25 July 2013
EMA/604105/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prezista

International non-proprietary name: DARUNAVIR

Procedure No. EMEA/H/C/000707/II/0054

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

3TC	lamivudine
ABC	abacavir
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AZT	zidovudine
b.i.d.	bis in die, twice daily
C_{0h}	predose plasma concentration
DRV	darunavir, formerly TMC114
EC_{50}	50% effective concentration in cell-based assays
EMA	European Medicines Agency
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
ETR	etravirine, formerly TMC125
FDA	US Food and Drug Administration
GI	gastrointestinal
HDL	high-density lipoprotein
HIV(-1)	human immunodeficiency virus (type 1)
ITT	intent-to-treat
LDL	low-density lipoprotein
LPLV	last patient last visit
NC = F	noncompleting equals failure
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OBR	optimized background regimen
PDCO	Paediatric Committee
PENTA	Paediatric European Network for Treatment of AIDS
PI	HIV-1 protease inhibitor
PR	protease
PSUR	Periodic Safety Update Report
q.d.	quaque die, once daily
RAM	resistance-associated mutation
RNA	ribonucleic acid
RT	reverse transcriptase
rtv	low-dose ritonavir
SAE	serious adverse event
SE	standard error
SmPC	Summary of Product Characteristics
TLOVR	time to loss of virologic response
VF	virologic failure

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 7 November 2012 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 requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication in the HIV infected treatment naive patients aged 12 to 18 years.

The Package Leaflet was proposed to be updated in accordance.

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

1.2. Steps taken for the assessment

The Rapporteur and Co-Rapporteur appointed by the CHMP:

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

Submission date:	7 November 2012
Start of procedure:	23 November 2012
Rapporteur's preliminary assessment report circulated on:	20 January 2013
Co-Rapporteur's preliminary assessment report circulated on:	18 January 2013
Joint Rapporteur's updated assessment report circulated on:	19 February 2013

Request for supplementary information and extension of timetable adopted by the CHMP on:	21 February 2013
MAH's responses submitted to the CHMP on:	26 April 2013
PRAC Rapporteur's assessment report:	16 May 2013
PRAC RMP advice and assessment overview adopted by PRAC:	16 May 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 May 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	30 May 2013
MAH's responses submitted to the CHMP on:	21 June 2013
Joint Rapporteurs' assessment report circulated on:	10 July 2013
CHMP opinion:	25 July 2013

Information on Paediatric requirements

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

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

The PDCO issued an opinion on compliance for the PIP P/138/2010.

2. Scientific discussion

2.1. Introduction

Prezista (darunavir, DRV) is a protease inhibitor.

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 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.

These dosing regimens have been established based on the results of the Phase 3 studies TMC114-C211 (ARTEMIS, Phase III Randomized, Controlled, Open-label Trial to Investigate the Antiviral Activity, Tolerability and Safety of DRV/rtv in Treatment- Naive HIV-1 Infected Patients; application X/016, opinion adopted 20/11/2008) and TMC114-C229 [ODIN, randomised (1:1 ratio), open-label non-inferiority trial comparing DRV/ rtv 800/100 mg q.d versus DRV/rtv 600/100 mg b.i.d (both in combination with an individually selected OBR consisting of ≥ 2 NRTIs) in treatment-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs; application II/32, opinion adopted 20/01/2011], respectively.

The paediatric clinical development program of DRV/rtv included the following studies:

- Trial TMC114-C212 in treatment-experienced paediatric patients from 6 to < 18 years of age (application II/0025, opinion adopted 23/04/2009),
- Trial TMC114-C228 in treatment-experienced paediatric patients from 3 to < 6 years of age (application X/0041/G; opinion adopted 19/07/2012). 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. The pharmacokinetics data are presented within this report.

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-C230.

The indication proposed by the MAH as part of the present application was as follows:

"*PREZISTA, co-administered with low-dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of 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 and ART-naïve paediatric patients from the age of 12 years and at least 40 kg.*"

This proposed indication was supported in the present application by the Week-48 pharmacokinetic, efficacy and safety data from the Phase II study TMC114-C230 and extrapolation of efficacy data from adults and the known safety profile of DRV/rtv b.i.d. in subjects aged 3 to < 18 years.

Study TMC114-C230 results were previously submitted in accordance with Article 46 of Regulation (EC) No1901/2006 to the CHMP (P46-64 with a second round for assessment of the responses P46-66; concluded in September 2012). The CHMP concluded that the product information should be updated with the results of this study. In addition, a few points were left for clarification during the variation procedure.

An extrapolation of the data to the treatment-experienced adolescents aged 12 to 17 years and weighing more than 40kg with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥ 100 cells x 10^6/L was proposed as part of this application.

2.2. Non-clinical aspects

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.

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).

The new indication 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 CHMP agreed with the MAH that no increase in the environmental exposure was expected.

2.3. GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Union were

carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study No. **(Country)**	**Trial Period** **Total Enrollment / Enrollment Goal**	**Study Design**	**Study Objective**	**Treatment Arms** **(Drug, Dose, Route, Frequency)** **Duration**	**Subjects by Treatment** **Total No. (M/F)** **Median Age (Range)**	**Dropouts (reason)**	**Patient Selection**
TMC114-C230 Week 48 Multicenter (France, Italy, Spain, Ukraine, United Kingdom, United States)	Completed 12/12	Open-label trial	To evaluate the PK, safety, tolerability, and efficacy of DRV/rtv (800/100 mg q.d.) + OBR	DRV/rtv, oral, 800/100 mg q.d. (F030) Total treatment duration: 48 weeks	12 (4/8) 14.4 (13; 17)	0	ARV treatment-naïve HIV-1-infected adolescents aged between 12 and < 18 years and weighing ≥ 40 kg and with a viral load of ≥ 1,000 HIV-1 RNA copies/mL.

2.4. Clinical Pharmacology aspects

2.4.1. Analysis of data submitted

The use of DRV/rtv in treatment-naïve HIV-1 infected adolescents between 12 to < 18 years of age and weighing ≥ 40 kg has been evaluated in the 48-week, Phase II, open-label trial TMC114-C230, involving 12 subjects (male and female). See Section 2.5 for further details on the study design.

Methods

During the first 2 weeks of the study, DRV/rtv had to be taken in the morning to facilitate the rich pharmacokinetic 24-hour sampling for all subjects at Week 2 (Day 14 and 24-hour sample at Day 15). After completion of the 24-hour intensive pharmacokinetic sample collection at Week 2, subjects had the choice to take the DRV/rtv dose in the morning or in the evening. In case a subject preferred to switch to dosing in the evening, they had to do so minimally 2 weeks before the next sparse blood sampling day. At the time of switching to dosing in the evening, drug administration took place within 30 to 36 hours after the last morning dose of DRV/rtv.

Cytochrome P450 (CYP) 3A4 inducers were not allowed from 14 days prior to baseline until the end of the treatment period and CYP3A4 substrates with a narrow therapeutic index were not allowed from baseline until the end of the treatment period.

At Week 2, pharmacokinetic blood sampling was performed at 6 time points over 24 hours for evaluation of the pharmacokinetics. At Week 4, 24, and 48, 2 plasma samples were drawn for assessment of DRV population pharmacokinetics. Two samples were drawn at least 1 hour apart from each other.

Bioanalytical analyses

Plasma concentrations of DRV and rtv were determined using a validated liquid chromatographic – mass spectrometry/mass spectrometry (LC-MS/MS) method.

