)	62.3 (18.0)	60.6 (17.0)	61.6 (17.9)	68.9 (25.7)	67.6 (29.4)

N = number of subjects with data

[a] Studies TMC114-C202, TMC114-C213, TMC114-C208, TMC114-C215, TMC114-C214, TMC125-C206, TMC125-C216

[b] Study TMC114-C228

However, these results should be interpreted with caution due to the facts that:

- In total only a very limited number of pediatric subjects with weight < 15 kg was evaluated,
- No children with weight < 12 kg (who are expected to have lower exposures) have been enrolled in the study,
- These young children have different AAG levels which influence DRV clearance: low AAG levels contribute to a higher clearance of DRV.

On the other hand, the pharmacokinetic data available with the dose of DRV/rtv 25/3 mg/kg b.i.d. in children weighting 10 to < 15 kg have shown an exposure that is considerably higher than the reference dose in adults (Week 48 data).

2.4.5. Conclusions on clinical pharmacology

The revised analyses showed that the DRV exposure in children weighting 10 to < 15 kg increased up to 150% of the adult target exposure with the DRV/rtv 25/3 mg/kg b.i.d..

The presented pharmacokinetic data on week 2 with the dose of DRV/rtv 20/3 mg/kg b.i.d. are in line with the pharmacokinetic data in adults obtained in other trials. However, these PK data were obtained in a very limited number of children with no representation of the children < 12 kg who could have different AAG levels and consequently an increased DRV clearance.

The CHMP recognized the concern of a possible overdosing with the DRV/rtv dose of 25/3 mg/kg b.i.d.. However, the CHMP felt that the MAH didn't submit sufficient data to support the proposal dose of DRV/rtv dose of 20/3 mg/kg b.i.d. especially in the view of the uncertainties related to extrapolation of these data in children with low AAG levels or weighting < 12 kg.

Due to the above mentioned limitations of the study, the CHMP considered that the data was insufficient to conclude on a dose recommendation in children weighting 10 to < 15 kg. The MAH agreed with the CHMP's conclusion. Hence, during the course of the application, the MAH decided not to pursue anymore the claim for an indication in children aged 3 to 6 years and weighting 10 to < 15 kg.

The CHMP recognised though the need for additional data in this population. Hence, the committee recommended that the MAH generates further data in this population to support dosing recommendations in children aged 3 to 6 years and weighting 10 to < 15 kg. The MAH agreed to submit a protocol outline for such a study by end of December 2012.

In children weighting 15 to < 20 kg, the CHMP considered that the proposed dose of DRV/r of 375/50 mg BID was sufficiently substantiated.

2.5. Clinical efficacy

2.5.1. Main study

Methods

Study TMC114-TiDP29-C228 is a phase II open-label, pharmacokinetic study to determine the recommended paediatric dose of DRV/rtv, and evaluation of short-term safety, tolerability and efficacy in treatment-experienced, HIV-1 infected children between 3 and < 6 years of age (10-20 kg).

Study Participants

Inclusion Criteria

The main inclusion criteria were as follows:

1. Male or female children, aged between 3 to < 6 years at screening.
2. Subjects with documented HIV-1 infection (by any of the local standard diagnostic methods, such as HIV PCR-DNA, ELISA, or Western blot test for HIV antibodies, etc.).
3. Body weight from 10 to < 20 kg at screening.
4. Subjects currently on stable ART for ≥ 12 weeks, who needed to change their ARV regimen because it was currently failing, with a viral load of > 1000 copies/mL.
5. Screening genotype resistance test results showing < 3 DRV RAMs. (DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V)

Exclusion Criteria

The main exclusion criteria were as follows:

1. Subjects with presence of any currently active conditions included in the listing of WHO Clinical Stage 4 and subjects with presence of a non-HIV encephalopathy.
2. Use of disallowed concomitant therapy: all other PIs, other NNRTIs than efavirenz or nevirapine; raltegravir, maraviroc, enfuvirtide.
3. Administration of any ARV or non-ARV investigational medication or investigational vaccine within 30 days prior to screening, except for those medications where dose recommendations for children were available.
4. Life expectancy < 6 months, according to the judgment of the investigator.
5. Co-enrollment in other clinical and/or cohort studys without written permission of the Sponsor.
6. Any active clinically significant disease (e.g., tuberculosis, cardiac dysfunction, pancreatitis, acute viral infections) or findings during screening of medical history or physical examination that, in the investigator's opinion, would compromise the subject's safety or outcome of the study.
7. Subjects with a laboratory abnormality > grade 2 as defined by age appropriate Division of AIDS (DAIDS) grading scheme (grade 3 and 4 thrombocytopenia were allowed).

Treatments

DRV was administered as an oral suspension, using a pipette with a 0.2-mL accuracy gradation. Rtv was administered an oral solution, using a pipette with a 0.1-mL accuracy gradation. See Section 2.4.2 for further details on the doses.

Objectives

See table 10.

Outcomes/endpoints

See table 10.

Sample size

See table 10.

Randomisation

Not applicable in this setting.

Blinding (masking)

Not applicable in this setting.

Statistical methods

The main analysis was an intent-to-treat (ITT) analysis.

Results

Recruitment

The study started on 29 September 2009 and ended on 28 February 2011.

Conduct of the study

See GCP inspection findings in Section 2.4.1.

Baseline data

Approximately half of the subjects were female (52.4%, 11 subjects). The majority (57.1%) were Black or African American (12 subjects) and 28.6% were White (6 subjects). The subjects' median age was 4.4 years (range: 3 to 6 years) and the median weight was 14.9 kg (range: 12 to 20 kg).

