EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/100690/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Prezista

Darunavir

Procedure No: EMEA/H/C/000707

P46 066

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

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1. RECOMMENDATION

Based on the review of the data on pharmacokinetics, safety and efficacy from study TMC114-TÍDP-C230, the Rapporteur considers that the Article 46 paediatric study submission is fulfilled. However, further data are expected in the context of a variation application, prior any final conclusion is made.

Indeed, the submission of a type II variation application to extend the indication to treatment-naïve HIV-1 infected paediatrics aged 3 to <18 years of age, is planned in the 2nd half of 2012. The data of trial TMC114-TÍDP29-C230 will need to be complemented with Population Pharmacokinetic modeling results and requires the prior registration of the darunavir (DRV) Oral Suspension to allow for dosing in the young age groups. However, one concern related to pharmacokinetics from study TMC114-TÍDP-C230 remains outstanding and should be dealt with at the time of submission of this variation application. Moreover, the concern about safety in children has been sufficiently addressed for now, but requires further evaluation at the time of submission of this variation application (see section 11).

The Rapporteur's assessment of the Applicant's response to the request for supplementary information and conclusions are given in sections 10 and 11 (page 14 and following)

2. EXECUTIVE SUMMARY

2.1 Problem statement

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

Trial C230 [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.] in accordance with Article 46 of Regulation (EC) No 1901/2006, is subject of this Article 46 submission.

The applicant, on behalf of Janssen-Cilag International NV, states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for PREZISTA and therefore do not require to take further regulatory action on the marketing authorisation for PREZISTA.

A type II variation application to extend the indication to treatment-naïve HIV-1 infected paediatrics aged 3 - <18 years of age, based on study C230 and complemented with Population Pharmacokinetic modeling results, is planned for submission to EMA in the 2nd half of 2012, as it requires the prior registration of the darunavir Oral Suspension to allow for dosing in the young age groups. The evaluation of the Oral Suspension is currently under review (EMEA/H/C/707/X041G).

Therefore, any issues identified during the current assessment should be taken into account within the intended type II variation, but no recommendations will be made on the inclusion of paediatric data into the SmPC. This will await the assessment of the full data package within the Type II application.

A line listing of all the studies included in the development program is shown below:

PREZISTA EMEA/H/C/000707 PAEDIATRIC PROGRAM

Study title	Study number TMC114-TiDP29-	Date of completion (LPLV)	Date of submission of final study report
A Phase I, open label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of darunavir (DRV) to that of the commercial 300 mg tablet formulation in the presence of low dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low dose ritonavir	C169	18/08/08	CSR included in application EMEA/H/C/000707/X41G, submitted to EMA May 4th 2011.
A Phase II, open label trial to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV in combination with low dose ritonavir (DRV/rtv) in treatment-experienced HIV-1 infected children from 3 years to < 6 years of age.	C228	28/02/11	The 24 weeks and 48 weeks study reports for TMC114-TiDP29-C228 are included in the response to questions on EMEA/H/C/000707/X/41G (March 22nd, 2012).
A Phase II, open label trial, to investigate pharmacokinetics, safety, tolerability and antiviral activity of TMC114/rtv b.i.d. in treatment-experienced HIV-1 infected children and adolescents.	C212	08/10/2011 (main phase); 30/03/2011 (long term extension)	24 weeks data of this study was the initial scope of application EMEA/H/C/000707/X/020, submitted to EMA June 27th 2008. 48 weeks data have been submitted in the Response to Questions of this same application, submitted to EMA February 18th 2009. The final study report has been submitted in an Article 46 submission on September 30th, 2011. The response to questions has been submitted on January 17th, 2012.
A Phase II, open label trial, to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV/rtv once daily in treatment-naïve HIV 1 infected adolescents aged between 12 and < 18 years.	C230	31/03/2011	Since the final study report of C230 makes reference to the revised C228 study report, after consultation with the EMA-PTL it has been agreed to postpone Article 46 of TMC114-TiDP29-C230 until the finalisation of the corrected TMC114-TiDP29-

			C228 final report (notification letter Suzy Verheyen dd Dec 9th 2011; fax EMA/CHMP/978281/2011 dd December 19th, 2011). The final study report for TMC114-TiDP29-C230 is now included in this Article 46 submission. A Type II variation to extend the indication is planned for the second half of 2012.

3. GCP aspects

The applicant has declared that all studies were performed in accordance with ICH requirements for GCP.

4. Orphan Medicinal Products

N/A

5. CLINICAL PHARMACOLOGY

Pharmacokinetics

Based on the results of trial C211 in ART-naïve adults and trial C212 in treatment-experienced HIV-1 infected children and adolescents, it was expected that the dose of DRV/rtv 800/100 mg q.d., recommended for treatment-naïve HIV-1 infected adults, would also be appropriate for treatment-naïve HIV-1 infected subjects aged between 12 and < 18 years, and weighing ≥ 40 kg.

The use of DRV/rtv in treatment-naïve HIV-1 infected adolescents between 12 to < 18 years of age has been evaluated in the 48-week, Phase II, open-label trial TMC114-C230, involving 12 subjects (male and female). This study was initiated in August 2009 and the last visit of the last patient in the study took place on March 31, 2011. The 12 adolescents were included in 6 countries: France, UK, Italy, Spain (each one subject), Ukraine (6 subjects), USA (2 subjects).