Empirical Bayesian estimates for AUC_{24h}, average steady-state plasma concentration ($C_{ss,ave}$), C_{0h} and CL/F were obtained for each subject at each visit, and the median estimate determined within each subject.

Population pharmacokinetics

A population pharmacokinetic model for darunavir in adults was already available. The PK model has previously been adjusted to accommodate the difference in exposure after administration of the clinical trial and the commercial tablet formulation and further adjusted to accommodate data from children between the ages of 3 to <18 years old treated b.i.d. This adjusted 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). It is a two-compartment pharmacokinetic model with first-order absorption with apparent oral clearance dependent on the concentration of alpha1- acid glycoprotein (AAG) and body weight; and the apparent volume of the central compartment is dependent on body weight.

The model was updated after inclusion of the data after once daily intake in the TMC114-C228 sub-study and in the TMC114-C230 trial. This update 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 consisted of 659 observations from 102 subjects (72 children and 30 adults). The 6 trials included in the dataset are summarized in Table 1.

Table 1. Summary of Clinical Trial Data Selected for Updating the DRV Population Pharmacokinetic Model

Trial	**TMC114-C228 (Main Study)**	**TMC114-C228 (q.d. Substudy)**	**TMC114-C230**	**TMC114-C212 Part I**	**TMC125-C206, TMC125-C216**
N	24	10	12	41	30
Dose of DRV/rtv	20/3 mg/kg b.i.d.	40/6.66 mg/kg q.d. for subjects <15 kg, 600/100 mg q.d. for subjects ≥15 kg	800/100 mg q.d.	300 - 600/50 - 100 mg b.i.d.	600/100 mg b.i.d.
Age range	3 to 5 years	3 to 5 years	12 to 17 years	6 to 17 years	18 to 66 years
DRV formulation(s)	100-mg/mL suspension (F052)	100-mg/mL suspension (F052)	400-mg tablet (F030)	75-mg tablet (F027), 300-mg tablet (F016)	300-mg tablet (F016)
Ritonavir formulation(s)	80-mg/mL solution	80-mg/mL solution	100-mg capsule	80-mg/mL solution	100-mg capsule
Samples per subject	5	6	6	5	8
Time range	0 to 12 hours	0 to 24 hours	0 to 24 hours	0 to 12 hours	0 to 12 hours

N = maximum number of subjects with data.

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.

The parameter estimates obtained from the model update are shown in Table 2. 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. Intra-individual variability (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.

The distributions of the individual estimates for the random effects of clearance, inter-compartmental clearance and absorption rate constant appeared normal with a median value close to zero. Almost no shrinkage is detected for the distribution of the individual CL/F parameters. However for KA and Q/F, a relative high value of shrinkage is observed, which may be explained by the fact that parameters are estimated at steady-state, giving less information on the distribution of KA and Q/F.

Table 2. Darunavir population PK parameters after update.

Parameter	Parameter Estimate	Parameter SEE (CV%)	IIV Estimate (CV%)	IIV SEE (CV%)
CL_{int}/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)

2.4.2. Results

The pharmacokinetics obtained for darunavir and ritonavir at week 2 are shown in tables 3 and 4. One subject had higher plasma concentrations at 24h after administration compared to 12h after administration. This sample was not taken into account as it was presumed that the sample was taken after the next intake. In addition, for another subject the 24h sample was not taken. Therefore AUC and Cl/F was calculated for 10 subjects.

Table 3. Pharmacokinetic results of darunavir at week 2 after administration of darunavir/ritonavir q.d. in treatment-naïve HIV-1-infected subjects aged between 12 and < 18 years.

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	**800/100 mg DRV/rtv q.d. + Background Regimen**		
n	10[a]		
Week 2			
C_{0h}, ng/mL	2172	±	1096
C_{min}, ng/mL	1589	±	768.2
C_{max}, ng/mL	6721	±	1700
t_{max}, h	3.00 (1.00-6.00)		
AUC_{24h}, ng.h/mL	81880	±	26300
FI, %	158.1	±	46.86
CL/F, L/h	11.28	±	5.776

[a] n = 12 for C_{0h}, C_{max} and t_{max}

Table 4. Pharmacokinetic results of ritonavir at week 2 after administration of darunavir/ritonavir q.d. in treatment-naïve HIV-1-infected subjects aged between 12 and < 18 years.

Pharmacokinetics of rtv (mean ± SD, t_{max}: median [range])	**800/100 mg DRV/rtv q.d. + Background Regimen**		
n	10[a]		
Week 2			
C_{0h}, ng/mL	101.0	±	107.8
C_{min}, ng/mL	51.66	±	24.39
C_{max}, ng/mL	1173	±	976.3
t_{max}, h	3.04 (1.00-6.15)		
AUC_{24h}, ng.h/mL	9468	±	6906
FI, %	260.1	±	53.73
CL/F, L/h	14.48	±	7.183

[a] n = 12 for C_{0h}, C_{max} and t_{max}

Population pharmacokinetics

Substudy TMC114-228 q.d. dosing

Individual darunavir pharmacokinetic parameters for subjects involved in the TMC114-C228 q.d. substudy were derived during the population pharmacokinetic analysis described before. Simulation records were added to the dataset to obtain an estimation of the darunavir plasma concentrations at the trough where plasma concentration was assessed.

The goodness-of-fit plots from the model adjustment but containing only the data from the TMC114-C228 q.d. substudy subjects indicated that the model predictions appeared to be accurate, with no detectable bias present for individual predictions.

The arithmetic mean darunavir exposure was 120 µg.h/ml (see table 5) which represented 129% of the target (exposure arithmetic mean of 93.0 µg.h/ml in TMC114-C211). The geometric mean darunavir exposure was 115 µg.h/ml which represented 128% of the target geometric mean (exposure geometric mean of 89.7 µg.h/ml in TMC114-C211 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; therefore, low clearances and high exposures were expected.

Study TMC114-C230

The model described above was applied to darunavir plasma concentrations from the TMC114-C230 trial up to 48 weeks of treatment to provide individual empirical Bayesian estimates for AUC_{tau}, $C_{ss,ave}$, C_{0h} and apparent oral clearance (CL/F).

The geometric mean AUC_{24h} for DRV exposure was 77.8 µg.h/mL at Week 24 and 80.7 µg.h/mL at Week 48, which represented 86.7% and 90.0%, respectively, of the geometric mean of the target DRV exposure in treatment-naïve HIV-1 infected adults in the substudy of trial TMC114-C211 (89.7 µg.h/mL).

The summary of the population pharmacokinetic analysis is shown in table 6.

Table 6. Summary of the population pharmacokinetic analysis at week 2, 4, 24 and 48.