The weight distribution is consistent with international reference standards. According to the World Health Organization (WHO) Child Growth Standards, the median weight (50th percentile) for a 3-year-old child (boy/girl) is 14.3/13.9 kg, while the 25th percentile is 13.2/12.7 kg, and the 5th percentile is 11.8/11.3 kg. For a 4-year old child, these percentiles are 16.3/16.1 kg, 15.0/14.7 kg, and 13.3/12.9 kg, respectively; and for a 5-year old child, 18.3/18.2 kg, 16.7/16.5 kg, and 14.7/14.4 kg, respectively.

From study start up to the Week-48 analyses, the mean duration of treatment with DRV/rtv was 47.9 weeks. Before the dose adjustment, the mean duration was 13.1 weeks, and after the dose adjustment, the mean duration was 36.6 weeks.

Overall, the subjects' baseline disease characteristics were reflective of the young age and early to moderately advanced stage of HIV-1 disease. All children have been infected with HIV-1 by mother-to-child transmission (MTCT), and the median time since HIV-1 infection diagnosis was 4.0 years. The median baseline $\log_{10}$ viral load was 4.34 $\log_{10}$ copies/mL, the median baseline CD4+ percentage was 27.7%, and the median absolute CD4+ cell count was 927 x 10^6/L cells.

The median number of ARVs previously used in this population was 4 (range: 3 to 8). Sixteen subjects (76.2%) had previously used ≥ 1 PI (12 subjects had used 1 PI and 4 subjects had used ≥ 2 PIs). All subjects had previously used ≥ 2 NRTIs (17 subjects had used 2 NRTIs, 4 subjects had used ≥ 3 NRTIs). Thirteen subjects (61.9%) had used ≥ 1 NNRTI.

The majority of subjects had no primary PI mutations (17 subjects, 81.0%) and no DRV RAMs (19 subjects, 90.5%) at baseline. Fifteen subjects (71.4%) had ≥ 3 PI RAMs. The median number of primary PI mutations, DRV RAMs, and PI RAMs was 0, 0, and 4, respectively. As a relatively large proportion of subjects came from an NRTI and/or NNRTI failing regimen, 18 subjects (85.7%) had ≥ 1 NRTI RAM (17 subjects harbored the M184V mutation) and 12 subjects (57.1%) had ≥ 1 NNRTI RAM. The median number of NNRTI RAMs and NRTI RAMs was 1 for both.

Consistent with the low level of PI experience (median: 1 PI), a relatively low level of phenotypic PI resistance was observed. All subjects were infected with viruses susceptible to DRV (the median DRV fold change in EC_{50} [FC] was 0.55) and tipranavir at baseline, and most subjects also had viruses susceptible to the other commercially available PIs (ranging between 82.4% and 94.1% for the different PIs). The majority of subjects (16, 94.1%) were susceptible to ≥ 3 NRTIs; 14 subjects (77.8%) were susceptible to ≥ 1 NNRTI.

As defined in the study protocol and in line with the current treatment guidelines, an OBR consisting of ≥ 2 active ARV agents (i.e., a combination of NRTI[s] and/or allowed NNRTI[s]) had to be given. For all subjects, the initiated OBR consisted of NRTIs only (19 subjects used 2 NRTIs and 2 subjects used 3 NRTIs). Based on Antivirogram®, a large proportion of subjects (64.7%) had ≥ 2 susceptible NRTIs in the background regimen, indicating that for most subjects, an adequate ARV combination regimen had been constructed.

Table 6. Relevant Baseline Disease Characteristics – Study TMC114-C228

Parameter	TMC114-C228 N = 21
Baseline Disease Characteristics, Median (range)	
Log_{10} viral load (log_{10} copies/mL)	4.34 (2.9; 5.7)
CD4+ %	27.7 (15.6; 51.1)
CD4+ cell count (x 10^6/L)	927 (209; 2429)
Duration of HIV-1 infection (years)	4.0 (0; 5)
Previous ARV Experience, n (%)	
PI: ≥ 1	16 (76.2)
NRTI: ≥ 2	21 (100.0)
NNRTI: ≥ 1	13 (61.9)
Baseline Phenotype[b] and Genotype[c]	
8 susceptible PIs, n (%)[d]	14 (77.8)
≥ 3 susceptible NRTIs, n (%)	16 (94.1)
≥ 1 susceptible NNRTI, n (%)	14 (77.8)
DRV FC, median (range)	0.55 (0.2; 2.3)
Mutations, median (range)[e]	
Primary PI mutations	0 (0; 3)
PI RAMs	4 (1; 14)
DRV RAMs	0 (0; 2)
NRTI RAMs	1 (0; 5)
NNRTI RAMs	1 (0; 4)

b. Based on Antivirogram.
c. Based on the 2010 IAS-USA list of mutations[8].
d. All currently available PIs = (fos)amprenavir, atazanavir, indinavir, LPV, nelfinavir, saquinavir, tipranavir, and DRV.
e. Data at baseline and prebaseline were concatenated to calculate resistance baseline values.

Numbers analysed

Per study protocol, approximately 24 HIV-1 positive subjects were to be selected, with between 10 and 14 children for each of the 2 following weight bands: 10 to < 15 kg and 15 to < 20 kg. Priority had to be given to have ≥ 10 subjects recruited in the lower weight group.

These requirements were fulfilled, as a total of 27 subjects were actually enrolled in study TMC114-C228. Of these 27 subjects, 21 (11 in the lower weight group and 10 in the higher weight group) were included in the analyses. The remaining 6 subjects were excluded following the critical findings of the EMA site inspection (see Section 2.4.1).

