London, 19 February 2009
EMA/632870/2012EMA/632870/2012
Committee for Medicinal Products for Human Use (CHMP)

Norvir

(ritonavir)

Procedure No. EMEA/H/C/000127/P45/037

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Doc. Ref:

Rapporteur's Preliminary Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

P45 - Paediatric Article 45 Follow Up Measure 037

Norvir (ritonavir)

EMEA/H/C/000127

Marketing Authorisation Holder: Abbott Laboratories Ltd.

Rapporteur:	Barbara van Zwieten-Boot
Start of the procedure:	21 December 2008
Date of this report:	4 February 2009
Deadline for Rapporteur's AR:	28 January 2009
Deadline for CHMP member's comments:	11 February 2009

INTRODUCTION

The MAH submitted 1 completed paediatric study **W97-225** for Norvir, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. One other study, **R&D/04/110**. (a retrospective patient registry/observational Cohort study in Switzerland comparing lopinavir/ritonavir, nelfinavir, and ritonavir) is also mentioned. This has not been accessed, but will be discussed in relation to the submission for Kaletra in view of the type of comparisons in this study.

A short critical expert overview has also been provided. In this document the two pediatric studies mentioned above were identified and reviewed in which ritonavir was administered as an antiretroviral agent. The pharmacokinetics, safety, and efficacy demonstrated by these two studies are consistent with the ritonavir product label.

Ritonavir is already approved by the CHMP for the indication of treatment of HIV-1 infected adults and children.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Norvir and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the clinical study(ies)

In study **W97-225** Ritonavir (Norvir, RTV, ABT-538) was supplied by Abbott in oral suspension (80 mg/mL) or in 100 mg capsules.

Non-clinical aspects

NA

Clinical aspects

1. Introduction

The two pediatric studies which were identified and reviewed by the MAH in which ritonavir was administered as an antiretroviral agent are summarised in the following table.

Table 1. Ritonavir Studies in Article 45 Line Listing

Study number/ Lead Author/ Title	Study Design	N	Baseline Characteristics	Duration	Results/Conclusions
W97-225: Open-label, Randomized, Dose Ranging Study of Two Different Doses of Ritonavir in Combination with 3TC+d4T in Children Infected with HIV	Open-label, randomized study to assess the safety, tolerability, pharmacokinetics, and efficacy of either 350 or 400 mg/m^2 ritonavir in combination with lamivudine and stavudine.	76	6 months to 12 years, naïve to protease inhibitors and to either stavudine or lamivudine	24 weeks	**Pharmacokinetics (PK):** C_{max} and AUC similar to or higher than 600mg BID in adults. C_{min} a little lower. **Safety:** incidence of AEs was low and discontinuations due to AEs were low (6.6%) and were all in the 350 mg/m^2 group. **Efficacy:** Viral loads <400 copies/ml were 38.9% and 44.1% for ritonavir 350 or 400 mg/m^2, respectively at week 24.
R&D/04/110: Retrospective Analysis of the Effect of Kaletra (lopinavir/ritonavir) Compared with Viracept (nelfinavir) and Norvir (ritonavir) in HIV-Infected Pediatric Patients.	Retrospective patient registry/observational Cohort study in Switzerland comparing lopinavir/ritonavir, nelfinavir, and ritonavir.	133	HIV-1 infected children 1.0-17.3 years who had received antiretroviral treatment with at least 1 of the 3 PIs of interest were analyzed. Subjects may have received lopinavir/ritonavir, nelfinavir, and/or ritonavir as a first-, second-, or third line or higher PI-based therapy.	N/A	**Safety:** No clinically relevant differences in AEs between treatment groups. Treatment emergent AEs related to underlying HIV disease. **Efficacy:** Virologic and immunologic response sustained through the first 48 weeks of treatment with lopinavir/ ritonavir, nelfinavir, and ritonavir regardless of the line of PI therapy and in second-line PI use.

The MAH submitted a report for:

- **W97-225**

2. Clinical study(ies)

Study W97-225: Open-label, Randomized, Dose Ranging Study of Two Different Doses of Ritonavir in Combination with 3TC and d4T in Children Infected with HIV

- **Description**
- **Methods**

- *Objective(s)*

The objectives of this study were to evaluate the safety, efficacy, and pharmacokinetics of 2 doses of ritonavir in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine (3TC, Epivir) and stavudine (d4T, Zerit) in HIV-1 infected children of 6 months to 12 years of age.