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, consisting of either zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC, over a 24-week treatment period in ARV treatment-naïve HIV 1 infected adolescents aged between 12 and < 18 years and weighing ≥ 40 kg.

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.

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 ≥ 2 NRTIs (AZT/3TC or ABC/3TC). The combination of a rtv-boosted PI and 2 NRTIs is a recommended treatment for ARV-naïve HIV-1 infected subjects aged between 12 and < 18 years and adults.

12 patients, 4 males and 8 females, aged 12.6 – 17.3 years, were included. Subjects received 2 x 400-mg DRV tablets (formulation F030) combined with 1 x 100-mg rtv capsule once daily, in combination with an investigator-selected background regimen (AZT/3TC or ABC/3TC).

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 whether 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.

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

The pharmacokinetics obtained for darunavir and ritonavir obtained at week 2 are shown in tables PK 1 and 2 and figure PK 1 and 2. One subject (001) had higher plasma concentrations at 24h after administration compared to 12h after administration. This sample was not taken into account as it was expected that the sample was taken after the next intake. In addition, for subject 008 the 24h sample was not taken. Therefore AUC and Cl/F was calculated for 10 subjects.

Table PK 1. 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 PK 2. 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}

Figure PK 1. Mean plasma concentration-time curves of darunavir (including standard deviation bars) at week 2 after administration of darunavir/ritonavir q.d. in treatment-naïve HIV-1-infected subjects aged between 12 and < 18 years.

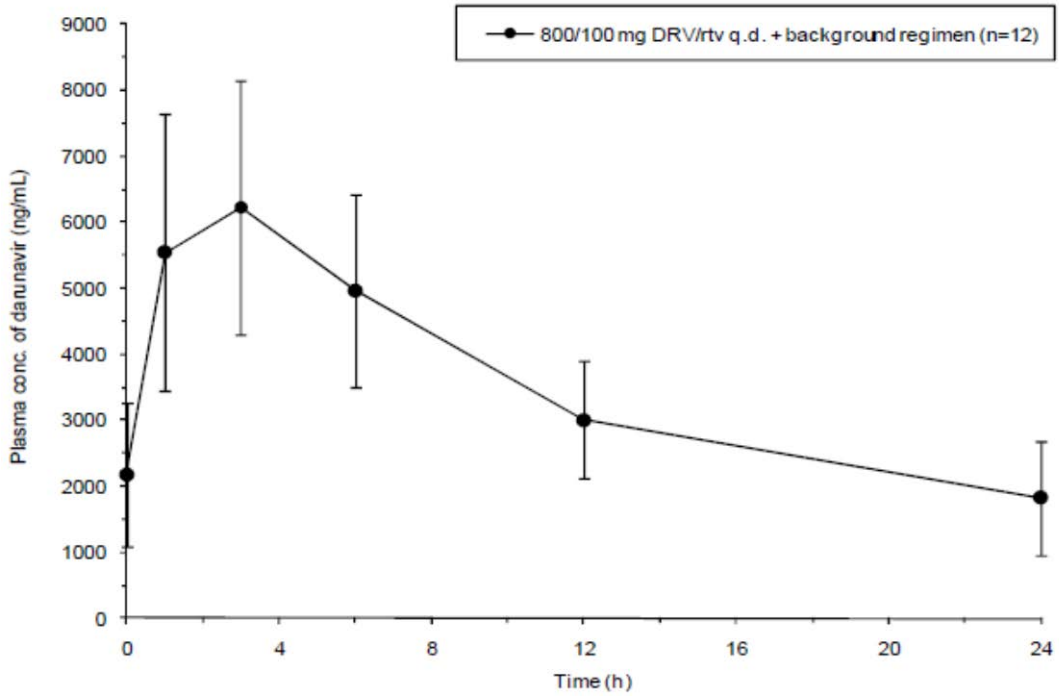
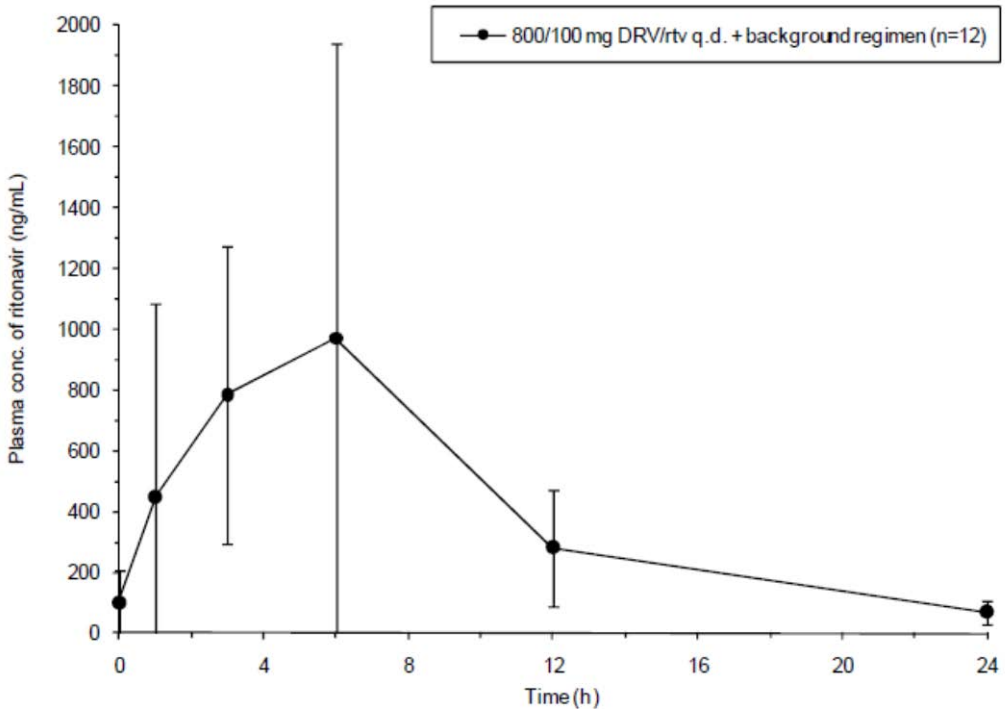