Outcomes and estimation

Antiviral Efficacy

The response rates for the primary efficacy parameter plasma viral load < 50 copies/mL (ITT - TLOVR), as well as the secondary parameters plasma viral load < 400 copies/mL and ≥ 1.0 log_{10} decrease from baseline in plasma viral load (ITT - TLOVR), and the change in log_{10} viral load from baseline (ITT - NC = F) at Week 24 and Week 48 are shown in Table 7.

Table 7. Percentage of Subjects With Plasma Viral Load < 50 and < 400 Copies/mL, ≥ 1.0 $\log_{10}$ Decrease in Plasma Viral Load From Baseline (ITT - TLOVR), and Change in $\log_{10}$ Viral Load From Baseline (ITT - NC = F) – Study TMC114-C228, Week-48 Analyses

Parameter	**DRV/rtv**		
	N	**n (%)**	
Plasma viral load < 50 copies/mL			
Week 24	21	12 (57.1)	
Week 48	21	17 (81.0)	
Plasma viral load < 400 copies/mL			
Week 24	21	17 (81.0)	
Week 48	21	18 (85.7)	
≥ 1.0 $\log_{10}$ decrease from baseline in plasma viral load			
Week 24	21	17 (81.0)	
Week 48	21	19 (90.5)	
Change in $\log_{10}$ viral load from baseline		**Mean (SE)**	**Median (Range)**
Week 24	21	-2.04 (0.244)	-2.26 (-4.0; 0.0)
Week 48	21	-2.14 (0.257)	-2.30 (-4.0; 0.3)

N = number of subjects; n = number of responders; SE = standard error

For all virologic efficacy parameters the results were consistent and were confirmed by the performed sensitivity analyses. The results of the FDA snapshot analysis were also in line with the TLOVR results (see Table 8).

Table 8. Outcome Table (Virologic Response Defined as the Percentage of Subjects With Viral Load < 50 Copies/mL, FDA Snapshot Analysis) – Study TMC114-C228, Week-48 Analyses

n (%)	**DRV/rtv N = 21**
Virologic success (< 50 copies/mL) at Week 48[a]	15 (71.4)
Virologic failure[b]	5 (23.8)
No virologic data at Week 48 - Discontinued due to AEs/death[c,d]	1 (4.8)

N = number of subjects; n = number of subjects with that observation
Visit window; Week 44 to 52
Includes a) subjects who had ≥ 50 copies/mL in the Week-48 window, b) subjects who discontinued prior to Week 48 for lack or loss of efficacy, c) subjects who had a switch in their OBR that was not permitted by the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of study medication), and d) subjects who discontinued for reasons other than AEs/death, and lack or loss of efficacy (provided their last available viral load was detectable).
Includes subjects who discontinued due to an AE or death at any time point from Day 1 through the Week-48 time window if this resulted in no virologic data on treatment during the specified window (provided the earliest AE leading to permanent stop was not preceded by a switch in the OBR that was not permitted by the protocol). One subject had an AE (vomiting, grade 2) that led to permanent discontinuation of study medication.

Comparison of the performance of DRV/rtv in study TMC114-C228 versus study TMC114-C212 (treatment-experienced children aged 6 to < 12 years) and study TMC114-C214 (treatment-experienced adults) showed that a lower proportion of TMC114-C228 subjects achieved a viral load < 50 copies/mL at Week 24. By Week 48, the proportion of TMC114-C228 subjects with complete viral suppression was similar to that in studies TMC114-C212 and TMC114-C214. In addition, the response rates for viral load at Week 48 in study TMC114-C228 were relatively high compared to those observed in prior studies.

Other virologic efficacy parameters (plasma viral load < 400 copies/mL, ≥ 1.0 $\log_{10}$ decrease in plasma viral load from baseline, and change in $\log_{10}$ plasma viral load from baseline) were also

comparable between the subjects in study TMC114-C228 and the subjects in studies TMC114-C212 and TMC114-C214, and confirmed the potent antiviral activity of DRV/rtv in the age range studied.

Immunologic Change

The antiviral activity of DRV/rtv was mirrored in the increases in the CD4+ cell count. The beneficial effect of DRV/rtv on restoration of the immune function was seen for both absolute and % CD4+ cell count (see Table 9). These findings are generally comparable to the immunologic changes observed after 48 weeks in study TMC114-C212 and TMC114-C214.

Table 9. Change in CD4+ Cell Count (Absolute and Percentage) From Baseline per Time Point (ITT - NC = F) – Study TMC114-C228, Week-48 Analyses

Parameter	DRV/rtv		
	N	Mean (SE)	Median (Range)
Change in CD4+% from baseline			
Week 48	21	4 (1.3)	4 (-6; 19)
Change in CD4+ absolute cell count (x 10^6/L) from baseline			
Week 48	21	187 (76.7)	180 (-561; 869)

N = number of subjects; SE = standard error
Source: Module 2.7.3 (15-Mar-2012)/Section 2.2.7.3 and Table 10

Growth and Development

At baseline, the mean age-adjusted z-scores indicated that subjects in study TMC114-C228 were below the normal population median with respect to height (-1.2), weight (-0.9), and body mass index (BMI, -0.3). At Week 48, the within-group comparison of the changes from baseline for the age-adjusted z-scores showed small mean changes for all parameters (height: -0.10; weight: 0.01; BMI: 0.11). None of these changes were statistically significant or considered clinically relevant. Although the mean age-adjusted z-scores at Week 48 remained below the normal population median for all parameters, the subjects grew according to the expected curves.