- *Study design*

This was a Phase I/II open-label, randomized study that evaluated two dose levels of ritonavir namely 350 or 400 mg/m^2 in combination with lamivudine and stavudine. Patients were naïve to protease inhibitors and to at least 1 of the 2 nucleoside agents used in the study. Patients were to remain on their assigned treatment regimen for 24 weeks. After completion of the 24-week treatment period, patients were eligible to continue therapy during a 24-week extension treatment period.
The revised[1] randomization method used a block size of 2 and provided for a stratified randomization procedure (by the 2 age groups, children between **6** and 24 months and children 2 to 12 years of age). In both cases, the block size was fixed.

- *Study population /Sample size*

Main inclusion criteria: Participating patients were to be between the ages of 6 months and 12 years with a HIV- 1 infection diagnosis based on a positive ELISA test and with viral loads above 5000 copies/mL. They were protease inhibitor naive, naive to at least 1 of the 2 nucleosides, and showed absence of acute infections requiring treatment.
In total 76 patients from **Brazil** (out of the 106 screened) were enrolled and randomised; 42 patients were assigned to receive the 350 mg/ m^2 dose , and 34 were assigned to receive the 400 mg/m^2 dose.
Only a subgroup participated in the pharmacokinetic sub-study.

- *Treatments*

Ritonavir (Norvir, RTV, ABT-538) was supplied by Abbott in oral suspension (80 mg/mL) or in 100 mg capsules. Doses of ritonavir were administered twice each day (approximately 12 hours apart), preferably with food, and could have been given together with stavudine and lamivudine. During the first 7 days of dosing, patients received the standard dose of lamivudine and stavudine along with escalating doses of ritonavir.

Stavudine was supplied in capsules containing 15 or 20 mg of stavudine, and also as a paediatric powder blend yielding a 1 mg/mL concentration following reconstitution. Doses of stavudine did not exceed 40 mg BID and were dependent upon body weight, as follows:

Table 2. Stavudine dosing

Weight	Dose
≤30 kg	1 mg/kg BID
>30 kg and <60 kg	30 mg BID
≥60 kg	40 mg BID

Lamivudine was supplied in a syrup formulation with a concentration of 10 mg/mL. Doses of lamivudine were always 4 mg/kg BID.
Both lamivudine and stavudine were administered beginning on Day 1**.**
Dosage of all study medications was recalculated at each visit. When a patient's weight or body surface area (BSA) changed the new dose was adjusted.

[1] Revised after dropping the originally planned 300 mg/m^2 dose group.

The patients for PK evaluations were identified at enrolment and underwent additional procedures at the Week 4 visit if they had been receiving the study drugs at the assigned doses for at least 1 week preceding the visit. Patients were required to report to the study site without taking any of the morning's study medication. If patients had taken the medication, they were permitted to return within 3 days for the pharmacokinetic study procedures. Blood sampling was initiated with a pre-dosing sample within 10 minutes of 0800 hours. The 3 drugs were administered simultaneously (with or without food) under the observation of study personnel. Subsequently 1 to 2 ml, blood samples were taken at 09:00, 10:00, 12:00, 14:00, 16:00, and 20:00 hours.
Compliance was assessed based on all medication bottles which were returned to the study site at each visit for assessment of the number of solid formulation doses remaining or the amount of liquid formulation remaining, as appropriate. The assessments were recorded in the case report form.

- *Outcomes/endpoints*

The primary efficacy variable was the time-normalized area under the curve (AUC) through Week 24 for the change from baseline in $\log_{10}$ viral load. Secondary variables included: the number of patients with viral loads below the limit of quantification (LOQ: <400 copies/mL); the time-normalized AUC for the change from baseline in $\log_{10}$ viral load during the extension treatment period from the end of Week 24 to Week 48; the $\log_{10}$ viral loads at each visit and at endpoint; the time-normalized AUCs through Week 24 and through Week 48 for the change from baseline in log CD_4 cell count; $\log_e$ CD_4 cell count at each visit and at endpoint; and progression of CDC disease stage.

PK parameters included C_{max}, C_{min}, predose concentration (C_0 or C_{trough}), T_{min}, the area under the plasma concentration-time curve from hour 0 to hour 12 (AUC_{12}), and the apparent clearance (CL/F).