Figure PK 2. Mean plasma concentration-time curves of ritonavir (including standard deviation bars) at week 2 after administration of darunavir/ritonavir q.d. in treatment-naïve HIV-1-infected subjects aged between 12 and < 18 years.



The existing paediatric population pharmacokinetic model describing the pharmacokinetics of DRV (in combination with low-dose rtv) in adults and children aged between 3 and < 18 years was updated including the data after once-daily administration in the study C230, as well as the pharmacokinetic sub-study of C228 in 3-to-6-year-old children.

Empirical Bayesian estimates for AUC24h, average steady-state plasma concentration (Css,ave), C0h and CL/F were obtained for each subject at each visit, and the median estimate determined within each subject.

The summary of the population pharmacokinetic analysis is shown in table PK 3.

Table PK 3. 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

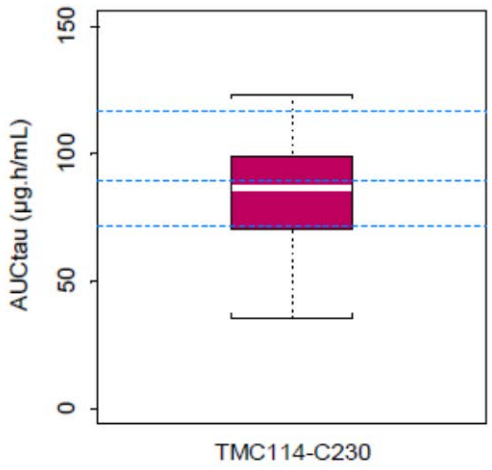
Based upon the population pharmacokinetics, one subject (no.0011) had a darunavir C0h plasma concentration at week 2 of 530 ng/ml, at week 4 of 478 ng/ml, at week 24 of 751 ng/ml and at week 48 555 ng/ml. Subject 007 had C0h values ranging from 771 (week 48) – 1122 ng/ml (week 2 and 4). All other subjects had darunavir C0h values above 1000 ng/ml.

The DRV AUC24h was compared to the AUC24h 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 PK 4 for the descriptive statistics at week 48 and figure PK 3).

Table PK 4. 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

Figure PK 3. Median, 25% and 75% percentiles, minimum, and maximum of drv auc24h after administration of drv/rtv 800/100 mg q.d. for 48 weeks in treatment-naïve hiv-1-infected subjects aged between 12 and < 18 years.



Dotted horizontal lines represent the target adult DRV exposure, and 80% and 130% of the target exposure.

Rapporteur's comment:

The data indicate that the applied dose of 800/100 mg DRV/RTV in treatment-naïve HIV-1 infected adolescents resulted in an exposure 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.

An adult target range of 89.7 µg.h/ml was applied. The MAH should explain this target, as in study C211 (800/100 mg in adults) the population pharmacokinetic analysis revealed a value of 87.9 µg.h/ml (see table below).

Results of the population pharmacokinetic analysis for AUCtau in study C211:

Treatment	N	Mean (µg.h/mL)	CV%	Median (µg.h/mL)	Min (µg.h/mL)	Max (µg.h/mL)
Darunavir	335	93.0	29	87.9	45.0	219

One subject (no. 0011) showed consistent low darunavir plasma concentrations, with C0h values below or around the EC50 value of 550 ng/ml.

The bioanalytical report and the population pharmacokinetic analysis report could not be retrieved from the submitted dossier. ***These should be submitted.***

A type II variation application to extend the indication, based on TMC114-TÍDP-C230, is planned for submission to EMA in the 2nd half of 2012. From a PK point of view the data submitted do not influence the benefit-risk balance for PREZISTA. However, before submission of the type II variation application, the concerns identified should be addressed.

6. CLINICAL EFFICACY

The primary efficacy parameter was 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%].

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). Interestingly, 5 from these 12 had vertically transmitted HIV, that only required treatment after a prolonged period at this age > 12 years. Still, most were not severely ill, because only 1 was categorized as WHO Stage 3. At baseline median CD4+ cell count was 282 x 106/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, and 1 subject had 1 DRV Resistance Asscociated Mutation (RAM) (V11I), but this subject had a confirmed virologic response during the study. 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.

Treatment

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. The mean duration of DRV/rtv intake during the study was 49.6 weeks. The total patient-years of DRV/rtv exposure was 11.4 years. No discontinuations occurred.