Medication Adherence and DRV Taste Evaluation

A review of 17 studies regarding pediatric HIV-1 treatment adherence found adherence ranging between 49% and 100%; three quarters of the studies showed adherence rates of 70% to 75%. The medication adherence in study TMC114-C228, assessed using selected questions from the PENTA Study Adherence Questionnaire for Caregivers, was in line with published literature. At endpoint, 61.9% of subjects were reported to be adherent to DRV/rtv and 66.7% of subjects were reported to be adherent to the OBR. Virologic response was 84.6% in subject adherent to DRV/rtv and 75.0% in nonadherent subjects.

Medication adherence in study TMC114-C228 was also analyzed by using drug accountability data obtained by the weighing of bottles of dispensed and returned investigational medication (DRV and rtv). The results from this analysis showed no evidence of a relationship between adherence and virologic response, either for DRV or for rtv.

The taste of the DRV oral suspension was evaluated (using a 5-point pictorial scale of facial expressions) in the target population in study TMC114-C228. The taste evaluation was performed at baseline (after the dose of DRV and before the dose of rtv): a high proportion of subjects responded that they either liked the taste (10 subjects, 47.6%) or gave a neutral response (4 subjects, 19.0%),

whereas 7 subjects (33.3%) responded that they did not like the taste. No taste evaluation of the rtv solution was performed.

Dose Response

Study TMC114-C228 was not designed to evaluate the efficacy of DRV/rtv by dose, and no formal comparison was performed with respect to the antiviral activity or immunologic changes before and after the dose adjustment.

Long-Term Efficacy

No information on the efficacy of treatment with DRV/rtv beyond Week 48 in study TMC114-C228 is available. However, the long-term efficacy of DRV/rtv is well established in adults. In addition, the Week-48 efficacy results in study TMC114-C228 are comparable with the virologic response rates up to Week 48 in treatment-experienced HIV-1 infected children aged 6 to < 12 years (study TMC114-C212).

Overview of Resistance

At baseline, 2 subjects harbored DRV RAMs (1 subject had L33F and L76V and one subject had L76V). Both subjects responded at Week 24 and 48 (plasma viral load < 50 copies/mL).

Post baseline resistance testing was performed on samples with plasma viral load ≥ 50 copies/mL. The development of a mutation was defined as one that could be detected by resistance testing (population sequencing) at endpoint while not present at baseline or screening.

There were 3 subjects (14.3%) with virologic failure when using the virologic response parameter plasma viral load < 50 copies/mL (TLOVR non-VF-censored) over time. Two of these subjects were never suppressed and 1 subject was considered a rebounder. Two subjects with virologic failure were non adherent and 1 was adherent to treatment based on the PENTA Study Adherence Questionnaire for Caregivers.

Paired baseline/endpoint genotype data were available for 8 subjects, including 2 subjects with virologic failure. No development of any IAS-USA PI or NRTI RAM was observed. The viruses of both subjects with virologic failure remained susceptible to DRV. Both subjects with virologic failure, for who paired baseline/endpoint phenotypes were available and who were susceptible to all NRTIs in the OBR at baseline, remained susceptible to those NRTIs postbaseline.

In general, development of resistance (developing PI and NRTI RAMs and loss of phenotypic susceptibility to PIs and NRTIs) was lower in study TMC114-C228 than in studies TMC114-C212 and TMC114-C214.

Ancillary analyses

Not applicable.

Summary of main study(ies)

The following table summarise the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10. Summary of Efficacy for study TMC114-TiDP29-C228

Study identifier	TMC114-TiDP29-C228		
Design	Open-label, Phase II study to evaluate the pharmacokinetics, safety and antiviral activity to support dose recommendations by body weight of DRV/rtv, in combination with other ARVs, in treatment-experienced HIV-1 infected children aged from 3 to < 6 years and weighing between 10 and < 20 kg. In addition, efficacy, safety and tolerability of DRV/rtv were evaluated in combination with other ARVs over a 48-week treatment period.		
	Duration of main phase:	48 weeks	
	Duration of Run-in phase:	Screening maximum 4 weeks	
Hypothesis	Exploratory: The primary objectives were: - To evaluate the pharmacokinetic profile of DRV in combination with low-dose rtv administered twice daily (b.i.d.) at steady-state in children aged from 3 to < 6 years and weighing between 10 and < 20 kg. - To support dose recommendation of DRV/rtv to be used in this population by comparing the DRV exposure achieved in these treatment-experienced HIV-1 infected children to that in HIV-1 infected adults and older children weighing > 20 kg. - To evaluate short-term safety, tolerability, and antiviral activity of DRV/rtv b.i.d. in treatment-experienced children aged from 3 to < 6 years over a 2-week treatment period. - To evaluate safety, tolerability and antiviral activity of DRV/rtv b.i.d. and other ARVs over a 24-week treatment period at the selected dose for HIV-1 infected children aged from 3 to < 6 years. The secondary objectives were: - To evaluate long-term safety, tolerability and efficacy of DRV/rtv b.i.d. and other ARVs over a 48-week treatment period at the selected dose for HIV-1 infected children aged from 3 to < 6 years. - To evaluate immunology, resistance, pharmacokinetics, and pharmacokinetic/pharmacodynamic relationships over a 48-week treatment period.		
Treatments groups	Single treatment group, labeled DRV/rtv		
Endpoints and definitions	Primary endpoint	Confirmed virologic response (<50 copies/mL, ITT-TLOVR) at Week 48	Virologic response defined as percent of subjects with confirmed plasma viral load < 50 HIV-1 RNA copies/mL at Week 48. The FDA TLOVR algorithm was used to derive response, i.e., response and loss of response had to be confirmed at 2 consecutive visits and subjects who prematurely discontinued were considered nonresponders after discontinuation. Subjects with intermittent missing viral load values were considered responders if the preceding and succeeding visits indicated response. In all other cases, intermittent values were imputed with nonresponse.
	Secondary endpoints	- Viral load < 400 copies/mL, - ≥ 1.0 log10 decrease from baseline in viral load (copies/mL), - Viral load change from baseline (log10 copies/mL), - CD4+ % change from baseline, - CD4+ cell count change from baseline (x 106 cells/L),	

Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	Analysis population: intent-to-treat population: the set of all treated subjects, i.e. all subjects with baseline or post baseline data, regardless of their compliance with the protocol or their ineligibility, are to be included in the analysis.	
Descriptive statistics and estimate variability	Treatment group	DRV/rtv
	Number of ITT subjects (N)	21
	Number (percentage) of subjects with confirmed virologic response (<50 copies/mL, ITT-TLOVR) at Week 24 (from Week 48 analysis)	12 (57.1)
	Number (percentage) of subjects with confirmed virologic response (<50 copies/mL, ITT-TLOVR) at Week 48	17 (81.0)
Analysis description	**Secondary analyses**	
Analysis population and time point description	Analysis population: intent-to-treat population: the set of all treated subjects, i.e. all subjects with baseline or post baseline data, regardless of their compliance with the protocol or their ineligibility, are to be included in the analysis.	
Descriptive statistics and estimate variability	Treatment group	DRV/rtv
	Number of ITT subjects (N)	21
	Viral load < 400 copies/mL, n (%)	18 (85.7)
	≥ 1.0 log10 decrease from baseline in viral load (copies/mL), n (%)	19 (90.5)
	Viral load change from baseline (log10 copies/mL), mean (SE)	-2.14 (0.257)
	CD4+ % change from baseline, mean (SE)	4.0 (1.30)
	CD4+ cell count change from baseline (x 106 cells/L), mean (SE)	187 (76.7)

Clinical studies in special populations

No efficacy analyses by gender, race, age, region, or parameters with respect to baseline disease characteristics, or weight were performed for study TMC114-C228, due to the limited sample size of the overall population and of any subgroup.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This was an open-label, Phase II study to evaluate the pharmacokinetics, safety and antiviral activity to support dose recommendations by body weight of DRV/rtv, in combination with other ARVs, in treatment-experienced HIV-1 infected children aged from 3 to < 6 years and weighing between 10 and < 20 kg. In addition, efficacy, safety and tolerability of DRV/rtv were evaluated in combination with other ARVs over a 48-week treatment period.

Since the antiviral activity of DRV have already been established in efficacy studies in the adult population, the Phase II study TMC114-C228 was not designed to re-evaluate the efficacy of DRV in the paediatric population. This is in line with the recommendations of the guideline on the Clinical development of medicinal products for treatment of HIV infection (EMEA/CPMP/EWP/633/02).

Efficacy data and additional analyses

The efficacy rates observed in study TMC114-C228 are in line with previously reported in study TMC114-C212 (treatment-experienced children aged 6 to < 12 years) and study TMC114-C214 (treatment-experienced adults).

However, the reduction of the sample size to 21 children due to GCP issues compromised the interpretability of results since the initial sample size calculation was based on a number of 24 patients to obtain a 50% success rates with a 95% confidence interval of 30-70%.

In addition, the dose of DRV/rtv 20/3 mg/kg b.i.d. in children weighting 10 to < 15 kg has not been evaluated for more than 2 weeks. This was of concern for the CHMP since limited number of children in this weight band was enrolled in the study with no children weighting < 12 kg.

The taste of the DRV oral suspension was evaluated in study TMC114-C228. Seven 7 patients (33.3%) responded that they did not like the taste. The MAH clarified that there are technical limitations to come to a taste-neutral formulation.

Low adherence rates (care-giver reported rates of 70%) may possibly be associated with the taste of the suspension. However, the relationship between taste appreciation and adherence could not be established because the adherence data were unreliable: either due to self-reported overestimation or due to incorrect weight-based drug accountability systems that reported >100% adherence.

2.5.3. Conclusions on the clinical efficacy

The population enrolled in study TMC114-C228 was heterogeneous and small. However, based on the week 48 data on virologic and immunologic response, the responses observed in the previous DRV studies, the CHMP is of the opinion that DRV/rtv is effective in treatment-experienced HIV infected paediatric patients from 3 to < 6 years of age at the recommended dose regimen of 375 mg/50 mg BID in children 15 to < 20 kg. No serious NRTI or PI mutations appeared that would compromise treatment options.

However, the CHMP was of the opinion that the dose of DRV 20 mg/kg has not been sufficiently evaluated in the weight group of 10 to < 15 kg. As further detailed in section 2.4.5 the MAH agreed with the CHMP and decided to revise the claimed indication removing the claim for an indication in children aged 3 to 6 years weighting 10 to < 15 kg.

Adherence data in the study were unreliable, therefore any association of taste appreciation and adherence is hard to establish. However, since 33% of the children disliked the taste, the CHMP concluded that this patient group should be monitored for virological breakthrough and underdosing in the RMP.