Time Point	Parameter	Body weight (kg)	AAG (mg/dL)	AUC_{24h} (µg.h/mL)	C_{0h} (ng/mL)	CL/F (L/h)	$C_{ss,ave}$ (ng/mL)
Week 2	N	12	12	12	12	12	12
	Mean	50.5	80.1	87.9	2269	10.1	3665
	Geometric mean	50.0	77.1	84.1	2045	9.51	3505
	SD	7.35	23.8	24.2	905	4.37	1010
	CV (%)	15	30	28	40	43	28
	Median	50.5	74.5	91.0	2349	8.80	3793
	Min	40.0	52	35.1	530	6.30	1461
	Max	61.6	120	127	3931	22.8	5294
Week 4	N	12	12	12	12	12	12
	Mean	50.5	76.8	86.0	2202	10.5	3582
	Geometric mean	50.0	73.4	81.4	1940	9.83	3391
	SD	7.35	25.5	27.5	1041	4.76	1144
	CV (%)	15	33	32	47	45	32
	Median	50.5	69.5	81.7	2059	9.81	3405
	Min	40.0	51	33.1	478	5.67	1381
	Max	61.6	137	141	4496	24.1	5883
Week 24	N	12	12	12	12	12	12
	Mean	50.9	73.8	82.2	2062	10.5	3426
	Geometric mean	50.6	71.4	79.2	1879	10.1	3301
	SD	6.46	20.0	22.2	846	3.41	925
	CV (%)	13	27	27	41	32	27
	Median	49.9	71.5	83.9	2114	9.54	3494
	Min	42.0	49	42.9	751	6.69	1786
	Max	64.4	108	120	3620	18.7	4983
Week 48	N	12	12	12	12	12	12
	Mean	53.3	77.7	84.8	2166	10.7	3533
	Geometric mean	52.6	74.5	80.2	1916	9.98	3340
	SD	8.96	22.5	27.2	927	4.56	1135
	CV (%)	17	29	32	43	43	32
	Median	51.3	80	91.2	2403	8.78	3798
	Min	43.5	45	36.0	555	6.27	1499
	Max	72.4	108	128	3515	22.2	5316

Based upon the population pharmacokinetics, one subject had DRV C_{0h} plasma concentration values ranging from 478 ng/ml (week 4) to 751 ng/ml (week 24). Another subject had C_{0h} values ranging from 771 (week 48) to 1122 ng/ml (week 2 and 4). All other subjects had DRV C_{0h} values above 1000 ng/ml.

The DRV AUC_{24h} was compared to the AUC_{24h} in adults (target exposure was between 80% to 130% of the geometric mean adult exposure of 89.7 µg.h/ml achieved with DRV/rtv 800/100 mg q.d.) as determined in study C211 (see table 7 for the descriptive statistics at week 48).

Table 7. Descriptive statistics of population PK-parameters.

PK PARAMETER (MEDIAN)	N	MEAN	95% C.I.<a>	S.E.	S.D.	MIN	Q1	MEDIAN	Q3	MAX	MEAN <b>
AUCtau(ng.h/ml)	12	84391.25	(69404.115;99378.385)	6809.285	23588.054	35527.0	70463.50	86741.50	99072.00	123330.0	80736.58
C0H(ng/ml)	12	2140.58	(1590.850; 2690.313)	249.766	865.215	542.5	1679.35	2233.65	2652.15	3775.6	1930.28
CLF(l/h)	12	10.51	(7.781; 13.234)	1.239	4.291	6.5	8.09	9.23	11.47	22.5	9.92
CSSAVE(ng/ml)	12	3516.25	(2891.825; 4140.675)	283.702	982.774	1480.3	2935.95	3614.20	4127.95	5138.5	3363.99

Week 24 analysis and Bayesian feedback study TMC114-C230

The dataset for the empirical Bayes estimation at week-24 contained 115 observations from 12 children in trial TMC114-C230. No observations were excluded from the darunavir plasma concentration-time analysis.

Simulation records were added to the dataset to obtain an estimation of the plasma concentrations at the trough for each visit where a plasma concentration was assessed. For the determination of CL/F, the body weight at the visit was used, which was carried forward if no value was available at a later visit. Similarly, the AAG value was interpolated between visits, or carried forward if no value was available at a later visit.

The goodness-of-fit plots for the feed-back analysis indicate that the model predictions appear to be accurate, with no detectable bias present for individual predictions.

The overall summary statistics of pharmacokinetic parameters of darunavir, showed a geometric mean of darunavir exposure of 77.8 µg.h/ml which represents 86.7% of the target geometric mean (exposure geometric mean of 89.7 µg.h/ml in TMC114-C211 study).

Week 48 analysis study TMC114-C230

The model that was used to provide Bayesian estimates of individual pharmacokinetic parameters at Week 48 was the same model used for the Week 24 analysis. This model was based on Week 2 richly sampled data combined with previous data in both adults and children. The model is not time-dependent, so the results presented in the Week 24 report are valid for any steady-state evaluation. Therefore, simulation data at Week 48 was not performed as it would be the same as the results in the Week 24 report.

2.4.3. Discussion

The bioanalytical method and the pharmacokinetic model used by the MAH were considered acceptable by the CHMP.

The data from study TMC114-C230 indicate that the applied dose of 800/100 mg DRV/RTV in treatment-naïve HIV-1 infected adolescents resulted in an exposure at week 24 and at week 48 in the target range of adult patients. The results at week 2, 4 and 24 were comparable to those obtained at week 48.

In conclusion, the pharmacokinetic results support the dose of 800/100 mg DRV/RTV once daily in treatment-naïve HIV-1 infected adolescents. The weight limit applies as patients enrolled in study C230 had a weight of at least 40kg.

Treatment-experienced adolescents with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥ 100 cells x 10^6/L

The objective in study TMC114-C230 was to determine a dosing regimen in adolescents that would provide a comparable exposure to that achieved in HIV-1 infected adults when treated with DRV/rtv 800/100 mg once daily. The targeted exposure was to be within 80% to 130% of the geometric mean exposure of 89.7

μg.h/mL as observed at steady-state in treatment-naïve adults treated with DRV/rtv 800/100 mg once daily in study TMC114-C211.

In the population pharmacokinetic analyses for the Phase 2 study TMC114-C230 in HIV-1 infected paediatric subjects aged 12 to <18 years and weighing $\geq$ 40 kg, the DRV/rtv dose of 800/100 mg once daily appeared to be adequate, resulting in a geometric mean exposure of 77.8 μg.h/mL, which represents 86.7% of the target adult exposure of 89.7 μg.h/mL. The median (range) predose plasma concentration (C_{0h}) values in study TMC114-C230 and study TMC114-C211 were also comparable.

The DRV exposures and trough concentrations observed at steady-state in the population pharmacokinetic analyses for study TMC114-C229 in treatment-experienced adults with no DRV RAMs receiving DRV/rtv 800/100 mg once daily were similar to those observed in the population pharmacokinetic analyses for study TMC114-C211 in treatment-naïve adults. The median (range) DRV area under the plasma concentration-time curve from time of administration to 24 hours after dosing (AUC_{24h}) and C_{0h} values in these 2 study populations were:

- TMC114-C211: AUC_{24h}: 87.9 (45.0 - 219.2) μg.h/mL, C_{0h}: 2041 (368 - 7242) ng/mL;

- TMC114-C229: AUC_{24h}: 87.8 (45.4 - 236.9) μg.h/mL, C_{0h}: 1896 (184 - 7881) ng/mL.

In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (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. The exposure of the once daily regimen (800 mg) in adolescents was within the target range of adult patients. Hence, it was concluded that the approved dose of 800/100 mg DRV/RTV once daily in adults with prior exposure to antiretroviral medicinal products but without DRV RAMs could be extrapolated, with the same restrictions, to the adolescents from the age of 12 years and at least 40 kg.

2.5. Clinical Efficacy aspects

2.5.1. Analysis of data submitted

TMC114- C230 (DIONE): 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.

Subjects were considered treatment-naïve if they had never received treatment with an ARV drug, including both investigational as well as commercially available ARVs indicated for the treatment of HIV-infection and ARVs for the treatment of hepatitis B infection with anti-HIV activity (e.g., adefovir, lamivudine (3TC), emtricitabine, entecavir).