Table 9: Baseline Characteristics

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

Efficacy

Primary efficacy parameter: the results of the efficacy analysis for this trial demonstrated that virologic response defined as the percentage of subjects with confirmed plasma

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 log10 viral load from baseline was -3.03 (0.172) log10 copies/mL, at Week 48 this change was -2.98 (0.182) log10 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 (0008) and 1 rebounder (0011). 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 analyzed 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.

Rapporteur's comment:

In the phase II study 12 treatment-naïve HIV-infected adolescents between 12 and < 18 years of age and weighing ≥ 40 kg were treated with DRV/rtv and either AZT/3TC (n=6) or ABC/3TC (n=6), that were selected based on resistance profile, standard of care and/or HLA B057 determination. Tenofovir-based regimens are not approved in Europe in children and adolescents and could not be administered.

These adolescents were newly infected in the preceding years, because they had a duration of infection of mean 3.8 years.

Efficacy in this small sample size is comparable to that in treatment-naïve adults (83.7% in the ARTEMIS trial).

Adherence was meager, since 5 subjects (41.7%) were < 95% adherent to DRV/rtv. Regardless of this poor adherence, no apparent relevant relationships were observed between DRV AUC24h or C0h and virologic response defined as plasma viral load < 50 copies/mL at Week 48 or the change in log10 viral load from baseline at Week 48.

Two subjects deserve scrutiny: one (0008) was never suppressed, maybe because of non-adherence, but PK analysis did not reveal any substantially diminished DRV concentrations. However, this patient seemed to be extremely sensitive to normal DRV concentrations or to Ritonavir, since he experienced Grade 2 disorders (nausea, vomiting).

In addition, another subject (0011) was a rebounder, who appeared to be adherent using both the questionnaire and pill count, but had lowest PK values in the PK-analysis. The low concentrations were only marginally effective because of the reported rebound, and these low concentrations contradict the reported adherence performance.

These observations in 2 from 12 subjects about conflicting outcomes and the complex mutual interaction of PK measures, viral suppression rates, adherence monitoring and occurrence of AEs should be the focus of GCP inspections of the participating study sites and subsequent examination of patient data.

So far these continuous or incident viral load increases did not result in resistance mutations that could compromise treatment with the prescribed medication or alternative ARVs.

7. CLINICAL SAFETY

Safety DRV/rtv 800/100 mg q.d.

Mean Exposure to DRV was 49.6 weeks. AEs were reported:

Table 25: Adverse Events: 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

Most common AEs were vomiting 4 (33.3%), anemia 3 (25.0%), nausea 3 (25.0%). Two subjects had GI AEs considered at least possibly related to DRV: grade 1 nausea and grade 1 vomiting in 1 subject, and grade 2 abdominal pain, grade 2 diarrhea, and grade 2 nausea in 1 subject. Treatment was not discontinued.

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.

Clinical Laboratory

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 hematology laboratory parameters: grade 4 decreased hemoglobin 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.

Cardiovascular Results

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

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.

Rapporteur's comment:

Additional safety concerns could not be identified in this small group, although Grade 2 abnormalities for total cholesterol were observed in 4 subjects (33.3%), and for LDL cholesterol in 3 subjects (25.0%). Whether these changes are contributing as an additional cardiovascular risk factor in the future decades of chronic treatment in these adolescents and to what quantitative extent, is currently unknown. Apparently, DRV concentrations were not proportionally associated with safety warnings. Most hematologic AEs were related to AZT. Developmental parameters demonstrated normal pubertal development.

Normal growth in puberty is rapid: in US children growth during the year of Peak Height Velocity (PHV) in the normal female averages 9 cm/yr and varies normally from 5.4 cm to 11.2 cm. In the normal male, the PHV averages 10.3 cm/yr and varies normally from 5.8 cm to 13.1 cm per year. According to the MAH the subjects grew and gained weight according to the CDC Child Growth Standards, but this change was only very modest; weight parameters were hardly affected over 1 year of treatment. The low growth rate is related to HIV, but any additional effect of ARVs cannot be excluded. Comparisons of different regimens on pubertal growth spurts are lacking.

Week 48 data did not demonstrate additional safety alerts compared to week 24 data. Lipids (total cholesterol and LDL) were affected in adolescents, but the clinical relevance remains to be determined.

8. Conclusions

In conclusion, the adult dose of DRV/rtv 800/100 mg QD has demonstrated antiretroviral activity in a limited number of treatment-naïve HIV infected adolescents 12 to <18 years and weighing ≥ 40 kg in combination over 48 weeks regardless of poor adherence. Safety warnings in this particular age group included increased lipids and relatively slow growth, but clinical relevance remains to be determined. The results in this limited sample of treatment-naïve adolescents confirm the PK findings, efficacy results and safety issues as identified in adults using this once daily dose. The conflicting findings in 2 from 12 paediatric subjects stress the importance of on-site examination of study data to examine the interaction between PK data, adherence, efficacy rates and AEs.

A type II variation application to extend the indication based on TMC114-TÍDP29-C230 is planned for submission to EMA in the 2nd half of 2012.

The assessment of the B/R in treatment-naïve HIV infected patients 3-18 yrs needs to be based on the full data package.

Two concerns related to pharmacokinetics and one concern about safety in children (the clinical relevance of the increased lipids and relatively slow growth) are identified which should be addressed as part of the present Article 46 procedure.