2.6. Clinical safety

Patient exposure

After dose adjustment 20 children were exposed to optimized dose during mean 36.6 weeks. One patient discontinued treatment on day 1. Reliable comparisons to other patient groups are not possible based on this limited exposure. However, the CHMP considered that the number of patients included in this study was acceptable for this type of paediatric application.

Adverse events

The most frequent (> 4 subjects overall, > 20%) adverse events (AEs) were upper respiratory tract infection in 6 subjects (28.6%) and diarrhea, tinea capitis and cough in 5 subjects (23.8%) each. Most AEs were grade 1 or 2 in severity. None of the subjects had a grade 3 AE. Two 2 subjects (9.5%) had a grade 4 AE that were not considered related to DRV by the investigator. One subject (4.8%) had an AE considered at least possibly related to DRV by the investigator (ECG QT prolonged, but normal QTcF interval) that did not result in discontinuation. There were no relevant effects of the dose adjustment after Week 2 on the type, incidence, or severity of AEs. With the exception of the gastrointestinal AEs (8 subjects, 38.1%), the incidence of AEs of special interest was low. Diarrhea was at most grade 1 and did not result in discontinuations. No new safety concerns were identified following review of the data of study TMC114-C228 versus the known safety profile of DRV/rtv.

Serious adverse event/deaths/other significant events

SAE were reported in 3 patients and were not considered at least possibly related to DRV. No subjects died during the 48 week study period.

Laboratory findings

The overall incidence of laboratory abnormalities of interest in study TMC114-C228 was low and no clinically relevant mean change from baseline was observed for any laboratory parameter during the treatment period. All laboratory abnormalities were grade 1 or 2 in severity, except for 1 case of a grade 3 decrease in neutrophils at Week 24.

Discontinuation due to adverse events

Treatment discontinuation was reported only in 1 subject due to vomiting on day 1 which was not considered at least possibly related to DRV by the investigator.

2.6.1. Discussion on clinical safety

The majority of AEs were grade 1 or 2 in severity. Grade 3 or 4 events were reported in 5 subjects. SAE were reported in 3 patients and were not considered at least possibly related to DRV. No new safety concerns emerged from the study TMC114-C228. The data from this study do not indicate new issues when compared with the known data in children > 6 years of age. However, the CHMP

acknowledged that the safety data was issued from a very small group of 20 children of 3 to < 6 years of age.

2.6.2. Conclusions on the clinical safety

In study TMC114-C228, DRV/rtv in the dose 25/3 mg/kg B.I.D. in children weighting 10 to < 15 kg and 375/50 mg B.I.D. in children weighting 15 to < 20 kg was generally safe when administered as part of an individually optimized ART in ARV treatment-experienced HIV-1 infected children aged from 3 to < 6 years.

Since the safety profile of the DRV/rtv in the dose 25/3 mg/kg B.I.D. in children weighting 10 to < 15 kg did not raise specific concerns, the MAH's proposal to re-adjustment the dose to DRV/rtv 20/3 mg/kg B.I.D. did not raise specific safety issue. However, as further discussed in Section 2.4, the CHMP was of the opinion that this dose has not been sufficiently evaluated in the weight group of 10 to < 15 kg. The MAH agreed with the CHMP and decided not to pursue any longer the claim for an indication in children aged 3 to 6 years weighting 10 to < 15 kg.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk Management Plan

The MAH submitted a risk management plan.

Table 11. Summary of the risk management plan

Safety Concern	**Pharmacovigilance Activities (routine and additional)**	**Risk Minimisation Activities (routine and additional)**
Important identified risks:		
Severe Skin Reactions	Routine pharmacovigilance	Listed in the Special warnings and precautions for use section of the SmPC (Section 4.4), including recommendations to discontinue PREZISTA/rtv immediately if signs or symptoms of severe skin reactions develop, a statement on increased risk in treatment-experienced patients receiving regimens containing PREZISTA + raltegravir compared to patients receiving PREZISTA without raltegravir or raltegravir without PREZISTA, and a caution statement for the use of PREZISTA in patients with a known sulphonamide allergy since darunavir contains a sulphonamide moiety.

		Rash (including macular, maculopapular, papular, erythematous and pruritic rash), pruritus, angioedema, generalised rash, allergic dermatitis, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and (drug) hypersensitivity are listed as ADR in Section 4.8 Undesirable effects of the SmPC. In Section 4.8 of the proposed SmPC (procedure EMEA/H/C/707/II/047), acute generalised exanthematous pustulosis has been added as ADR.
Hepatotoxicity	- Routine pharmacovigilance - Additional pharmacovigilance Participation in the HAART-OC trials. If needed, the risks will be further characterised by assessing the comparative frequency of hepatotoxicity events occurring in independent HIV cohorts (such as D:A:D/EuroSida).	Hepatotoxicity is a subsection in the Special warnings and precautions for use section of the SmPC (Section 4.4), including: a statement on increased risk of liver function abnormalities in patients with pre-existing liver dysfunction; advice on appropriate laboratory test monitoring prior and during therapy with PREZISTA/rtv and on increased AST/ALT monitoring in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pretreatment elevations of transaminases; recommendation to consider interruption or discontinuation of PREZISTA/rtv treatment in case of evidence of new or worsening liver dysfunction. Also hepatic impairment is listed in the Special warnings and precautions for use section of the SmPC (Section 4.4). Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use, and Section 5.2 Pharmacokinetic properties of the SmPC includes a caution statement for the use of PREZISTA in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Section 5.2 Pharmacokinetic properties states that the effect of severe hepatic

