21 June 2012
EMA/100490/2013
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 064

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 data submitted do not influence the benefit-risk balance for PREZISTA.

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, two concerns related to pharmacokinetics from study TMC114-TÍDP-C230 and one concern about safety in children are identified which should be addressed before submission of this variation application (see section 9).

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 treatmentnaïve 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.

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

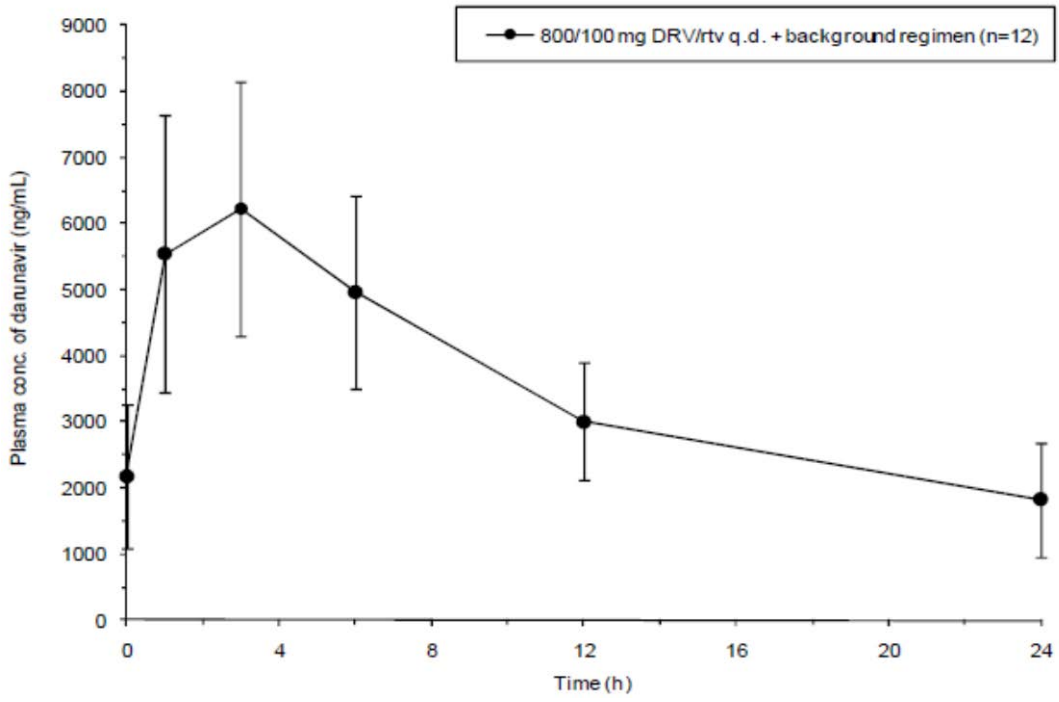
[a] n = 12 for C_{0h}, C_{max} and t_{max}

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.

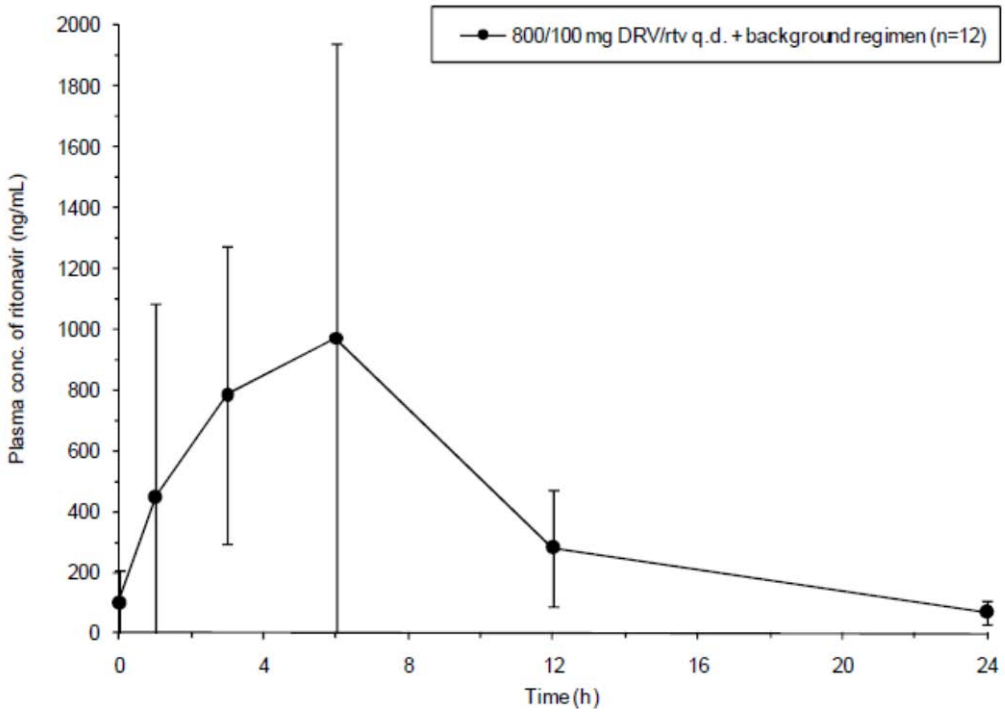
Pharmacokinetics of rtv (mean ± SD, t_{max}: median [range])	**800/100 mg DRV/rtv q.d. + Background Regimen**		
n	10[a]		
Week 2			
C_{0h}, ng/mL	101.0	±	107.8
C_{min}, ng/mL	51.66	±	24.39
C_{max}, ng/mL	1173	±	976.3
t_{max}, h	3.04 (1.00-6.15)		
AUC_{24h}, ng.h/mL	9468	±	6906
FI, %	260.1	±	53.73
CL/F,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

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

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.



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.

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

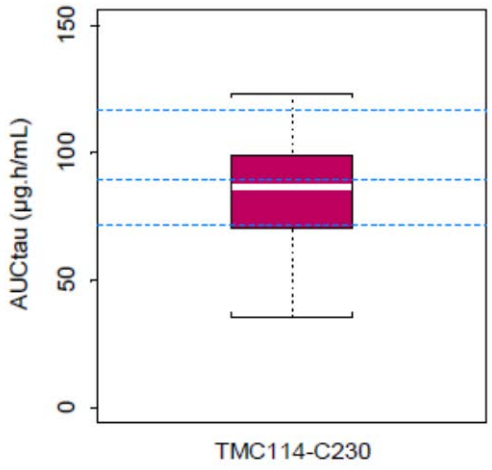
Based upon the population pharmacokinetics, one subject (no.0011) had a darunavir C0h plasma concentration at week 2 of 530 ng/ml, at week 4 of 478 ng/ml, at week 24 of 751 ng/ml and at week 48 555 ng/ml. Subject 007 had C0h values ranging from 771 (week 48) – 1122 ng/ml (week 2 and 4). All other subjects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

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.

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:

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. The current benefit- risk ratio of DRV is not influenced by the findings of this study.

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 before the submission of this variation application.

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 before the submission of the type II variation:

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.