Safety evaluations included analysis of AEs and HIV-related events using COSTART III summarization, and changes from baseline vital signs and laboratory determinations

- *Statistical Methods*

The primary analysis of efficacy was based on the comparison of the primary variable for observed cases without retrieved dropouts in the ITT population. Secondary analyses included analyses of completers population with retrieved dropouts, for completers with and without retrieved dropouts, for the PP cohort without retrieved dropouts, and for PP completers without retrieved dropouts. These comparisons were performed via analysis of variance (ANOVA) using randomization group, study center, and group/center interaction as factors. The same cohorts were analyzed for all secondary variables.

[For the handling of dropouts or missing data, the LOCF method was used for assessment of efficacy parameters at endpoint].

In addition, the absolute changes from baseline in viral load and CD4 Cell count at each weekly visit and at endpoint were evaluated with analysis of covariance (ANCOVA). The ANCOVA model included Randomization Group and Study Center as factors tested for main effects and for interaction.
The number of patients with viral loads below the limit of quantification at each study visit was tested with Fisher's exact test to examine possible differences between randomization groups. In addition, a post-hoc analysis was performed on subsets of patients based on the patients' previous treatment with nucleoside reverse transcriptase inhibitors (NRTIs). Patients were classified as naïve to all 3 of the drugs used in the study or naïve to 2 of the 3 drugs used in the

study. This subset analysis was performed to determine if a greater proportion of patients who were naïve to all 3 of the drugs used in the study would achieve viral loads below the LOQ.
For the purpose of the pharmacokinetic analysis, dose group (two levels) and gender were used as classification factors, while age, body surface area (BSA) and one of two disease factors (baseline CD, cell count or baseline viral load) were used as covariates in the two-way ANCOVA models. In particular, one ANCOVA model included effects for dose group, gender, age, age-by-gender interaction (i.e., males and females had separate slopes for age), BSA, and baseline CD4 cell count. The other ANCOVA model included effects for dose group, gender, age, age-by-gender interaction, BSA, and baseline viral load (HIV RNA). Additionally, the partial Pearson correlation with classification by dose group was calculated to assess the association between each pharmacokinetic variable and age or BSA. The statistical test of the association was performed under the null hypothesis of zero correlation between the pharmacokinetic variable and either age or BSA.

- **Results**

  - *Recruitment/ Number analysed*

The numbers of patients analysed are presented in the following Table.
Of 106 patients screened, 76 were eligible to participate and were assigned to treatment according to the randomization list. The first 24-week course of dosing was completed by 35 of 42 patients (83.3%) receiving 350 mg/m^2 and all 34 patients (100%) receiving 400 mg/m^2.
A total of 10 patients (all from the 350 mg/m^2 group) discontinued the study, **7** during the initial 24-week phase and **3** during the 48-week extension. The most common reason for discontinuation was adverse event (AE) (5/10 patients, all from the 350 mg/m^2 dose group).

Table 3. Distribution of Patients Within Safety and Efficacy Analysis Cohorts

	Randomization Group		Total
Analysis Cohort	350 mg/m^2	400 mg/m^2	
ITT-Safety	42	34	76
ITT-Efficacy*	40	34	76
24-Week Completers	35	34	69
48-Week Completers	23	21	44
Retrieved Dropouts	0	0	0
Per-Protocol	39	34	73

* 2 patients discontinued before Week 4 visit and had no post-baseline efficacy assessments.

  - *Baseline data*

Demographic characteristics of randomised patients are presented in the following table

Table 4. Patient demographics and disease characteristics at baseline

Parameter	350 mg/m² n = 42	400 mg/m² n = 34	Total n = 76
Gender, n (%)			
Male	20 (47.6)	20 (58.8)	40 (52.6)
Female	22 (52.4)	14 (41.2)	36 (47.4)
Age (months)			
Mean	68.0	71.9	69.8
Median	56.0	73.0	66.5
Range	13.0-153.0	6.0-134.0	6.0-153.0
Age <2 years (24 months), n (%)	6 (14.3%)	3 (8.8%)	9 (11.8%)
Age ≥2 years (24 months), n (%)	36 (85.7%)	31 (91.2%)	67 (88.2%)
Race, n (%)			
White	26 (47.6)	20 (58.8)	40 (52.6)
Black	5 (11.9)	2 (5.9)	7 (9.2)
Asian	0 (0.0)	1 (2.9)	1 (1.3)
Other	11 (26.2)	11 (32.4)	22 (28.9)
Height (cm)			
Mean	105	109	107
Median	102	111	105
Range	72-154	64-144	64-154
Weight (kg)			
Mean	18.8	19.9	19.3
Median	16.6	17.6	16.9
Range	7.5-49.5	7.1-40.1	7.1-49.5
Any Prior Antiretroviral Medication Usage, n (%)	40 (95.2)	32 (94.1)	72 (94.7)
zidovudine (AZT, ZDV)	37 (88.1)	30 (88.2)	67 (88.2)
didanosine (ddI)	36 (85.7)	30 (88.2)	66 (86.8)
lamivudine (3TC)	20 (47.6)	18 (52.9)	38 (50.0)
stavudine (d4T)	1 (2.4)	2 (5.9)	3 (3.9)
Baseline Viral Load (log_{10} copies/mL)			
Mean	4.92	4.74	4.84
Median	4.94	4.71	4.81
Range	3.72-6.22	3.21-6.03	3.21-6.22
Baseline CD_4 count (log_e count)			
Mean	6.54	6.07	6.33
Median	6.58	6.16	6.35
Range	4.55-7.96	3.56-7.85	3.56-7.96