		impairment on the pharmacokinetics of darunavir has not been studied. Section 4.2 Posology and method of administration, Section 4.3 Contraindications, and Section 4.4 Special warnings and precautions for use state that PREZISTA should not be used/is contraindicated in patients with severe (Child-Pugh Class C) hepatic impairment.
		Increased alanine aminotransferase, increased aspartate aminotransferase, hepatitis, cytolytic hepatitis, hepatic steatosis, hepatomegaly, increased transaminase, increased blood alkaline phosphatase, and increased gamma-glutamyltransferase are listed as ADR in Section 4.8 Undesirable effects of the SmPC. Details on undesirable effects in HIV/hepatitis B or C co-infected patients are also provided in Section 4.8 Undesirable effects of the SmPC.
Hyperglycaemia	- Routine pharmacovigilance - Additional pharmacovigilance Participation in the HAART-OC trials. If needed, the risks will be further characterised by assessing the comparative frequency of hyperglycaemia events occurring in independent HIV cohorts (such as D:A:D/EuroSida).	Listed in the Special warnings and precautions for use section of the SmPC (Section 4.4). Diabetes mellitus, hyperglycaemia, and insulin resistance are listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Lipid Abnormalities	- Routine pharmacovigilance - Additional pharmacovigilance Participation in the HAART-OC trials.	Hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia, and decreased high density lipoprotein are listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Pancreatitis	Routine pharmacovigilance	Increased blood amylase, pancreatitis, and increased lipase are listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Fat Redistribution	Routine pharmacovigilance	Listed in the Special warnings and precautions for use section of the SmPC

		(Section 4.4), including: a statement on the increased risk of lipodystrophy associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. recommendations on the monitoring and management of fat redistribution. Lipodystrophy (including lipohypertrophy, lipodystrophy and lipoatrophy) is listed as ADR in Section 4.8 Undesirable effects of the SmPC
Immune Reconstitution Syndrome	Routine pharmacovigilance	Listed in the Special warnings and precautions for use section of the SmPC (Section 4.4). Immune reconstitution syndrome is listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Development of Drug Resistance	- Routine pharmacovigilance - Drug resistance is monitored by national and international collaborative programmes (such as EuroSIDA, SPREAD and CDC projects) and frequently reported. The prevalence of HIV-1 drug resistance is followed for all classes of drugs, including the PIs. - Additional pharmacovigilance the dose regimen will be taken into account in all resistance monitoring reports (e.g. PSUR)	Section 4.1 Therapeutic indications of the SmPC mentions that in deciding to initiate treatment with PREZISTA/rtv careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of PREZISTA.
Important potential risks:		
Coronary Artery Events	- Routine pharmacovigilance - Additional pharmacovigilance Participation in the HAART-OC trials If needed, the risks will be further characterised by assessing the comparative frequency of coronary artery events occurring in independent	Acute myocardial infarction, myocardial infarction, and angina pectoris are listed as ADR in Section 4.8 Undesirable effects of the SmPC.

	HIV cohorts (such as D:A:D/EuroSida).	
Cardiac Conduction Abnormalities	Routine pharmacovigilance	Prolonged electrocardiogram QT is listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Hyper-bilirubinaemia	Routine pharmacovigilance	Increased blood bilirubin is listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Overdose/ medication error with the 400-mg tablet	Routine pharmacovigilance	The SmPC of PREZISTA 400 mg mentions in Section 4.2 (Posology and method of administration) clear dosing instructions and in addition Section 3 of the PL mentions that PREZISTA 400-mg tablets are only to be used to construct the once daily 800 mg regimen.
Convulsions	Routine pharmacovigilance	Convulsions is listed as ADR in Section 4.8 Undesirable effects of the SmPC.
Important missing information:		
Elderly	Routine pharmacovigilance	Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use, and Section 5.2 Pharmacokinetic properties state that there is limited information available in patients aged 65 and over and therefore Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use state that PREZISTA should be used with caution in this age group.
Pregnant and Breast-Feeding Women	- Routine pharmacovigilance - Additional pharmacovigilance Continued evaluation through the ongoing trial TMC114HIV3015 to assess the pharmacokinetics of DRV/rtv and/or ETR in 12 to 48 HIV-1 infected pregnant women. Participation in the APR	Section 4.6 Fertility, pregnancy and lactation of the SmPC states that there are no adequate and well-controlled studies with darunavir in pregnant women and it is not known whether darunavir is excreted in human milk. Therefore, PREZISTA/rtv should be used during pregnancy only if the potential benefit justifies the potential risk and, taking into account the potential of HIV transmission and the potential for adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed under any circumstances if they are receiving PREZISTA.

Children 3 - < 6 years of age (limited data are available from Phase II trial)	- Routine pharmacovigilance - Additional pharmacovigilance Pharmacovigilance study to define the long-term safety profile of darunavir in HIV-infected children and adolescents in Europe (TMC114-EPPICC).	Section 4.1 Therapeutic indications and 4.2 Posology and method of administration of the proposed SmPC (in procedure EMEA/H/C/707/X/041G) does include ART-experienced paediatric patients from 3 to 17 years of age and weighing at least 15 kg. Section 4.4 Special warnings and precautions for use, of the proposed SmPC (in procedure EMEA/H/C/707/X/041G) states that PREZISTA is not recommended for use in paediatric patients below 3 years of age or less than 15 kg body weight. Section 4.8 Undesirable effects (subsection Paediatric population) of the proposed SmPC (procedure EMEA/H/C/707/X/041G) states that overall, the safety profile in these paediatric patients was similar to that observed in the adult population. In addition, Section 5.3 Preclinical safety data states that due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, PREZISTA with low dose rtv should not be used in paediatric patients below 3 years of age.
Long-term safety data in children from 3 to 17 years of age	- Routine pharmacovigilance - Additional pharmacovigilance Pharmacovigilance study to define the long-term safety profile of darunavir in HIV-infected children and adolescents in Europe (TMC114-EPPICC). Continued access trial, TMC114-TiDP-C232, for paediatric patients who completed treatment with DRV in the clinical trials TMC114-C212, TMC114-TiDP29-C228 or TMC114-TiDP29-C230.	Section 4.8 Undesirable effects (subsection Children and adolescents) of the SmPC states that overall, the safety profile in the 80 children and adolescents included in the Phase II DELPHI trial was similar to that observed in the adult population. Section 4.8 Undesirable effects (subsection Paediatric population) of the proposed SmPC (procedure EMEA/H/C/707/X/041G) states that overall, the safety profile in these paediatric patients was similar to that observed in the adult population. Section 5.1 Pharmacodynamic properties (subsection Clinical experience) of the SmPC provides information on duration of exposure to DRV in respective