9. Request for supplementary information as proposed by the Rapporteur

The following concerns related to study TMC114-TÍDP-C230 should be addressed by the MAH as part of the present Article 46 procedure:

1. A adult target of range of 89.7 µg.h/ml was applied. The MAH should explain this target, as in study C211 (800/100 mg in adults) the population pharmacokinetic analysis revealed a value of 87.9 µg.h/ml.
2. The bioanalytical report and the population pharmacokinetic analysis report could not be retrieved from the submitted dossier and should be submitted.
3. The clinical relevance of the increased lipids and relatively slow growth need to be discussed by the applicant.

10. Responses provided by the MAH on the Request for Supplementary Information

Question 1

A adult target of range of 89.7 µg.h/ml was applied. The MAH should explain this target, as in study C211 (800/100 mg in adults) the population pharmacokinetic analysis revealed a value of 87.9 µg.h/ml.

The Applicant's Response

Per protocol 1, the appropriateness of the dose of darunavir/ritonavir (DRV/rtv) 800/100 mg q.d. in treatment-naïve adolescents will be assessed by comparing the mean steady-state exposure estimates (AUC24h, C0h) for adolescents (obtained by empirical Bayesian feedback using the population pharmacokinetic model) and determining if they are within 80% to 130% of those obtained with DRV/rtv 800/100 mg q.d. in adults. The population pharmacokinetic derived arithmetic mean, geometric mean and median DRV AUC24h in 335 adults receiving DRV/rtv 800/100 mg q.d. from study TMC114-C211 was 93.0, 89.7 and 87.9 µg.h/mL, respectively. The geometric mean was chosen as this best reflects the distribution of the data and is more appropriate for making comparisons.

Rapporteur's comment:

The MAH used the geometric mean instead of the median, which explains the difference in values.

Question resolved.

Question 2

The bioanalytical report and the population pharmacokinetic analysis report could not be retrieved from the submitted dossier and should be submitted.

The Applicant's Response

The bioanalytical report and the population pharmacokinetic analysis report are submitted with these responses.

Rapporteur's comment:

Bioanalytical report:

The report has been submitted by the MAH. Darunavir and ritonavir were analysed with a validated LC-MS/MS method.

First blood sampling was on 28 September 2009 and last sample analysis was on 13 April 2011. The maximum storage period between collection and analysis was 562 days and was not longer than the current validated storage period of 1597 days for darunavir and ritonavir at -20ºC in human plasma.

The calibration curves for darunavir and ritonavir ranged from 5 – 10000 ng/ml and the QC samples had concentrations of 15, 500 and 8000 ng/ml. Run performance was within acceptance range, i.e. accuracy of the QCs was within 15% deviation. No concerns are identified.

Question on bioanalytical part resolved.

Population pharmacokinetic analysis report:

The report has been submitted by the MAH.

A population pharmacokinetic model for darunavir in adults was already available, which had been previously 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 the ARIEL (TMC114-C228), DELPHI (TMC114-C212) and DUET (TMC125-C206 and TMC125-C216) trials. 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 is described in the assessment report of EMEA/H/C/707/X/41/G.

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

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

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

Equation 1:

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

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

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

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

The model parameters are shown in the table PK 5 below.

Table PK 5: Darunavir parameter estimates for the original pediatric population pharmacokinetic model.

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

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

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

The parameter estimates obtained from the model update are shown in Table PK 6. Only slightchanges in the parameter estimates are observed for CL/F and V2/F, compared to the modeldeveloped for children from 3 to ≤18 years old after b.i.d administration. The influence of body weight on CL/F and V2/F was unchanged. The major impact of the model adjustment was the increase of V3/F and Q/F. Due to the once daily dosing, more information was gathered on these parameters, allowing their estimation. IIV on V2/F and V3/F on the other hand were too small to be properly estimated compared to the previous model. The goodness-of-fit plots for the adjusted model showed that the bias in the individual prediction versus the observation is minimal.

Table PK 6: 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)

Individual parameters estimation for the 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 a 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 shown in figure PK 1 indicate that the model predictions appear to be accurate, with no detectable bias present for individual predictions.