The 2 dose groups were clinically similar in main demographic and disease characteristics. Approximately half of the patients (40/76 patients, 52.6%) was under the age of 6 years (i.e., **<72** months). The majority of patients in both groups became HIV-infected through maternal transmission (73/76, 96. 1 %)**.** Median age at time of diagnosis was 18 months for the 350 mg/m^2 group and 21 months for the 400 mg/m^2 group. Median duration of disease was 33.5 and 39.5 months for the 2 dose groups, respectively.

Pharmacokinetic Evaluations
A total of 33 patients from the 350 and 400 mg/m^2 dosing groups were enrolled in the PK sub-study. All patients participating in the pharmacokinetic evaluation were between the age of 2 and 12 years (range, 2 years, 6 months to 12 years, 9 months). There were 19 patients from the 350 mg/m^2 dose group (Group I) and 14 patients from the 400 mg/m^2 dose group (Group II).

- ***Efficacy results***

Virological response
Results from each analysis cohort for the time-normalized AUC for change from baseline in log_{10} viral load for the 24-week course of treatment and the extension to 48 weeks are shown in the following table.

Table 5. Summary of Time-Normalized Area Under the Curve for Change from Baseline in Log-Transformed Viral Load

Cohort	Randomization Group				p-value[A]		
	350 mg/m^2		400 mg/m^2				
	n	Mean	n	Mean	Randomized Group	Site	Randomized Group*Site
24-Week Treatment Course							
Intent to Treat[B]	**40**	**-1.372**	**34**	**-1.280**	**0.6855**	**0.2800**	**0.3875**
Completers	35	-1.508	34	-1.280	0.2806	0.2762	0.3527
Per-Protocol	39	-1.201	34	-1.186	0.8989	0.3085	0.1222
Per-Protocol Completers	34	-1.316	34	-1.186	0.8860	0.3039	0.0858*
48-Week Extension							
Intent to Treat	25	-1.748	21	-1.566	0.2961	0.2485	0.1301
Completers	23	-1.841	21	-1.566	0.1248	0.4852	0.2292
Per-Protocol	13	-1.711	13	-1.551	0.1415	0.0049*	0.0322*
Per-Protocol Completers	12	-1.874	13	-1.551	0.1832	0.5586	---

[A]Probability value from ANCOVA.
[B]The time-normalized AUC for change from baseline in log viral load for the intent-to-treat cohort (without retrieved dropouts) was designated *a priori* as the primary analysis for the study.

*Statistically significantly different (p<0.05 or <0.10).

The results for the lower dose level were better than for the higher dose level, although none of these differences achieved statistical significance in the ANCOVA comparison of randomization group. There were some statistically significant site interactions and randomization group-by-site interactions, but due to the limited number of subjects, no further investigation was performed. Results for mean change in viral load (log_{10} copies/mL) from baseline at each study visit for the ITT and PP analysis cohorts were similar for both dose levels. See the following table.