The study consisted of 3 phases:

- Screening phase of 4 weeks.
- Treatment phase of 48 weeks.
- Follow-up period of 4 weeks to follow up on any AEs or laboratory abnormalities until resolution or stabilization.

Methods

Study Participants

Main inclusion Criteria

- Male or female subjects, aged between 12 and < 18 years at screening.
- Subjects with a documented HIV-1 infection.
- Body weight of ≥ 40 kg at screening.
- Screening plasma HIV-1 RNA ≥ 1000 copies/mL.
- Subjects qualified for treatment initiation based on the investigator's assessments and/or according to treatment guidelines.

Main exclusion Criteria

- Subjects with presence of any currently active conditions included in the listing of WHO Clinical Stage 4.
- Any condition (including, but not limited to, alcohol and drug use), which, in the opinion of the investigator, could compromise the subject's safety or adherence to the study protocol.
- Previous or current use of ARVs (including both investigational as well as commercially available ARVs indicated for the treatment of HIV-infection and ARVs for treatment of hepatitis B infection with anti-HIV activity, e.g., adefovir, 3TC, emtricitabine, entecavir).
- Primary or acute HIV infection.

Treatments

In the TMC114-C230 study, the same once-daily dose schedule of DRV/rtv, as recommended for treatment-naïve HIV-1 infected adults, was investigated, i.e., DRV/rtv 800/100 mg q.d, in combination with an investigator-selected background regimen for 48 weeks. The investigator-selected background regimen was either zidovudine (AZT)/3TC or abacavir (ABC)/3TC, whichever was approved and marketed or considered local standard of care for subjects aged between 12 and < 18 years in a particular country.

Objectives

The primary objective of this study was to evaluate the pharmacokinetics, safety, tolerability, and efficacy of DRV/rtv administered at 800/100 mg q.d. in combination with an investigator selected background regimen over a 24-week treatment period in ARV treatment-naïve HIV 1 infected adolescents.

The secondary objectives were:

- to evaluate long-term safety, tolerability, and efficacy of DRV/rtv 800/100 mg q.d. (in combination with an investigator-selected background regimen) over a 48-week treatment period in this population;
- to evaluate immunology, resistance characteristics, pharmacokinetics, and pharmacokinetic/ pharmacodynamic (PK/PD) relationships over 48 weeks of treatment with DRV/rtv 800/100 mg q.d. (in combination with an investigator-selected background regimen) in this population.

Outcomes/endpoints

- Primary efficacy parameter: virologic response defined as percent of subjects with confirmed plasma viral load < 50 HIV-1 RNA copies/mL at Week 24 (TLOVR algorithm).

- Major secondary efficacy parameters were the proportion of subjects with confirmed plasma viral load < 50 copies/mL at other time points, and the proportion of subjects with confirmed plasma viral load < 400 copies/mL, change in log10 plasma viral load, time to virologic response, time to loss of virologic response, and change in CD4+ cell count over 48 weeks.

Sample size

The sample size of 12 was chosen because of PK calculations using adult data. Assuming a true response rate of 75% at Week 24 (primary parameter: plasma viral load < 50 copies/mL, ITT-TLOVR), this sample size of 12 subjects would result in a 2-sided 95% confidence interval for virologic response of [49%; 100%].

Statistical methods

Intent-to-treat analysis, descriptive statistics, frequency tabulations, Wilcoxon matched-pairs signed-ranks test, nonlinear mixed effects modelling were applied.

Results

Recruitment

TMC114-C230 was initiated in August 2009 and the last visit of the last patient in the study took place on 31st March 2011. The 12 adolescents were included in 6 countries: France, UK, Italy, Spain (each one subject), Ukraine (6 subjects), USA (2 subjects).

Baseline characteristics

From the 12 subjects 8 were females. The mean age of the group was 14.6 years; 7 were white and 5 black or Afro-American. All were treatment naïve. Mean duration of HIV infection was 3.8 years, median (range) 1.7 (0.1; 12.9). Five from these 12 had vertically transmitted HIV that only required treatment after a prolonged period at this age > 12 years. Most were not severely ill. At baseline median CD4+ cell count was 282 x 10^6/L (range 204; 515). One patient has concurrent chronic Hepatitis B infection, and was allowed to enter according to the inclusion criteria that spelled that chronic Hepatitis B infection that did not require treatment during the study, could be included.

None of the subjects had primary protease inhibitor (PI)-mutations. The median number of PI RAMs was 4 (range 1 - 6). None of the subjects harbored NRTI RAMs. Also phenotypically by use of Antivirogram: all subjects were susceptible to all commercially available PIs and NRTIs.

Concomitant ARVs were either AZT/3TC 6 (50.0%) or ABC/3TC 6 (50.0%). ABC could not be administered in those subjects where HLA-B*5701 was tested positive to prevent hypersensitivity reactions to ABC.

Table 8. Baseline Characteristic

Baseline Characteristic	DRV/rtv 800/100 mg q.d. N = 12
Log_{10} Viral Load (copies/mL)	
Mean (SE)	4.72 (0.172)
Median (Range)	4.92 (3.56; 5.52)
CD4+ Cell Count (x 10^6/L)	
Mean (SE)	317 (29.3)
Median (Range)	282 (204; 515)
Percentage CD4+	
Mean (SE)	20.6 (2.53)
Median (Range)	18.3 (12.1; 40.8)
Baseline Viral Load, n (%)	
< 20 000 copies/mL	2 (16.7)
20 000 - < 100 000 copies/mL	5 (41.7)
≥ 100 000 copies/mL	5 (41.7)
Duration of HIV Infection (years)	
Mean (SE)	3.8 (1.35)
Median (Range)	1.7 (0.1; 12.9)
DRV FC	
Mean	0.60
Median (Range)	0.6 (0.3; 1.2)
Clinical Stage of HIV Infection[33], n (%)	
Clinical Stage 1 (asymptomatic)	5 (41.7)
Clinical Stage 2 (mild symptoms)	6 (50.0)
Clinical Stage 3 (advanced symptoms)	1 (8.3)
Clinical Stage 4 (severe symptoms)	0
Hepatitis B or C Coinfection Status, n (%)	
Missing	4 (33.3)
Negative	7 (58.3)
Positive	1 (8.3)[a]
Mode of HIV Infection, n (%)	
Blood transfusion	1 (8.3)
Heterosexual contact	3 (25.0)
Mother to child transmission	5 (41.7)
Other	3 (25.0)
Clade, n (%)	
A1	2 (16.7)
B	4 (33.3)
C	1 (8.3)
CRF01_AE	2 (16.7)
CRF02_AG	3 (25.0)

N = number of subjects; n = number of observations

Numbers analysed

The intent-to-treat (ITT) population was defined as the set of all subjects who were enrolled and who had taken study medication, regardless of their compliance with the Protocol.

Outcomes and estimation

Primary efficacy parameter:

Viral load < 50 copies/mL (ITT - TLOVR) increased progressively over time up to 24 weeks:

- Week 24: 11 out of 12 subjects (91.7%);
- Week 48: 10 out of 12 subjects (83.3%) had a confirmed virologic response.

The results were confirmed by other sensitivity analyses, such as the FDA snapshot analysis.

Confirmed plasma viral load < 400 copies/mL was present

- At Week 24 in 12 subjects (100%),

- At week 48 in 11 subjects (91.7%).

The mean plasma viral load decreased during the study. At Week 24, the mean change (SE) in $\log_{10}$ viral load from baseline was -3.03 (0.172) $\log_{10}$ copies/mL, at Week 48 this change was -2.98 (0.182) $\log_{10}$ copies/mL from baseline.