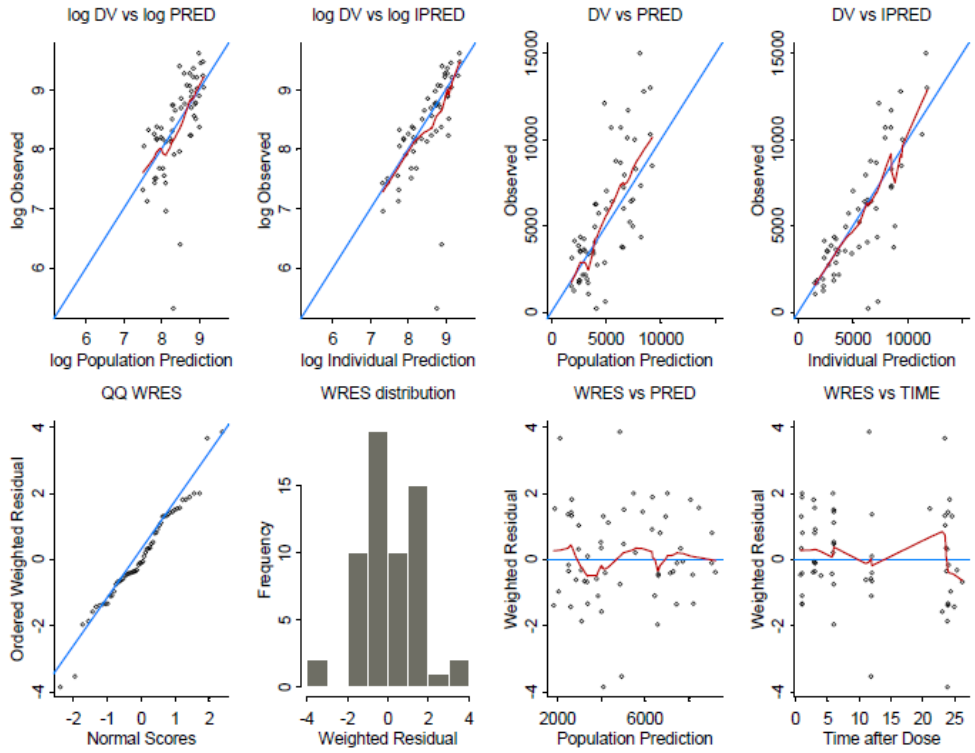


Figure PK 1: Basic goodness-of-fit plots for subjects involved in the TMC114-C228 q.d. substudy. The red/dark lines show the observed trend, the blue/light line the expected trend in the data.

The arithmetic mean darunavir exposure is 120 µg.h/ml (see table PK 7) which represents 129% of the target (exposure arithmetic mean of 93.0 µg.h/ml in ARTEMIS study). The geometric mean darunavir exposure is 115 µg.h/ml which represents 128% of the target geometric mean (exposure geometric mean of 89.7 µg.h/ml in ARTEMIS study).

Table PK 7. Summary statistics of the median individual pharmacokinetic parameters in the TMC114-C228 q.d. sub-study.

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

The fact that the mean exposure is on the upper side of the target may be explained by two individuals having a high exposure. These two subjects exhibited high AAG values and low body weight, as illustrated in figure PK 2, therefore, low clearances and high exposures were expected.

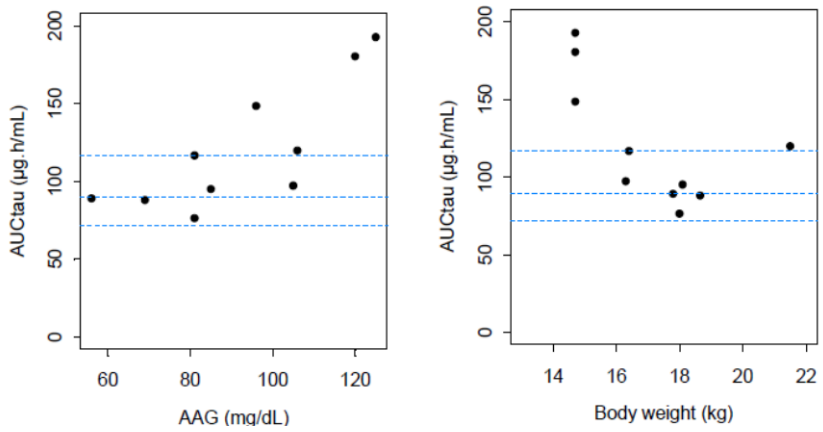


Figure PK 2: Correlation of the model-estimated AUCtau with AAG (left) and body weight (right). The blue dotted lines represent the target adult exposure (geometric mean) and its 80-130% associated interval.

It can be concluded that the steady-state geometric mean exposure in the TMC114-C228 q.d. substudy was comparable to that of the adult population.

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 shown in figure PK 3 indicate that the model predictions appear to be accurate, with no detectable bias present for individual predictions.

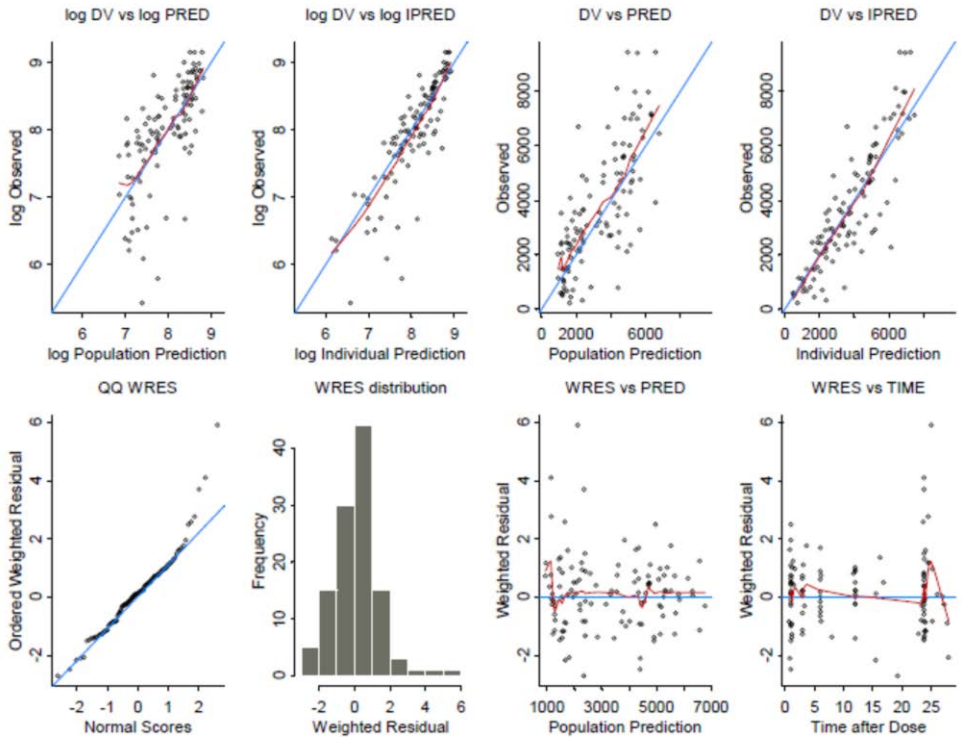


Figure PK 3: Goodness-of-fit plots for the empirical Bayes estimation. The red/dark lines show the observed trend, the blue/light line the expected trend in the data.