Table 6. Summary of mean change in viral load (log_{10} copies/mL) from baseline at each study visit for the ITT analysis cohort

ITT Cohort [A]	Randomization Group				p-value[B]		
	350 mg/m²		400 mg/m²				
	n	Mean Change (log_{10} copies/mL)	n	Mean Change (log_{10} copies/mL)	Randomized Group	Site	Randomized Group*Site
24-Week Treatment Course							
Endpoint	40	-1.09	34	-1.01	0.9791	0.5477	0.9012
Week 4	40	-1.51	34	-1.53	0.3724	0.5087	0.5855
Week 12	40	-1.31	34	-1.39	0.2726	0.9580	0.3176
Week 24	39	-1.38	34	-1.13	0.5047	0.9070	0.5661
48-Week Extension							
Endpoint	40	-1.09	34	-1.01	0.9791	0.5477	0.9012
Week 36	39	-1.16	34	-0.98	0.7647	0.7305	0.8670
Week 48	40	-1.09	34	-1.01	0.9791	0.5477	0.9012

[A]The time-normalized area under the curve for change from baseline in log viral load for the intent-to-treat cohort (without retrieved dropouts) was designated *a priori* as the primary analysis for the study.
[B]Probability value from ANCOVA.

Similar results were obtained for the number of patients achieving a plasma viral load below the LOQ in the 2 dose groups at each visit. Similar observations were seen for patients when results were analyzed by prior treatment with NRTIs. A greater proportion of patients who were naïve to all **3** of the drugs used in this study achieved viral loads below the LOQ at Week 24 compared to those patients who were naïve to only 2 of the **3** study drugs (total of 57.6% versus 27.0%**,** respectively). See the following table.

Table 7. Number of Patients with Plasma Viral Load Below Quantifiable Levels for the ITT Analysis Cohort by Prior NRTI Therapy

		Randomization Group				
		350 mg/m²		400 mg/m²		
Timepoint	**Subset**	**N**	**N (%)**	**N**	**N (%)**	**p-value***
Week 4	All patients	40	8 (20.0%)	34	6 (17.6%)	0.7626
	Naive to 3 Drugs	19	3 (15.8%)	14	2 (14.3%)	
	Naive to 2 Drugs	21	5 (23.8%)	20	4 (20.0%)	
Week 12	All patients	38	14 (36.8%)	34	15 (44.1%)	0.3613
	Naive to 3 Drugs	19	10 (52.6%)	14	9 (64.3%)	
	Naive to 2 Drugs	19	4 (21.1%)	20	6 (30.0%)	
Week 24	All patients	36	14 (38.9%)	34	15 (44.1%)	0.4369
	Naive to 3 Drugs	19	10 (52.6%)	14	9 (64.3%)	
	Naive to 2 Drugs	17	4 (23.5%)	20	6 (30.0%)	
Week 36	All patients	24	15 (62.5%)	21	10 (47.6%)	0.4379
	Naive to 3 Drugs	15	10 (66.7%)	11	9 (81.8%)	
	Naive to 2 Drugs	9	5 (55.6%)	10	1 (10.0%)	
Week 48	All patients	24	12 (50.0%)	21	12 (57.1%)	0.3772
	Naive to 3 Drugs	15	9 (60.0%)	11	10 (90.9%)	
	Naive to 2 Drugs	9	3 (33.3%)	10	2 (20.0%)	

*p-value for randomization group is based on Cochran-Mantel-Haenszel test

The difference between randomization groups was not statistically significant at any of the timepoints when analyzed using the Cochran-Mantel-Haenszel test (p-values ranged from 0.3613 to 0.763).

Immunological response
In all analyses, mean time-normalized AUC for change from baseline in CD4 cell count was higher in the 400 mg/m^2 dose group as compared to the 350 mg/m^2 group. These differences achieved statistical significance for the comparison in the primary analysis cohort (ITT) at Week 48, (p=0.0240) in the ANCOVA comparison of randomized group.
In the secondary analysis cohorts, there were several statistically significant effects in the ANCOVA comparison for randomized group. See the table below.

Table 8. Summary of mean time-normalized AUC for changes from baseline in log transformed CD4 cell count

Cohort	Randomization Group				p-value		
	350 mg/m^2		400 mg/m^2				
	N	Mean	n	Mean	Randomized Group	Site	Randomized Group *Site
24-Week Treatment Course							
Intent to Treat	40	0.057	34	0.4021	0.0798	0.1130	0.1101
Completers	35	-0.0001	34	0.4021	0.0594	0.1500	0.1240
Per-Protocol	39	0.2020	34	0.3640	0.0253*	0.0857	0.7175
Per-Protocol Completers	34	0.1720	34	0.3640	0.0054*	0.1145	0.8742
48-Week Extension							
Intent to Treat	25	0.2282	21	0.4656	0.0240*	0.1240	0.7450
Completers	23	0.2402	21	0.4656	0.0351*	0.1955	0.6206
Per-Protocol	13	0.2266	13	0.5362	0.0580	0.1860	0.9656
Per-Protocol Completers	12	0.2581	13	0.5362	0.0759	0.3716	---

*Statistically significantly different (p<0.05).