The median time to virologic response defined as < 50 copies/mL (TLOVR) was 16 weeks; to < 400 copies/mL (TLOVR) was 4 weeks; and to ≥ 1 log10 decrease in plasma viral load versus baseline was 2 weeks.

The CD4+ cell count increased during the study:

- at Week 24, the mean (SE) change in CD4+ cell count from baseline was 175 (19.5) x 10^6/L,
- at Week 48 this was 221 (22.4) x 10^6/L.

Lack of suppression and resistance

The 2 subjects that did not have viral load < 50 copies/ml at week 48 were 1 never-suppressed subject and 1 rebounder. The never-suppressed subject was non-adherent based on pill counts and questionnaire. Although this subject had a treatment-emergent primary PI mutation (M46I), he remained susceptible to all commercially available PIs (including DRV) and NRTIs, including the ARVs in the subject's background regimen (i.e., ABC and 3TC). The rebounder's viral load returned to undetectable (< 50 copies/mL) at Week 48, after rebound at Week 40, without non-adherence as measured by self-reported adherence or based on pill count . The subject had a treatment-emergent NRTI RAM (K219Q). The subject remained susceptible to all commercially available PIs and NRTIs included in the background regimen (i.e., AZT and 3TC).

Adherence

Treatment adherence to DRV/rtv was analysed based on pill count and on the results of the Study Adherence Questionnaire for Caregivers and Teenagers developed by the PENTA.

Based on pill count, 7 subjects (58.3%) were > 95% adherent to both DRV and rtv and 5 subjects (41.7%) were < 95% adherent to DRV/rtv over the course of the treatment period.

Based on the PENTA Study Adherence Questionnaire for Caregivers and Teenagers, the proportion of subjects classified as adherent to DRV/rtv (i.e., subjects who did not miss any dose of DRV and rtv cumulatively up to the time point of interest) was 100% until Week 8 and 83.3% (10 subjects) at Week 48; and adherence to the ARVs in the background regimen was 100% until Week 16 and 91.7% (11 subjects) at Week 48.

Summary of main study

The following table summarises 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 9. Summary of Efficacy for trial TMC114- C230

Title: 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.	
Study identifier	TMC114- C230 (DIONE)

Design	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.	
	Duration of main phase:	48 weeks
	Duration of Run-in phase:	4 weeks
	Duration of Extension phase:	4 weeks to follow up on any adverse events (AEs) or laboratory abnormalities until resolution or stabilization.
Treatments groups	A total of 12 ARV treatment-naïve subjects were included in the study. Subjects were considered treatment-naïve if they had never received treatment with an ARV drug, including investigational ARVs. Subjects received the recommended dose of DRV/rtv for treatment-naïve HIV-1 infected adults, i.e., 800/100 mg q.d., in combination with an investigator-selected background regimen for 48 weeks. The investigator-selected background regimen was either AZT/3TC or ABC/3TC, whichever was approved and marketed or considered local standard of care for subjects aged between 12 and < 18 years in a particular country.	
Endpoints and definitions	Primary endpoint	virologic response defined as percent of subjects with confirmed plasma viral load < 50 HIV-1 RNA copies/mL at Week 24 (TLOVR algorithm)
	Secondary endpoint	proportion of subjects with confirmed plasma viral load < 50 copies/mL at other time points, and the proportion of subjects with confirmed plasma viral load < 400 copies/mL
	Secondary endpoint	change in $\log_{10}$ plasma viral load, time to virologic response, time to loss of virologic response, and change in CD4+ cell count over 48 weeks
Database lock	31-Mar-2011	

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Intent to treat	
Descriptive statistics and estimate variability	Number of subject	12
	HIV 1 RNA < 50 copies/mla	83.3% (10)
	CD4+ percent change from baseline	14
	CD4+ cell count mean change from baseline	221

	≥ 1.0 $\log_{10}$ decrease from baseline in plasma viral load	100%

2.5.2. Discussion

A total of 12 male and female antiretroviral (ARV) treatment-naïve subjects were included in this Phase II study. Subjects received the recommended dose of DRV/rtv for treatment-naïve HIV-1 infected adults, i.e., 800/100 mg q.d., in combination with an investigator-selected background regimen for 48 weeks. The investigator-selected background regimen was either AZT/3TC (n=6) or ABC/3TC (n=6). Statistical analyses were performed at Week 24 (primary analysis) and at Week 48 (final analysis). The study methods were found acceptable by the CHMP.

Eight (8) of the 12 subjects were females. The mean age of the group was 14.6 years; 7 were white and 5 black or Afro-American. All were treatment naïve. Mean duration of HIV infection was 3.8 years, median (range) 1.7 (0.1; 12.9). Concomitant ARVs were either AZT/3TC 6 (50.0%) or ABC/3TC 6 (50.0%).

The Primary efficacy parameter [Viral load < 50 copies/mL (ITT - TLOVR) at week 24] was met for 11 out of 12 subjects (91.7%). The results were confirmed by other sensitivity analyses, such as the FDA snapshot analysis.

One of the main secondary parameter [Viral load < 50 copies/mL (ITT - TLOVR) at week 48] was met for 10 out of 12 subjects (83.3%) at week 48. Confirmed plasma viral load < 400 copies/mL was present at Week 24 in 12 subjects (100%) and at week 48 in 11 subjects (91.7%). The CD4+ cell count increased during the study as at Week 24, the mean (SE) change in CD4+ cell count from baseline was 175 (19.5) x 10^6/L and at Week 48 this was 221 (22.4) x 10^6/L.

Adherence was meager, since 5 subjects (41.7%) were < 95% adherent to DRV/rtv. However, efficacy in this small sample size was comparable to that in treatment-naïve adults (83.7% in the TMC114-C211 trial). Incident viral load increases did not result in resistance mutations that could compromise treatment with the prescribed medication or alternative ARVs.

In conclusion, the efficacy results support the dose of 800/100 mg DRV/RTV in treatment-naïve HIV-1 infected adolescents from the age of 12 years and at least 40 kg.

Treatment-experienced adolescents with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥ 100 cells x 106/L

The efficacy of DRV/rtv 800/100 mg once daily 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 Phase 3 study TMC114-C229.

The primary Week-48 analyses of study TMC114-C211 showed robust and sustained virologic and immunologic benefits of DRV/rtv 800/100 mg once daily, in combination with a fixed background regimen of tenofovir disoproxil fumarate and emtricitabine, over 48 weeks. In addition, DRV/rtv 800/100 mg once daily was proven non-inferior to lopinavir/rtv 400/100 mg twice daily or 800/200 mg once daily. The resistance analyses confirmed the high genetic barrier to the development of resistance to DRV.

The primary Week-48 analysis of study TMC114-C229 demonstrated that virologic efficacy with DRV/rtv 800/100 mg once daily was non-inferior to that observed with DRV/rtv 600/100 mg twice daily (both in combination with background regimen of ≥ 2 nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs]). DRV/rtv 800/100 mg once daily was associated with similar rates of virologic failure and similar low rates of emergence of resistance (to DRV and other protease inhibitors, and NRTIs in the optimized

background regimen) as DRV/rtv 600/100 mg twice daily in treatment-experienced patients with 0 DRV RAMs.

The Week-48 results of study TMC114-C230 were in line with those of study TMC114-C211. The efficacy data showed that DRV/rtv 800/100 mg once daily, in combination with zidovudine/lamivudine or abacavir/lamivudine, was effective in the studied population, and there were no relevant differences in virologic response to DRV/rtv 800/100 mg once daily between the treatment-naïve paediatric population in study TMC114-C230 and treatment-naïve adult population in study TMC114-C211.