The overall summary statistics of pharmacokinetic parameters of darunavir given in table PK 8 (up to week 24 data), 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 ARTEMIS study).

The data 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 in the target range of adult patients. As concluded before, results at week 2, 4 and 24 were comparable to those obtained at week 48. But simulation data at week 48 are lacking in the submitted report. The MAH should confirm that the same model is used to obtain the week 48 data and explain why these data are not included in the population pharmacokinetic analysis report.

Question partly resolved. Missing information should be provided at the time of submission of the type II variation application.

Question 3

The clinical relevance of the increased lipids and relatively slow growth need to be discussed by the applicant.

The Applicant's Response

Dyslipidemia, including elevations in total cholesterol and LDL cholesterol, is a common comorbidity in HIV-1 infected individuals, including pediatric patients. Lipid abnormalities can occur in up to 62% of children infected with HIV. Among HIV-infected children, the prevalence of hypercholesterolemia was up to 13% compared with 4.8% in HIV-uninfected children.

Although the full consequences of dyslipidemia are not known for these children and adolescents receiving highly active antiretroviral therapy (HAART), they do appear to be at greater risk of

development of atheroma and cardiovascular disease, similar to adults. It is generally accepted that HAART contributes to the metabolic abnormalities manifested in these patients, but it is not the sole etiology, as many of the same metabolic derangements have been reported in HIV-infected individuals not receiving HAART. When choosing whether or not to treat a patient with HAART, and when choosing what agents to use, the health care provider, patient, and parent/guardian must weigh multiple potential risks and benefits. Although various lipid abnormalities are known adverse drug reactions for HIV protease inhibitors (PIs) as a class, among the boosted PIs, atazanavir and DRV appear to have the most favorable lipid side-effect profile.

The true risk of hyperlipidemia on the development of cardiovascular disease requires long-term follow-up, which is not feasible within the setting of a clinical study. The Marketing Authorisation Holder (MAH) is conducting a long-term pharmacovigilance study through the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) of the Paediatric European Network for Treatment of AIDS (PENTA) and has a commitment to provide annual reports.

Hyperlipidemia and hypercholesterolemia are listed adverse drug reactions in the SmPC and should be monitored and treatment initiated according to generally accepted recommendations for the treatment of lipid abnormalities.

Poor growth is well documented in pediatric patients with HIV, and can be manifested as either an abnormality of height, weight or both. Impaired growth has been observed in up to 22% of HIV-infected children whereas bone age delay was observed in up to 33%. In addition, abnormalities of growth, pubertal progression, or both had been manifested in 43% of HIVinfected children. Several factors can contribute, including, but not limited to psychosocial factors, endocrine abnormalities, anorexia, altered energy/nitrogen balance, and micronutrient deficiencies.

The overall impact of antiretroviral (ARV) therapy has been a remarkably improved growth in HIV-infected pediatric patients. However, impaired growth does occur in some children receiving ARV therapy, its cause being multifactorial. This raises the possibility that ARV therapy itself could be a contributing factor. There is a well-accepted association between ARV therapy and lipodystrophy, and different classes tend to be more strongly associated with specific manifestations of lipodystrophy, whether lipoatrophy or fat accumulation. This suggests that the effects ARVs have on growth impairment could be class dependent. When the effect of specific ARVs on lipodystrophy was studied in the past, the need to utilize several agents together in a cocktail limits the ability to discern the effect of any one single agent on growth. There are no conclusive data that demonstrate preferential effects of one PI over another regarding growth in the HIV-infected adolescents.

From the literature, it is known that PI-containing combination therapies may have both positive effects on height and weight due to improvements in metabolism and nutrient absorption and negative effects resulting from diarrhea, nausea, vomiting, and loss of appetite. In study TMC114-TiDP29-C230, vomiting (33.3%), nausea (25.0%), and diarrhea (16.7%) have been observed, of which the majority were grade 1 or 2 in severity, none were considered serious, and none led to treatment discontinuation. The gastrointestinal AEs observed were thus not of a level that these would have prevented growth improvement.

When interpreting changes in growth parameters in study TMC114-TiDP29-C230, making comparison to the WHO growth charts is considered to be a conservative comparison given that these growth charts are based on healthy children. The mean age-adjusted z-scores at baseline indicated that the subjects were below the normal population median with respect to height (-0.36) and weight (-0.10), while not for body mass index (BMI) (0.06). In addition, approximately half of the subjects were HIV-infected since birth and therefore have been deprived of HAART for at least 12 years. It has been

documented that early ages have been associated with better catch-up in weight and height, and that increases in height are less pronounced when HAART is initiated later. After the start of treatment with DRV/rtv 800/100 mg q.d., subjects continued to grow, relative to what was expected, but did not clearly catch up from the growth retardation at baseline. The within-group comparison for the changes from baseline for the age-adjusted z-scores at Week 48 showed small mean increases for height (0.14), and small mean decreases for weight (-0.08) and BMI (-0.20), none of which were statistically significant. Significant increases in BMI have not been observed in other studies.

This may be related to the fact that children in contrast to adults increase their height parallel to their weight, and therefore, their BMI remains stable. Lower height z-scores than weight z-scores at baseline before the introduction of PIs suggest that HIV disease has a more pronounced effect on height than weight, and that children may have more opportunity to improve in height than weight growth. This may explain why a somewhat greater beneficial effect on height than on weight has been observed.

In the treatment-experienced population of children and adolescents treated with DRV/rtv 600/100 mg b.i.d. in study TMC114-C212, no impairment of growth was observed. In the Week-48 analysis of this study, the age-adjusted z-score values at baseline indicated that, on average, subjects were below the normal population median value with respect to BMI (mean: -0.7), height (mean: -1.4), and weight (mean: -1.4). Following initiation of treatment, a rapid and significant response was seen with respect to the weight, BMI, and height aged-adjusted z-scores. This positive trend was confirmed in the final analyses.

Rapporteur's comment:

Lipids

With the advent of new HIV-treatment options in children and adolescents a more selective approach of pediatricians can be adopted in the selection of a regimen to balance antiviral activity and adverse events associated with ARVs. Metabolic influences of ARVs on growth, lipodystrophy/fat abnormalities, hyperlipidemia, bone turnover and cognitive development in this age group need to be documented not only for DRV but also for other ARVs as well. The efforts of the MAH and EPPICC network in this respect are essential to allow comparison of different treatment regimens in children and adolescents also in the long term.

The MAH is requested to include the metabolic evaluation of the effect of DRV in children and adolescents in the forthcoming type II variation using the same parameters as have been documented in study TMC114-TÍDP29-C230. Comparison of these outcomes to those obtained in children on other regimens will be encouraged. Next to these short-term 48 week data or at most 96 week required for registration, hopefully additional long-term data will come available to appreciate metabolic changes in children and adolescents to full extent. These data will be collected in Post-marketing surveillance.

Growth

Much in the same line as mentioned above, the multifactorial causes of growth impairment in HIV infected children need to be evaluated and comparison between regimens is essential to appreciate the potential contribution of ART as a detrimental factor.

That also implies larger sample sizes than the currently submitted study in 12 treatment-naïve adolescents that will not allow reliable comparison between distinct ARVs and growth parameters in this age group. The results of the variation in the second half of 2012 are awaited to explore the effect of 1) viral suppression, 2) delayed initiation of cART and 3) ARV therapy itself (e.g.

malabsorption due to gastrointestinal adverse events associated with PIs) on growth parameters in all children and adolescents who have been prescribed DRV.

11. Conclusions

After review of the data on pharmacokinetics, safety and efficacy from study TMC114-TÍDP-C230, the Rapporteur considered that the article 46 paediatric study submission is fulfilled. However, further data are expected in the context of a variation application, prior any final conclusion is made.

Indeed, three concerns were expressed during the first part of the Article 46 procedure. Assessment of the MAH's responses on the two concerns related to pharmacokinetics from study TMC114-TÍDP-C230 and one concern about safety in children led to the following conclusions:

Pharmacokinetics:

- The data of the submitted population pharmacokinetic analysis in the response document 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 in the target range of adult patients. As concluded before, results at week 2, 4 and 24 were comparable to those obtained at week 48. But simulation data at week 48 are lacking in the submitted report. The MAH should confirm that the same model is used to obtain the week 48 data and explain why these data are not included in the population pharmacokinetic analysis report. This missing information should be provided at the time of submission of the type II variation application.
- The following aspects should be considered by the MAH for the submission of the planned Type II variation regarding the paediatric indication (treatment-naïve HIV-1 infected patients of 3 to <18 years of age):
    1. The current best practice of model qualification involves simulation based diagnostics, e.g. Visual Predictive Check. The MAH should use prediction corrected VPCs stratified by AAG level, body weight and age to qualify the combined adult and paediatric model.
    2. Since total plasma concentration (Ctot) is confounded by AAG it would be useful to have the calculated unbound exposure (AUCu) presented in addition to AUCtot in order to facilitate comparison between exposures in different subgroups.

Safety:

- The MAH is requested to include the metabolic evaluation of the effect of DRV in children and adolescents in the forthcoming type II variation using the same parameters as have been documented in study TMC114-TÍDP29-C230. Comparison of these outcomes to those obtained in children on other regimens will be encouraged.
- The results of the variation in the second half of 2012 are awaited to explore the effect of 1) viral suppression, 2) delayed initiation of cART and 3) ARV therapy itself (e.g. malabsorption due to gastrointestinal adverse events associated with PIs) on growth parameters in all children and adolescents who have been prescribed DRV.

To be noted:

DRV Oral Suspension is now registered to allow for dosing in the young age groups and consequently the submission of a type II variation application is awaited to extend the indication to treatment-naïve HIV-1 infected pediatric patients aged 3 to <18 years of age in the second half of 2012.