Similar trends were observed at the individual evaluation timepoints, the mean change in CD4cell count was numerically higher in the 400 mg/m^2 dose group as compared to the 350 mg/m^2 dose group**.**

Table 9. Mean changes from baseline in log$_e$ CD $_4$ cell count at each study visit.

Cohort	Randomization Group						p-value		
	350 mg/m^2			400 mg/m^2					
	N	Mean Change[A]	Geometric Mean[B]	N	Mean Change	Geometric Mean	Randomized Group	Site	Randomized Group* Site
24-Week Treatment Course									
Baseline Mean	40	6.50	666.46	34	6.07	434.57	---	---	---
Endpoint	40	0.29	893.84	34	0.50	714.73	0.3075	0.4807	0.2226
Week 4	40	0.14	850.43	34	0.37	630.52	0.2656	0.1581	0.3191
Week 12	40	0.24	843.20	34	0.44	673.49	0.0792	0.2294	0.0430*
Week 24	39	0.30	888.33	34	0.49	711.69	0.2083	0.8582	0.0961
48-Week Extension									
Endpoint	40	0.30	898.55	34	0.50	714.73	0.3475	0.4345	0.2500
Week 36	39	0.28	887.75	34	0.50	713.35	0.2653	0.4812	0.2316
Week 48	40	0.30	898.55	34	0.50	714.73	0.3457	0.4345	0.2500

[A]Calculated as Visit Mean – Baseline Mean at each timepoint.
[B] Mean CD$_4$ cell counts (reverse transformation performed on the log$_e$ mean value) at each visit.
*Statistically significant (p<0.05).

CDC staging. In both dose groups, there was no change in clinical or immunological staging during this study.

Efficacy results of this study in relation to other studies. The antiviral and immunologic findings from this study are consistent with those reported for other studies in similarly aged HIV-infected paediatric patients. As summarized in the table below.

Table 10. Virological and immunological results in study W97-225 versus other studies

Study	N	Dose	Weeks	Change in HIV RNA (log_{10})	HIV RNA <LOQ (% Pts)	Median Change in CD_4 ($cells/mm^3$)
Pediatric Studies						
This Study, W97-225	40	350 mg/m^2	24	-1.4	39%[B]	+232
	34	400 mg/m^2	24	-1.1	44%[B]	+277
This study, Naïve to 3 study drugs	19	350 mg/m^2	24	-1.6	52.6%[B]	+353
	14	400 mg/m^2	24	-1.5	64.3%[B]	+325
Thuret[9]	22	350-400 mg/m^2	18	-1.5	32%[C]	+472
Nachman[10]	100	350 mg/m^2	48	NR[A]	42%[B]	No Change
Adult Studies						
Lederman[11]	44	600 mg BID	12	NR[A]	88%[D]	No Change
Notermans[7]	34	600 mg BID	24	NR[A]	~80%[E]	~+180

[A]NR = Not Reported
[B]LOQ = 400 copies/mL
[C]LOQ = 200 copies/mL
[D]LOQ = 100 copies/mL
[E]LOQ = 251 copies/mL

Refrences

7. Notermans DW, Jurriaans S, de Wolf F, et al. Decrease of HIV- I RNA levels in lymphoid tissue and peripheral blood during treatment with ritonavir, lamivudine and zidovudine. AIDS. 1998;12:167-73.
9. Thuret **1,** Michel G, Chambost H, et al. Combination antiretroviral therapy including ritonavir in children infected with human immunodeficiency. AIDS 1999; 13(l):81-7.
10. Nachman SA**,** Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. JAMA 2000;283(4):492-8.
11. Lederman MM, Connick E, Landay A**,** et al. Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and ritonavir: results of AIDS Clinical Trials Group Protocol **315. J** Infect Dis 1998; 1 78(l):70-9.

The reductions in viral load observed in this study are comparable to the 1.5 log_{10} decrease reported by Thuret et al.[9] The percentage of patients with HIV RNA levels below the LOQ in this study are also comparable to those reported by Thuret et al[9] and Nachman et al[10]. However, these rates are all lower than those reported in studies in HIV-infected adults [7,11] despite the use of more sensitive viral load assays with lower LOQ in the adult studies. As mentioned previously, these lower rates are partly a function of the patients' prior NRTI therapy and vertical transmission of HIV at a time when the immune system is incompetent. This leads to a poor humoral and cellular primary response to HIV, associated higher viral loads in children compared to adults and a more rapid progression to AIDS in children (4.8 years) compared to adults (10.0 years). Like in adults, careful consideration must be given to a patient's previous antiretroviral treatment experience before NRTI therapy is prescribed.