Background therapy in the adult C229 study did include tenofovir + emtricitabine, which was not approved for adolescents at the time of the study C230. Consequently, only AZT+3TC and ABC+3TC were used as background therapy in the adolescents enrolled in study C230. However, the selected background therapy in adolescents does not contribute to changes in exposure of DRV/rtv.

In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (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. The exposure of the once daily regimen (800 mg) in adolescents was within the target range of adult patients. Hence, it was concluded that the results obtained with the once daily dose of 800 mg DRV/rtv in treatment-experienced adults patients in the C229 study can be extrapolated to adolescent patients who have been exposed to antiretroviral therapy previously with similar restrictions as in adults.

2.6. Clinical Safety aspects

2.6.1. Analysis of data submitted

Patient exposure

Mean Exposure to DRV was 49.6 weeks.

Adverse events

Table 10. AEs: summary table

n (%)	DRV/rtv 800/100 mg q.d. N = 12
≥ 1 AE	11 (91.7)
≥ 1 grade 3 or 4 AE	3 (25.0)
≥ 1 AE at least possibly related to DRV	2 (16.7)
≥ 1 AE ≥ grade 2 at least possibly related to the DRV	1 (8.3)
≥ 1 SAE	4 (33.3)
AEs leading to discontinuation	0
Deaths	0

N = total number of subjects with data; n = number of observations

The most frequent AEs were vomiting (4 subjects, 33.3%), anemia and nausea (3 subjects each, 25.0%). Diarrhea, pyrexia, furuncle, sinusitis, and cough were reported in 2 subjects each (16.7%).

Grade 3 GI AEs were reported in 1 subject, who experienced grade 3 diarrhea, nausea and vomiting. None of these events were considered related to DRV. None of the 4 hematologic AEs were considered related to DRV.

Laboratory findings

The overall incidence of laboratory abnormalities of interest was low. There was a trend for an increase from baseline in the mean values of lipids over time. No clinically relevant mean changes from baseline

were observed for any other laboratory parameter. Most laboratory abnormalities were grade 1 or 2 in severity. Grade 3 and 4 laboratory abnormalities were only observed for haematology laboratory parameters: grade 4 decreased haemoglobin was observed in 2 subjects (16.7%), who were both also receiving AZT. One (8.3%) of these 2 subjects also had grade 4 decreased neutrophils and grade 3 decreased WBC count.

As part of the evaluation of the Article 46 procedure (P46-66), the MAH was requested to discuss the metabolic effects of DRV in the present application. The MAH clarified that lipid- and glucose-related parameters were assessed under fasting conditions. Grade 2 abnormalities for total cholesterol were reported in 4 subjects (33.3%) and for low-density lipoprotein (LDL) in 3 subjects (25.0%). Grade 2 hyperglycemia was reported in 1 subject (8.3%). One subject had a high-density lipoprotein (HDL) level above normal and 1 subject below normal. There were no laboratory abnormalities for triglycerides. However, there was a trend for an increase from baseline in the mean values of lipids over time.

Hyperlipidemia and hypercholesterolemia are listed ADRs in the Product Information and should be monitored and treatment initiated according to generally accepted recommendations for the treatment of lipid abnormalities. The metabolic influences of DRV on growth, lipodystrophy/fat abnormalities, hyperlipidemia, bone turnover and cognitive development in this age group need to be further documented. In addition, the long-term clinical consequences of DRV-associated increase in lipids are unknown and long-term follow-up is required to assess the true risk of hyperlipidemia on the development of cardiovascular disease.

Since the assessment of the long-term consequences of the metabolic influences of DRV requires long-term follow-up, the MAH proposed to address it in a long-term study in collaboration with Paediatric European Network for Treatment of AIDS (PENTA) (see below and section 2.7 RMP). The CHMP endorsed this proposal.

Discontinuation due to adverse events

Treatment was not discontinued.

Cardiovascular Results

No clinically relevant mean changes from baseline were observed for vital signs or ECG parameters. There were no treatment-emergent vital signs related events or ECG abnormalities.

Other Safety Parameters

There were no unexpected safety findings from the physical examinations and no findings suggestive of delayed sexual maturation.

Growth and Development

As part of the evaluation of the Article 46 procedure (P46-66), the MAH was requested to discuss the effects of DRV on growth parameters in the present application. The MAH clarified that the within-group comparison for the changes from baseline (absolute values) at Week 48 showed an increase versus baseline for height (3.8 cm) and weight (2.8 kg). The changes for height during the study were statistically significant at the 0.05 level (Wilcoxon signed rank-test) and the changes for weight were not statistically significant. Changes in BMI were small during the study (0.1 kg/ m2 at Week 48) and were not statistically significant.

After the start of treatment with DRV/rtv 800/100 mg q.d., subjects in TMC114-C230 continued to grow, relative to what was expected, but did not clearly catch up from the growth retardation at baseline.

Since the assessment of the effects of DRV on growth parameters requires long-term follow-up, the MAH proposed to address it in a long-term study in collaboration with Paediatric European Network for Treatment of AIDS (PENTA) (see below and Section 2.7 RMP). The CHMP endorsed this proposal.

Pharmacovigilance study on the safety and use of DRV in HIV infected children and adolescents in Europe

The MAH is undertaking, in collaboration with PENTA, a post authorisation safety study (PASS) to define the long-term DRV/rtv safety profile in HIV-1 infected children and adolescents in Europe. This observational study involves the pooled analysis of individual patient data using merged datasets from prospective cohort studies participating within the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC). (see Section 2.7 RMP)

The overall aim of this study is to collect long-term safety data on DRV/rtv use in paediatric patients with HIV infection in a "real world" setting in Europe and neighbouring countries.

Primary objective:

- To define the safety profile of DRV/rtv with long-term use in HIV-infected paediatric patients aged 6-18 years, under "real-world" conditions of use in Europe. Paediatric patients are defined as being children from 6 to < 12 years of age or adolescents from 12 to ≤ 18 years of age.

Secondary objectives:

- To describe the clinical characteristics of HIV-infected paediatric patients aged 6-18 years and treated with DRV/rtv in Europe,
- To describe off-label use of DRV/rtv in paediatric patients <6 years of age (excluding in utero exposure).

The following relevant parameters are systematically collected:

- complete antiretroviral therapy dosing history from start to stop with DRV;
- weight and height from 3 months before starting with DRV;
- total cholesterol, HDL cholesterol, triglycerides for the 12 months prior to starting DRV up to present;
- viral load;
- any adverse events, with special attention to adverse events possibly related to the drugs.

The Year 2 report of the EPPICC observational study became available at the end of September 2012, and was reviewed by the CHMP as part of follow-up measure 051.5. This report included cumulative data of children reported to EPPICC cohorts up to the end of 2011, i.e., 157 patients ever on DRV with follow-up time outside of clinical studies:

- 36 patients were aged 12 to < 18 years and weighed ≥ 40 kg and were taking the DRV/rtv 800/100 mg q.d. dose (the currently proposed dosage of the present application),
- 64 patients were aged 6 to < 18 years and were taking the licensed b.i.d. dose,
- the remaining patients either were taking unlicensed or unboosted doses, were aged < 6 years or had important data missing.