		populations (up to 96 weeks for the adult population and up to 48 weeks for the paediatric population)
Impact of palatability of the oral suspension on adherence and efficacy in treatment-experienced children > 15 kg.	- Routine pharmacovigilance	No risk minimisation activities proposed

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- Full user testing was performed (n=37 participants) at the time of initial marketing authorization for the patient leaflet for PREZISTA 300 mg film-coated tablets.
- An additional readability testing was performed with the introduction of the paediatric strengths of the 75 or 150 mg strengths and extending the indication to treatment-experienced children above 6 years of age.
- With the currently proposed indication extension the target group of users will not fundamentally change (3 - <6 years of age). This is within the age group in which performing a readability testing was not considered relevant.
- Information concerning safe and effective use in the newly added patient leaflet is very similar to the current approved leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects

DRV/rtv is indicated in combination with ART for treatment naïve adults and treatment experienced adults and children 6 to 18 years.

The new oral suspension 100 mg/ml is suitable for the paediatric population or patients unable to swallow tablets. The quality of this oral suspension is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

The pharmacokinetic data available from study TMC114-C228 with the dose of DRV/rtv 375/50 mg/kg b.i.d. in children weighting 15 to < 20 kg have shown an exposure that is within the range of the reference dose in adults.

In study TMC114-C228, the virologic response to DRV oral suspension in combination with ritonavir and combination ART in treatment-experienced children 3 to < 6 years of age weighting 15 to < 20 kg was in line with the data from the studies supporting the indication in the older age group.

The plasma levels observed in study C228 were well above the protein binding corrected 50% effective concentration in cell-based assays (EC_{50}) value of 550 ng/ml for PI resistant virus. Adequate antiviral activity with subsequent benefits on prevention of treatment-emerging resistance, immunological improvement with an increase in CD4 lymphocyte counts and improvement of growth parameters were shown.

Uncertainty in the knowledge about the beneficial effects.

The sample size is limited as 27 children were enrolled in this Phase II study TMC114-C228. Following critical GCP findings identified in one study site during the EMA GCP inspection, the data from this site was excluded from the study (6 children out the 27 enrolled in the study) which further reduced the data available.

Risks

Unfavourable effects

The safety profile for DRV/rtv in treatment-experienced children 3 to < 6 years of age (15 to < 20 kg) is comparable to that the studies supporting the indication in the older age group. After dose adjustment 20 children were exposed to optimized dose during mean 36.6 weeks in study TMC114-C228. During this limited time, no new DRV associated AEs were reported.

Uncertainty in the knowledge about the unfavourable effects

Both the limited duration of the follow up (48 weeks for a life long treatment) and the total sample size (20 patients) did not allow for an extensive safety monitoring.

Adherence data in the study were unreliable, therefore any association of taste appreciation and adherence is hard to establish. However, since 33% of the children disliked the taste, the CHMP concluded that this patient group should be monitored for virological breakthrough and underdosing in the RMP.

Benefit-risk balance

The new oral suspension 100 mg/ml is suitable for the paediatric population or patients unable to swallow tablets. The quality of this oral suspension is considered to be acceptable.

In children 3 to < 6 years of age weighting 15 to < 20 kg, the CHMP considered that the proposed dose of DRV/r of 375/50 mg BID was sufficiently substantiated. The efficacy and safety of DRV oral suspension in combination with ritonavir and combination ART in this population was in line with the data from the studies supporting the indication in the older age group.

Therefore, the CHMP concluded that the benefit-risk balance of DRV in the treatment of of human immunodeficiency virus (HIV-1) infection in antiretroviral therapy (ART)-experienced paediatric patients from the age of 3 years and at least 15 kg body weight is favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Prezista oral suspension 100 mg/ml in the treatment of of human immunodeficiency virus (HIV-1) infection in antiretroviral therapy (ART)-experienced paediatric patients from the age of 3 years and at least 15 kg body weight is favourable and therefore recommends the granting of the marketing authorisation subject to the current conditions below.

In addition, the CHMP considers the following variation acceptable and recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Update the section 4.1 of the SmPC for the existing 75mg, 150mg, 300mg, 600mg film coated tablets with the new paediatric indication (3 to 6 years weighing 15 to < 20 kg, HIV positive, treatment experienced patients) and introduce consequential changes to sections 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC for the existing 75mg, 150mg, 300mg, 400mg 600mg film coated tablets. The PL was updated accordingly. Changes to the product information were introduced in line with the QRD template.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/138/2010) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet. However, the PIP was not yet completed as some measures were deferred.