PK results

The data show, relative ritonavir plasma exposures from the 2 dosing regimens appeared to be similar, probably as a result of relatively high intersubject variability and only a 14% increase in dose from 350 to 400 mg/m^2. See the following table.

Table 11. Mean ± SD Steady-State Pharmacokinetic Parameters from Week 4

Pharmacokinetic Parameter	Randomization Group 350 mg/m² (n = 18) Mean ± SD	Randomization Group 400 mg/m² (n = 14) Mean ± SD
T_{max} (hour)	3 ± 2	3 ± 2
C_{max} (µg/mL)	12.18 ± 3.66	11.94 ± 4.77
C_0 (µg/mL)	4.08 ± 4.31	4.77 ± 5.64
C_{min} (µg/mL)	2.02 ± 1.50	1.83 ± 1.54
AUC_{12} (µg•hr/mL)	85.90 ± 28.81	80.04 ± 34.64
CL/F (L/hr)	4.78 ± 2.54	6.29 ± 3.61

The mean (SD) plasma concentration-time profiles from Week 4, plotted on a linear scale, are presented in the following figure.

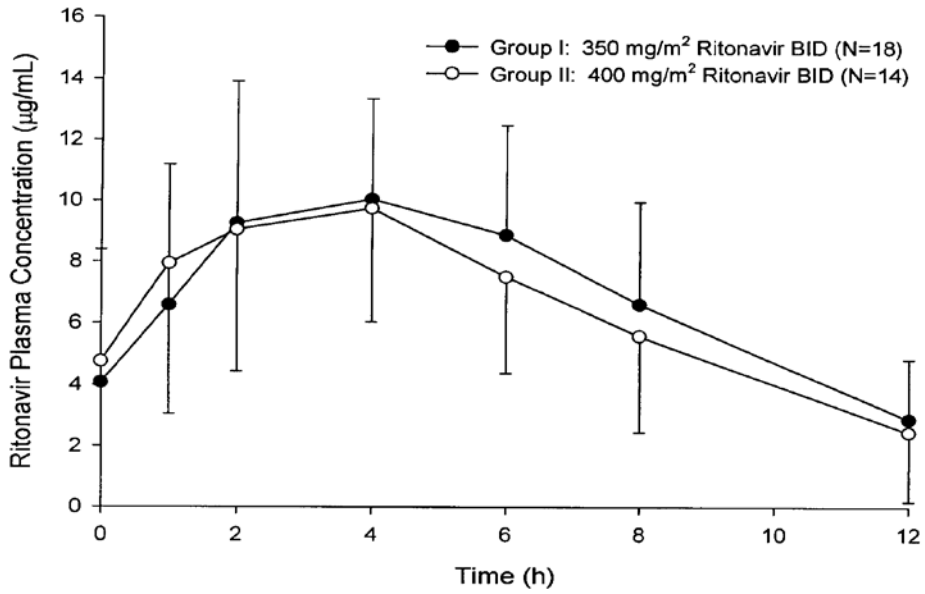

Figure 1. Mean (SD) plasma concentration-time linear profiles in paediatric patients receiving BID doses ritonavir based on body surface area

Age and BSA appear to be significant predictors of ritonavir pharmacokinetics when both are included as covariates; however, these factors are highly positively correlated, and results should be interpreted with caution. Gender has no significant effect on steady-state ritonavir pharmacokinetics in paediatric patients. Ritonavir concentrations do not appear to be dependent on disease factors, such as baseline CD4 cell count or baseline HIV RNA. In children older than 2 years of age receiving a dosing regimen of 350 mg/m^2 or 400 mg/m^2 BID, steady-state ritonavir concentrations appear to be similar to those reported in adults at 600 mg BID. Mean C_{min} in paediatric patients appeared to be somewhat lower than that noted in adult patients, see the following table.

Table 12. Comparison of Ritonavir Steady-State Pharmacokinetic Parameters in Adults vs. Children (2 to 12 Years of Age)

Patient Population	Dose Regimen	N	C_0 (µg/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC_{12} (µg•h/mL)
Adult[A]	600 mg BID	10	3.5 ± 2.5	11.2 ± 3.6	3.0 ± 2.1	77.5 ± 31.5
Pediatric[B]	350 mg/m^2 q12h	18	4.1 ± 4.3	12.2 ± 3.7	2.0 ± 1.5	85.9 ± 28.8
Pediatric[B]	400 mg/m^2 q12h	14	4.8 ± 5.6	11.9 ± 4.8	1.8 ± 1.5	80.0 ± 34.6

[A]Reference 1.
[B]This Study, W97-225.