Clinical events considered by the treating physician to be causally related to DRV were reported for only 3 patients, all on the b.i.d. dose (abdominal pain [non serious, n=1], and cholesterol increase [serious, n=2]). The overall rates of grade ≥ 3 laboratory abnormalities were 1 per 100 patient-years (95% confidence interval 0-6) for increased total cholesterol, and 2 per 100 patient-years (95% confidence

interval 0-7) for increased triglycerides, with no discernible trend by duration of exposure to DRV (although confidence intervals were relatively wide). Only 2 patients taking the DRV/rtv 800/100 mg q.d. dose discontinued DRV/rtv, both for patient-related reasons and not because of dyslipidemia.

The CHMP noted that only three patients experienced a possibly DRV associated AE. These AEs are included in the current SmPC as common AEs. However, the CHMP was of the opinion that the number of paediatric patients is too low to draw firm conclusions, in particular regarding children 6<18 years old on unlicensed doses (n=21) or children <6 years of age (n=3).

As the long-term clinical consequences of DRV-associated increase in lipids are unknown, input from the PENTA database is regarded essential. The database should also provide data on growth parameters. These data are awaited within the next submission of the annual PENTA report (September 2013).

As a result of the assessment of the present application, the Pharmacovigilance Plan of the RMP has been updated to state that the EPPICC study will address the following safety concerns: "children 3 to< 6 years of age (limited data are available from Phase 2 trial), and long-term safety data in children from 3 to 17 years of age" and also "growth abnormalities in the paediatric population". See section 2.7 for further details on the RMP.

2.6.2. Discussion

There were no new clinically relevant findings compared with the known DRV/rtv safety profile in HIV-1 infected adults and in treatment-experienced HIV-1 infected subjects between 12 and < 18 years in the twice daily dosage. Considering the fact that the once daily dosage of 800 mg DRV can also be proposed in treatment-experienced adolescents with similar restrictions on specific DRV-RAMs, viral load and CD4 count as have been imposed in adults, this known safety profile can be expanded to treatment-experienced adolescents as well.

Grade 2 abnormalities for total cholesterol were reported in 4 subjects (33.3%) and for low-density lipoprotein (LDL) in 3 subjects (25.0%). Grade 2 hyperglycemia was reported in 1 subject (8.3%). One subject had a high-density lipoprotein (HDL) level above normal and 1 subject below normal. There were no laboratory abnormalities for triglycerides. However, there was a trend for an increase from baseline in the mean values of lipids over time.

Hyperlipidemia and hypercholesterolemia are listed ADRs in the Product Information and should be monitored and treatment initiated according to generally accepted recommendations for the treatment of lipid abnormalities. However, the metabolic influences of DRV on growth, lipodystrophy/fat abnormalities, hyperlipidemia, bone turnover and cognitive development in this age group need to be further investigated. In addition, the long-term clinical consequences of DRV-associated increase in lipids are unknown and long-term follow-up is required to assess the risk of hyperlipidemia on the development of cardiovascular disease.

After the start of treatment with DRV/rtv 800/100 mg q.d., subjects in TMC114-C230 continued to grow, relative to what was expected, but did not clearly catch up from the growth retardation at baseline.

Much in the same line as for the lipid abnormalities, the multifactorial causes of growth impairment in HIV infected children need to be further evaluated to appreciate the potential contribution of DRV.

Larger sample sizes than the study C230 (which included 12 treatment-naïve adolescents) are required to assess the long term effects of DRV on lipid abnormalities and growth parameter. 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 (see Section 2.7 RMP). Annual reports from the on-going PASS study are being submitted to the CHMP -the next submission being due in September 2013. In addition, the MAH will

initiate a study to compare of the data on growth from children treated with darunavir and other ART products (see Section 2.7 RMP).

2.7. Risk Management Plan

2.7.1. PRAC advice

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

PRAC Advice

The MAH submitted an updated RMP (version 17.1) with the responses to the RSI. In this update, the MAH have included the following changes which have been endorsed by the PRAC:

- The risk of lipid abnormalities in paediatric patients has been included under the heading of the already included risk of lipid abnormalities and was addressed adequately throughout the RMP.
- The risk of Growth Abnormalities in the Paediatric Population has been included as an important potential risk and addressed adequately throughout the RMP.

The MAH was requested to provide a comparison of the data on growth from children treated with darunavir and other ART products. A study to assess growth abnormalities in the paediatric population using PREZISTA for comparison with like data in EPPICC or elsewhere in children on other ART products will be conducted. The final protocol is planned for December 2013. The final study results are expected by August 2015.

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

Safety concerns

Important Identified Risks

Severe Skin Reactions

Hepatotoxicity

Hyperglycaemia

Lipid Abnormalities

Pancreatitis

Fat Redistribution

Immune Reconstitution 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

Missing Information

Elderly (65 years and above)

Pregnant and breast-feeding women

Children 3 to < 6 years of age (limited data are available from Phase 2 trial)

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

Pharmacovigilance plans

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, Category 3	To assess the PK of DRV/rtv in HIV-1-infected pregnant women	Pregnant and breast-feeding women (Important 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: 2Q 2012 Final data: PSUR following finalisation of the trial. Q4 2013
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.	Children 3 to < 6 years of age (limited data are available from Phase 2 trial) 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 Submission third annual report: September 2013 Submission fourth annual report: September 2014 Submission fifth annual report: September 2015

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)
A planned study to assess growth abnormalities (height) in children using PREZISTA in which data will be compared with data from EPPICC or other data in children on other ARV. No study name is available at this time, Category 3	To assess growth abnormalities (height) in children using PREZISTA.	Growth abnormalities in the paediatric population	Planned	Submission of the final protocol: December 2013. Final study results are expected by August 2015.

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)
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 data in children from 3 to 17 years of age	Started	Final data: December 2014

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	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties) of the SmPC.	
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 Syndrome	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Development of Drug Resistance	Adequate information and guidance to help the prescriber is provided in Sections 4.1 (Therapeutic indications) and 4.4 (Special warnings and precautions for use) of the SmPC.	None
Overdose due to Medication Error	Adequate information and guidance to help the prescriber is provided in Sections 4.1 (Therapeutic indications) and 4.2 (Posology and method of administration) of the SmPC, and in the PIL.	None
Drug-Drug Interactions	Adequate information and guidance to help the prescriber is provided in Sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and 4.8 (Undesirable effects) of the SmPC, and in the PIL.	None
Important Potential Risks:		
Coronary Artery Events	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Cardiac Conduction Abnormalities	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Convulsions	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Growth Abnormalities in the Paediatric Population	None proposed.	None
Missing Information:		
Elderly (65 years and above)	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), and5.2 (Pharmacokinetic properties) of the SmPC.	None
Pregnant and breast-feeding women	Adequate information and guidance to help the prescriber is provided in Sections 4.6 (Fertility, pregnancy and lactation) of the SmPC.	None
Children 3 to < 6 years of age (limited data are available from Phase 2 trial)	Adequate information and guidance to help the prescriber is provided in Sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), and 5.3 (Preclinical safety data) of the SmPC.	None
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-experienc ed 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

The CHMP endorsed this advice without changes.

2.8. Update of the Product Information

The MAH submitted a proposal for an update of the SmPC for the oral suspension, the 400mg and the 800mg film-coated tablets formulations with a new indication in ART-naïve paediatric patients (12 to 17 years of age and weighing at least 40 kg). The recommended dose regimen was 800 mg once daily with ritonavir 100 mg once daily taken with food. Consequential changes were introduced in the product information of the 75mg, 150mg, 300mg and the 600mg film-coated tablets formulations. The Package Leaflets were updated accordingly.

During the procedure, the following additional amendments were introduced in the Product Information:

An extrapolation of the data to the treatment-experienced adolescents aged 12 to 17 years and weighing

more than 40kg with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ⩾100 cells x 10^6/L was found acceptable by the CHMP. The product information of the 100mg/ml oral suspension, the 400mg and the 800mg film-coated tablets formulations were updated with this indication.

Consequential changes were introduced in the product information of the 75mg, 150mg, 300mg and the 600mg film-coated tablets formulations. The Package Leaflets are updated accordingly.

User consultation

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

- full user testing in compliance with the legislative requirements was performed (n=37 participants) on the initial patient leaflet for Prezista 300 mg film-coated tablets, that was approved on 12 February 2007;
- with the additional update to the indication for treatment-naïve paediatric patients, no new route of administration is proposed;
- no additional safety issues have been identified;
- new proposed text is in line with currently approved text;
- no other changes are introduced.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (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.

A total of 12 male and female antiretroviral (ARV) treatment-naïve subjects were included in this Phase II study TMC114-C230. Subjects received the recommended dose of DRV/rtv for treatment-naïve HIV-1 infected adults, i.e., 800/100 mg q.d., in combination with an investigator-selected background regimen for 48 weeks. Statistical analyses were performed at Week 24 (primary analysis) and at Week 48 (final analysis).

The data from study C230 indicate that the applied dose of 800/100 mg DRV/RTV in treatment-naïve HIV-1 infected adolescents resulted in an exposure at week 24 and at week 48 in the target range of adult patients. The results at week 2, 4 and 24 were comparable to those obtained at week 48.

Hence, study C230 demonstrated that the once-daily dose schedule of DRV/rtv, as recommended for treatment-naïve HIV-1 infected adults i.e., DRV/rtv 800/100 mg q.d., in combination with ≥ 2 NRTIs could be extrapolated to treatment-naïve HIV-1 infected adolescents from the age of 12 years and at least 40 kg. The weight limit applies as patients enrolled in study C230 had a weight of at least 40kg.

From an efficacy perspective, the Primary efficacy parameter [Viral load < 50 copies/mL (ITT - TLOVR) at week 24] was met for 11 out of 12 subjects (91.7%). The results were confirmed by other sensitivity analyses, such as the FDA snapshot analysis.

One of the main secondary parameter [Viral load < 50 copies/mL (ITT - TLOVR) at week 48] was met for 10 out of 12 subjects (83.3%) at week 48. Confirmed plasma viral load < 400 copies/mL was present at Week 24 in 12 subjects (100%) and at week 48 in 11 subjects (91.7%). The CD4+ cell count increased during the study as at Week 24, the mean (SE) change in CD4+ cell count from baseline was 175 (19.5) x 10^6/L and at Week 48 this was 221 (22.4) x 10^6/L.

Incident viral load increases did not result in resistance mutations that could compromise treatment with the prescribed medication or alternative ARVs.

The exposure of the once daily regimen (800 mg) in adolescents was within the target range of adult patients. Hence, in line with the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (EMEA/CPMP/EWP/633/02), it was concluded that the results obtained with the once daily dose of 800 mg DRV/rtv in treatment-experienced adults patients in the C229 study can be extrapolated to adolescent patients who have been exposed to antiretroviral therapy previously with similar restrictions as in adults.

Uncertainty in the knowledge about the beneficial effects.

Despite the supportive PK/PD data and the good virological and immunological response rates, the design of study C230 presents some limitations (e.g. open label trial, small number of patients enrolled). However, in line with the provisions of the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (EMEA/CPMP/EWP/633/02), the CHMP was of the opinion that the study design was adequate for an antiretroviral agent that has been shown to be efficacious in adults as it is the case for darunavir and that the results are sufficient to support an extrapolation from adults to the paediatric population.

Adherence was meager, since 5 subjects (41.7%) were < 95% adherent to DRV/rtv. However, efficacy in this small sample size was comparable to that in treatment-naïve adults.

Risks

Unfavourable effects

There were no new clinically relevant findings compared with the known DRV/rtv safety profile in HIV-1 infected adults and in treatment-experienced HIV-1 infected subjects between 12 and < 18 years.

Lipid abnormalities and growth impairment were identified as potential risks related to the use of darunavir in treatment-naïve HIV-1 infected adolescents and are being addressed in the RMP.

Uncertainty in the knowledge about the unfavourable effects

Larger sample sizes than the study C230 are required to better 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. The next submission is due in September 2013. In addition, the MAH will initiate a study to compare of the data on growth from children treated with darunavir and other ART products. Please refer to Section 2.7 RMP.

Benefit-risk balance

As stated in the CHMP guideline on the clinical development of medicinal products for the treatment of HIV infection (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.

Study C230 demonstrated that the once-daily dose schedule of DRV/rtv, as recommended for treatment-naïve HIV-1 infected adults i.e., DRV/rtv 800/100 mg q.d., in combination with ≥ 2 NRTIs could be extrapolated to treatment-naïve HIV-1 infected adolescents from the age of 12 years and at least 40 kg.

This is supported also by the satisfactory virological and immunological response rates in Study C230.

In addition, the safety data in the paediatric population 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.

Overall, the similar DRV exposures in adolescents (observed and estimated) versus adult subjects after DRV/rtv once daily administration, the favourable safety profile with DRV/rtv once daily and twice daily regimens in paediatric subjects, the favourable long-term safety profile in adults, together with the efficacy results after DRV/rtv once daily administration observed in treatment-naïve adolescents in study TMC114-C230, treatment-naïve adults in study TMC114-C211, and treatment-experienced adults with no DRV RAMs in study TMC114-C229, all together support a dosing regimen of DRV/rtv 800/100 mg once daily in combination with other ARV agents and with food for use in paediatric subjects aged 12 to <18 years and weighing ⩾40 kg who are treatment-naïve or treatment-experienced with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ⩾ 100 cells x 10^6/L.

For treatment-experienced HIV-1 infected paediatric subjects with 1 or more DRV RAMs, and for treatment-experienced HIV-1 infected paediatric subjects for whom genotypic testing should not feasible, the currently approved DRV/rtv twice daily dosing recommendations will be maintained.

As a consequence, the CHMP concluded that the benefit /risk balance is favourable for use of darunavir 800/100 mg QD in treatment-naïve HIV-1 infected adolescents and adolescents with prior exposure to antiretroviral medicinal products but without DRV RAMs and who have plasma HIV 1 RNA < 100,000 copies/ml and CD4+ cell count ⩾ 100 cells x 10^6/l from the age of 12 years and at least 40 kg.

4. Recommendations

Final Outcome

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 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 sections 4.1, 4.2, 4.8, 5.1 and 5.2 of SmPC of the 100mg/ml oral suspension, the 400mg and the 800mg film-coated tablets formulations with an indication for use of DRV/rtv once daily regimen in paediatric patients 12 to 17 years of age and weighing at least 40 kilograms who are antiretroviral treatment naïve or with prior exposure to antiretroviral medicinal products but without DRV RAMs and

who have plasma HIV 1 RNA < 100,000 copies/ml and CD4+ cell count ⩾ 100 cells x 10^6/l. As a consequence of these changes, sections 4.2, 4.8, 5.1 and 5.2 of SmPC of the 75mg, 150mg, 300mg and the 600mg film-coated tablets formulations have been updated. Editorial changes were made in the section 4.5 of all the presentations. The Package Leaflet is updated accordingly.

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

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.