Ref.1 . Danner SA**,** Carr **A,** Leonard JM**,** et al. **A** short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV- I protease. **N** Engl J Med. 1995;333:1228-33.

- ***Safety results***

A higher percentage of patients in the 350 mg/m^2 group had at least 1 adverse event (34/42, 81.0%) compared with the 400 mg/m^2 group (25/34, 73.5%). While the percentage of patients with at least 1 moderate-to-severe adverse event was higher in the 350 mg/m^2 group (16/42, 3 8. 1 %) compared with the 400 mg/m^2 group (9/34, 26.5%), the percentage with serious adverse events (SAEs) was comparable between the 2 groups (8/42, 19.0% and 7/34, 20.6%**,** respectively). No death occurred during this study. Five patients (11.9%) in the 350 mg/m^2 group discontinued due to adverse events. Only 1 patient (2.4%, 350 mg/m^2 group) was reported to have a ritonavir dose reduction of study medication due to an adverse event.
Adverse events that were considered to be related to study medication mostly involved the digestive system and showed that the 2 (slightly different) dose levels had comparable adverse event profiles. See the following table.

Table 13. Non-HIV Related Adverse Events Considered to Be Related to Treatment

	Study Drug Treatment					
	RTV		3TC		d4T	
Adverse Event	n = 76	(%)	n = 76	(%)	N = 76	(%)
Vomiting	14	(18.4%)	11	(14.5%)	11	(14.5%)
Diarrhea	9	(11.8%)	7	(9.2%)	7	(9.2%)
Nausea	4	(5.3%)	0	(0.0%)	0	(0.0%)
Abdominal Pain	4	(5.3%)	4	(5.3%)	4	(5.3%)
Nausea and Vomiting	2	(2.6%)	0	(0.0%)	0	(0.0%)
Leukopenia	2	(2.6%)	2	(2.6%)	2	(2.6%)
Lymphadenopathy	1	(1.3%)	1	(1.3%)	1	(1.3%)
Dehydration	1	(1.3%)	1	(1.3%)	1	(1.3%)

*Adverse events are listed in order of decreasing incidence in the total population.

The overall incidence of HIV related adverse events (e.g. infection, hepatomegaly) was low in this study, with no HIV-related adverse event occurring in more than 2 patients.

Laboratory data analysis revealed a pattern of drug effects that are typical of antiretroviral agents (i.e., effects on haematological, hepatic, and pancreatic parameters). The analysis revealed no strong trends favouring either dose group. Low red-cell indices tended to be more frequent in the 400 mg/m^2 group.

3. Discussion on clinical aspects

Ritonavir is generally used at lower doses as *PK enhancing* PI in the EU and most countries in the world. The provided study in HIV-infected children from 6 months to 12 years of age, the tested ritonavir *therapeutic dosing* regimens of 350 mg/m^2 or 400 mg/m^2 in combination with lamivudine and stavudine demonstrated similar antiviral and immunological results at Week 24 and Week 48. The results are consistent with data from a couple limited published data in the literature and do not raise new safety concerns. Of note, the number of patients younger than 2 years of age remains limited to 9 patients (approx. 12% of the tested population).

Rapporteur's Overall Conclusion AND RECOMMENDATION

- **Overall conclusion**

The new data with therapeutic doses of ritonavir in combination with two NRTIs (lamivudine and stavudine) from this study in paediatric patients from Brazil add further support to the approved posology for paediatric patients (2 years of age and above) in the EU as mentioned in the Norvir SmPC; the recommended dosage of Norvir solution in children is 350 mg/m² orally twice daily and should not exceed 600 mg twice daily. Norvir should be started at 250 mg/m² and increased at 2 to 3 day intervals by 50 mg/m² twice daily. In this regard there is no need to amend section 4.2 in the SmPC.

Issues which need Type II variation:

Section 5.1 can be expanded with a brief summary of few lines mentioning the present results at the end of subsection **Clinical pharmacodynamic data** in a similar fashion as the other brief results in paediatric patients using the therapeutic ritonavir doses.

- **Recommendation**

X Fulfilled –

ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable