EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Telzir

(fosamprenavir)

Procedure No. EMEA/H/C/000534/P46/0060

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

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

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I. EXECUTIVE SUMMARY

In accordance with Article 46 of Regulation (EC) No1901/2006, the applicant has submitted the final study report (week 168) for paediatric study APV20003. This study explored the use of Fosamprenavir/Ritonavir once daily in paediatric patients aged 2 to 18 years.

Since the once-daily regimen of Telzir is not approved in UE and since the applicant is not willing to seek authorisation for such a regimen, the data derived from study APV20003 are regarded as simply informative.

Of note, the 48-week study report of study APV20003 was already assessed by the CHMP in the setting of the Telzir II18 variation.

II. RECOMMENDATION

Based on the submitted data, no further regulatory action is required.

This procedure is considered fulfilled.

III. INTRODUCTION

The MAH has submitted the final paediatric study report of **study APV20003** for Telzir (fosamprenavir), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. The study has not been conducted in accordance with an agreed paediatric investigation plan.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study do(es) not influence the benefit risk for Telzir and that there is no consequential regulatory action.

Telzir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, adolescents and **children of 6 years and above** in combination with other antiretroviral medicinal products.

Telzir oral suspension is the recommended option for the most accurate dosing in children based on body weight.
In paediatric patients, the oral suspension should be taken **with food** in order to aid palatability and assist compliance.
The recommended dose is **18 mg/kg of fosamprenavir** (0.36 ml/kg) **twice daily** [maximum of 700 mg or 14 ml] together with **3 mg/kg of ritonavir twice daily**.
The adult dose of Telzir tablet 700 mg twice daily with ritonavir 100 mg twice daily may be used in children weighing at least 39 kg and able to swallow tablets.

Study APV20003 was aimed to explore the FPV/RTV once daily regimen in paediatric patients aged 2 to 18 years. The FPV/RTV QD regimen is currently not approved in the UE and the applicant does not intend to seek authorisation for a QD regimen of FPV/RTV. Therefore, the data derived from study APV20003 are regarded as simply informative. Moreover, the 48-week results of study APV20003 were already assessed by the CHMP in the setting of Telzir II18 variation for the extension of indication of Telzir to paediatric patients.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Telzir tablets and oral suspension were used in the APV20003 study.

IV.2 Clinical aspects

1. Introduction

As a reminder, to support the extension of indication of Telzir to paediatric patients (Telzir II18), the applicant submitted the reports for two ongoing studies:

Study APV29005 (which was regarded as pivotal) evaluating the **FPV BID** regimen in PI-naïve patients aged 2 to <6 years old and the **FPV/RTV BID** regimen in PI-naïve and PI-experienced patients 2 to 18 years old. The report for week 24 data was submitted.

Study APV20003 (which was regarded as supportive) evaluating the **FPV/RTV QD** regimens in PI-naïve and PI-experienced patients aged 2 to 18 years old. After a protocol amendment, PI-experienced patients were allowed to switch to a **FPV/RTV BID** regimen. The report for week 48 data was submitted.

In both studies APV29005 and APV20003, subjects that successfully completed 48 weeks of therapy will continue to receive FPV until approved for use in paediatrics and local supplies are available.

Moreover, the safety, tolerability, pharmacokinetics, and antiviral activity of FPV ± RTV dosing in paediatric subjects 6 weeks to <2 years of age is being studied in protocol APV20002.

Whereas the final study report for study APV20003 has just been submitted, the final study report for studies APV290005 and APV20002 are planned to be submitted by Q1 2014 (see table below).

Product Name: Telzir Active substance: fosamprenavir calcium

Study title	Study number	Planned Date of completion	Planned Date of submission of final study report
A 48 Week, Phase II, Non-Comparative, Open-Label, Multi-Cohort, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of GW433908/Ritonavir BID when Administered to HIV-1 Infected, PI-naive and Experienced, Pediatric Subjects, 2 to 18 Years Old and of GW433908 BID Administered to PI-naive, Pediatric Subjects 2 to <6 Years Old	APV29005	Q3 2013	Q1 2014
A 48 Week Phase II, Open-label, 2-cohort, Multicenter Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of GW433908 and GW433908/RTV When Administered to HIV-1 Infected Protease Inhibitor (PI) Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years.	APV20002	Q3 2013	Q1 2014

Rapporteur's comment:
Whereas the 24-week report for study APV290005 was submitted by Q4 2006, the 48-week final study report is only planned to be submitted by Q1 2014. The Rapporteur would like the applicant to discuss the reasons for such a long period between both submissions.

2. Clinical study

Design

<table>
<tr><td>Title</td><td>A 48 Week, Phase II, Open-label, Multi-Cohort, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Fosamprenavir/Ritonavir QD and Fosamprenavir/Ritonavir BID when Administered to HIV-1 Infected, Antiretroviral I and Experienced, Pediatric Subjects 2 to 18 Years Old</td></tr>
<tr><td>Phase</td><td>2</td></tr>
<tr><td>Study centers</td><td>38 centers in North America and Europe: 13 in the United States, 9 in Spain, 8 in Italy, 3 in Portugal, 2 in Canada, 2 in Romania, and 1 in Netherlands.</td></tr>
<tr><td>Study period</td><td>Initiation Date: 12-Jul-2002
Completion Date: 14-Oct-2008
Date of Report: April 2009</td></tr>
<tr><td>Study objectives</td><td><u>Primary</u>
• To evaluate the safety and tolerability of FPV/RTV given once daily in combination with NRTI therapy for 48 weeks in HIV-1 infected, antiretroviral therapy (ART)-naïve and experienced, paediatric subjects 2 to ≤ 18 years of age
• To characterize plasma APV PK following administration of FPV/RTV once daily and twice daily to paediatric subjects 2 to ≤ 18 years of age

<u>Secondary</u>
• To assess whether FPV has systemic exposure when administered to HIV-1 infected paediatric subjects 2 to ≤18 years of age
• To characterize plasma RTV PK following administration of FPV/RTV once daily and BID to pediatric subjects 2 to ≤18 years of age
• To investigate the relationship of plasma APV PK to changes in plasma HIV-1 RNA concentrations, CD4+ cell counts and to the occurrence of adverse events (Aes)
• To assess viral resistance patterns and to compare these patterns with treatment outcome
• To assess subject adherence, shaking of FPV oral suspension, and parent/guardian perceptions of study medications
• To evaluate the antiviral activity and immunologic activity of FPV/RTV administered once daily in combination with NRTI therapy for 48 weeks in HIV-1 infected, ART-naïve and experienced, paediatric subjects 2 to ≤ 18 years of age
• To evaluate the safety, tolerability, antiviral activity, immunologic response and adherence of subjects who switch to a FPV/RTV BID regimen after initially receiving a FPV/RTV QD regimen</td></tr>
<tr><td>Study subjects</td><td>Subjects were either ART-naïve or ART-experienced, aged 2 to ≤ 18 years with screening HIV-1 RNA ≥ 400 copies/mL.</td></tr>
<tr><td>Number of subjects</td><td>A total of 69 subjects were enrolled and received FPV/RTV once daily, 10 of whom switched to receive FPV/RTV on a BID basis during the study.</td></tr>
<tr><td>Study design</td><td>Subjects were assigned to a cohort based on age. Once enrolment in cohorts 1, 2 or 3 was complete, further subjects in that age range were to enrol in Cohort 4.
<table>
<tr><th>Cohort</th><th>Age</th><th>Planned number of patients FPV/RTV QD</th></tr>
<tr><td>1</td><td>2 to < 6 years</td><td>16</td></tr>
<tr><td>2</td><td>6 to < 12 years</td><td>12</td></tr>
<tr><td>3</td><td>12 to 18 years</td><td>10</td></tr>
<tr><td>4</td><td>2 to 18 years</td><td>24</td></tr>
</table>
Subjects that successfully completed 48 weeks of therapy in APV20003 continued to receive FPV until commercial supplies of FPV became available locally.</td></tr>
<tr><td>Study drug administration</td><td>Subjects were given FPV and RTV as investigational products to be used with a background regimen of two active NRTIs. FPV was administered as either oral 700</td></tr>
</table>

and dosing	mg tablets or 50 mg/mL oral suspension. RTV was given as either 100 mg capsules or as 80 mg/mL oral solution. The FPV oral suspension and RTV oral solution were recommended to be administered with food to improve tolerability by masking taste. ART-naïve or ART-experienced paediatric subjects, 2 to ≤18 years of age (Cohorts 1, 2 and 3), began multiple dosing with **FPV 30mg/kg + RTV 6mg/kg QD** on Day 1, had a Week 4 PK profile over 24 hours (at 0, 1, 2, 4, 8, 12, and 24 hours post dosing) and had additional PK trough sampling at Weeks 8, 12, 24 and 48. The plasma PK samples collected on Week 4 were analysed for APV concentrations to confirm target plasma APV exposure was achieved. Based on the Week 4 plasma APV PK data from at least 6 subjects who receive the FPV oral suspension, the dose of the FPV oral suspension was to be adjusted for all subjects in the cohort. Subjects in Cohort 4 did not provide a PK profile at Week 4 but underwent PK trough sampling at Weeks 4, 8, 12, 24 and 48. The pivotal adult clinical trial APV30003, where both FPV/RTV QD and BID were evaluated in PI-experienced patients, demonstrated that FPV/RTV BID had similar efficacy to LPV/RTV BID whereas there was a lower rate of antiviral activity with the once daily regimen. Subsequently, **the protocol of study APV20003 was amended to allow PI-experienced subjects to switch from an FPV/RTV QD regimen to an FPV/RTV BID regimen**. Additionally, further enrollment in the study was limited to PI-naïve subjects. The FPV/RTV BID regimens implemented were based on preliminary plasma APV PK data available for the FPV/RTV QD regimens in these paediatric subjects: - Because plasma APV exposures achieved in 6 to 18 year old subjects receiving the FPV/RTV 30/6mg/kg QD regimen appeared to be similar to historical adult data for FPV/RTV 1400/200mg QD, an **FPV/RTV 15/3mg/kg BID regimen was implemented for subjects 6 to 18 years of age**. - Because plasma APV exposures achieved in 2 to 5 year old subjects receiving the FPV/RTV 30/6mg/kg QD regimen appeared to be approximately 25% lower compared to historical adult data for FPV/RTV 1400/200mg QD, **an FPV/RTV 20/4mg/kg BID regimen was implemented for subjects 2 to 5 years of age**. - Subjects receiving FPV/RTV 1400/200mg QD were switched to the standard adult dosage regimen of FPV/RTV 700/100mg BID.
Efficacy analyses	For endpoints using continuous viral load and CD4+ cell count data, the **'observed' analysis** was used in which all non-missing data up to a visit was used to calculate the summary data for that particular visit. This method was used for the analysis of changes from baseline. For proportions, endpoint using viral load data a time to loss of virologic response **(TLOVR) analysis** was used. For this analysis, positive responders were those who had a confirmed plasma HIV-1 RNA response <400 copies/mL below baseline prior to the visit of interest, but without having experienced treatment failure. **Treatment failure** was defined as the first of the following events: confirmed plasma HIV-1 RNA above 400 copies/mL, permanent discontinuation of study drug or death. Only descriptive summaries of antiviral efficacy data were produced and no statistical testing was performed.
PK analyses	Plasma APV PK parameter including C_{max}, t_{max}, AUC(0-τ), Cavg (=AUC(0-τ)/τ) CL/F, t1/2 were calculated using non-compartmental methods.
Sample size	No power calculations were performed in order to derive the total sample size. Recruitment of 62 subjects was considered an appropriate number, balancing recruitment of sufficient subjects to obtain robust information on the safety and

	tolerability following administration of FPV/RTV once daily. Of these 62 subjects, 38 were planned to enrol in Cohorts 1, 2, and 3 and have a PK profile at Week 4 in order to obtain full PK profiles from 26 evaluable subjects. Based on plasma APV PK data from previous FPV studies, the highest variability was observed for the FPV suspension formulation in APV10008, where the inter-subject standard deviation (SD) of loge(AUC) was 0.42. Assuming this inter-subject SD, based on a two-side procedure with α=0.5 on log scale, and a sample size of 26 subjects, the width of the 95% confidence interval (CI) for plasma APV area under the concentration versus time curve during a dosing interval (AUC(0-τ)) would be 34% around the point estimate (geometric mean).

Results

Study population

Disposition of subjects

A total of 69 subjects were enrolled and received FPV/RTV once daily. Among them, 32 were PI-naïve and 37 were PI-experienced.

Of importance, 10 patients switched to receive FPV/RTV BID, after the protocol amendment.

Table 5 Summary of Subject Disposition

	FPV/RTV (N=69)
Completed, n(%)	16 (23)
Prematurely discontinued, n(%)	53 (77)
Reason for Discontinuation, n (%)	
Adverse event	12 (17)
Insufficient viral load response	9 (13)
Insufficient CD4 response	1 (1)
Lost to follow-up	4 (6)
Protocol violation	2 (3)
Subject decided to withdraw	7 (10)
Disease progression	0
Other	18 (26%)

Rapporteur's comment:
Fifty-three (77%) subjects discontinued study drug prematurely. The applicant underlined that this relatively high discontinuation rate could be related to the extended duration of the study (through Week 168). However, a high rate of discontinuation was already observed by Week 48 (43%). Overall, the high rate of discontinuation observed in this trial will impair the interpretation of data.

Table 43 Overview of Enrollment by Cohort and Formulation

Cohort	No. Subjects Enrolled	No. Subjects Received FPV Oral Suspension	No. Subjects Received FPV Tablets	No. Subjects Switched to FPV/RTV BID
Cohort 1 (2 to <6 years)	17	17	0	6
Cohort 2 (6 to <12 years)	16	16	0	3
Cohort 3 (12 to 18 years)	10	5	5	0
Cohort 4 (2 to 18 years)	26	7	19	1
Total	69	45 (65%)	24 (35%)	10

Demographic and other baseline characteristics

Among the 69 patients enrolled 57% were female and 43% were male; 51% were White/Caucasian, 35% were Black and 12% were American Hispanic.

Table 9 Summary of Demographic Characteristics for APV20003, ITT(E) Population

	FPV/RTV N=69
Age (years)	
Mean	10.2
Min, Max	2, 17
Sex, n (%)	
Female	39 (57)
Male	30 (43)
Race, n (%)	
White/Caucasian	35 (51)
Black[1]	24 (35)
African Heritage, n	7
African American, n	11
East & South East Asian	1(1)
American Hispanic	8 (12)
Other[2]	1 (1)
Median Weight, kg (range)	33.8 (11.2, 90.5)
Median Height, cm (range)	142 (79.8, 180.3)

Source Data: Table 6.11, Table 6.33 and Table 8.79

1. Six black subjects did not identify a sub-race category.
2. "Other"= African Heritage

30/69 patients (43%) were non or mildly symptomatic according CDC classification. 5 (7%) patients was Hepatitis B positive and 1 patient was Hepatitis C positive. The mode of contamination was mostly by vertical transmission (81%).

Table 12 Distribution of Plasma HIV-1 RNA Values and CD4+ Cell Counts at Baseline for APV20003 ITT(E) Population

	2-5 Years N=17	6-11 Years N=17	12-18 Years N=35	FPV/RTV N=69
Baseline HIV-1 RNA				
Median plasma HIV-1 RNA log_{10} copies/mL, (IQR)	4.8 (4.3, 5.2)	4.8 (4.3, 5.2)	4.9 (4.2, 5.3)	4.8 (4.3, 5.2)
HIV-1 RNA copies/mL, n (%)				
<400	1 (6)	0	1 (3)	2 (3)
400 – <5000	2 (12)	1 (6)	3 (9)	6 (9)
5000 – <100,000	8 (47)	10 (59)	16 (46)	34 (49)
100,000 – <250,000	2 (12)	3 (18)	10 (29)	15 (22)
250,000 – <500,000	1 (6)	2 (12)	2 (6)	5 (7)
≥500,000	3 (18)	1 (6)	3 (9)	7 (10)
Baseline CD4+ cell counts (absolute)				
Median CD4+ cells/mm^3 (IQR)	850 (680,1220)	440 (300, 710)	315 (200, 400)	390 (280, 710)
CD4+ cells/mm^3, n (%)				
<100	0	0	4 (13)	4 (6)
100 – <200	0	1(7)	4 (13)	5 (8)
200 – <350	1(6)	4 (27)	12 (38)	17 (27)
350 – <500	3 (18)	4 (27)	7 (22)	14 (22)
≥ 500	13 (76)	6 (40)	5 (16)	24 (38)
Baseline % CD4+ cells				
Median % CD4+ cells (IQR)	27 (16, 33)	27 (11, 28)	19 (12, 22)	21 (14, 28)
% CD4+ cells, n (%)				
<15	2 (12)	5 (29)	12 (34)	19 (28)
15 – <25	4 (24)	3 (18)	17 (49)	24 (35)
≥25	11 (65)	9 (53)	6 (17)	26 (38)

Of note, baseline plasma HIV-1 RNA levels, median CD4+ cell counts and CD4+ percentages were similar among PI-naïve and PI-experienced groups.

Previous medications

78% (54/69) of patients were ART-experienced, whereas 22% (15/69) of patients were ART-naïve.
The PI-experienced enrolled population had a higher number of prior NRTIs and NNRTIs exposures.
59% of PI experienced patients have previously received 1 PI, 30% have received 2 PIs and only 11% were pre-treated with 3 PIs.
The most commonly previously administered PIs were nelfinavir (59%), ritonavir (41%), indinavir (27%) and lopinavir/ritonavir (11%).

Table 7 Summary of Recruitment by Cohort and PI Status

Cohort[1]	Cohort	PI-naïve (N=32)	PI-experience (N=37)	Total (N=69)
1	2 to <6 years	6 (19)	11 (30)	17 (25)
2	6 to <12 years	6 (19)	10 (27)	16 (23)
3	12 to 18 years	4 (13)	6 (16)	10 (14)
4[2]	2 to 18 years	16 (50)	10 (27)	26 (38)

NRTI initial combinations

Per protocol, all ART-naïve subjects were to receive the abacavir/lamivudine NRTI combination and ART-experienced subjects were to optimize their background NRTIs based on screening resistance results.

The most frequent NRTI therapies received were lamivudine (68%) and abacavir (64%), followed by didanosine (32%), stavudine (29%) and zidovudine (16%).

Efficacy results

Antiviral response

ITT(E) Population (Observed Analysis)

Table 19 Median Change from Baseline HIV-1 RNA (log_{10} copies/mL) by Visit and PI status in APV20003 ITT(E) Population (Observed Analysis)

	HIV-1 RNA Change from Baseline (log_{10} copies/mL) Median [IQR]			
Week	PI-Naive N=32	n	PI-experienced N=37	n
Week 12	-2.85 [-3.12, -2.54]	26	-2.03 [-3.02, -0.64]	32
Week 48	-2.65 [-3.31, -1.44]	21	-1.65 [-2.76, -1.02]	29
Week 96	-2.52 [-3.14, -1.42]	20	-1.76 [-2.91, -0.57]	15
Week 156	-2.65 [-3.49, -1.27]	15	-2.51 [-3.10, -0.92]	14
Week 168	-2.88 [-3.49, -2.15]	13	-2.39 [-3.13, -0.94]	13

Proportion Analysis of ITT(E) Population (Time to Loss of Virologic Response [TLOVR] and Observed Analysis)

Table 21 Summary of Proportion of Subjects with Plasma HIV-1 RNA <400 copies/mL in APV20003 ITT(E) Population (TLOVR)

Actual Relative Time	PI-naïve N=32 n/N (%)	PI-experienced N=37 n/N (%)	Total N=69 n/N (%)
Baseline	1 / 32 (3)	1 / 37 (3)	2 / 69 (3)
Week 12	22 / 32 (69)	20 / 37 (54)	42 / 69 (61)
Week 24	21 / 32 (66)	21 / 37 (57)	42 / 69 (61)
Week 48	16 / 32 (50)	16 / 37 (43)	32 / 69 (46)
Week 72	14 / 32 (44)	11 / 37 (30)	25 / 69 (36)
Week 96	13 / 32 (41)	11 / 37 (30)	24 / 69 (35)
Week 120	12 / 32 (38)	9 / 37 (24)	21 / 69 (30)
Week 144	11 / 32 (34)	8 / 37 (22)	19 / 69 (28)
Week 168	11 / 32 (34)	7 / 37 (19)	18 / 69 (26)

Rapporteur's comment:
The rate of responders is quite low in this population of paediatric patients receiving the QD regimen of FPV/RTV.

The major reason for virologic failure in the PI-naïve and PI-experienced study population was due to a plasma HIV-1 rebound.

Table 22 Summary of Study Outcomes at Week 168 in APV20003 ITT(E) Population (TLOVR) by PI Status (<400 copies/mL)

Outcome	PI-naive N=32 n (%)	PI-experienced N=37 n (%)	Total N=69 n (%)
Responder	11 (34)	7 (19)	18 (26)
Nonresponder			
Virological failure	11 (34)	16 (43)	27 (39)
Plasma HIV-1 RNA rebound	10 (31)	10 (27)	20 (29)
Prem. disc. due to insufficient VL response	0	4 (11)	4 (6)
Never achieved VL suppression by Week 168	1 (3)	2 (5)	3 (4)
Discontinued study drug before achieving suppression	5 (16)	9 (24)	14 (20)
Other	1 (3)	6 (16)	7 (10)
Adverse event	3 (9)	2 (5)	5 (7)
Consent withdrawn	1 (3)	1 (3)	2 (3)
Discontinued study drug while suppressed	5 (16)	5 (14)	10 (14)
Adverse event	1 (3)	4 (11)	5 (7)
Other	2 (6)	1 (3)	3 (4)
Consent withdrawn	1 (3)	0	1 (1)
Protocol violation	1 (3)	0	1 (1)

Table 23 Summary of Proportion of Subjects with Plasma HIV-1 RNA <50copies/mL in APV20003 ITT(E) Population (TLOVR)

Week	PI-naïve N=32 n/N (%)	PI-experienced N=37 n/N (%)	Total N=69 n/N (%)
Baseline	0/32	0/37	0/69
Week 12	15/32 (47)	13/37 (35)	28/69 (41)
Week 24	16/32 (50)	15/37(41)	31/69 (45)
Week 48	14/32 (44)	13/37 (35)	27/69 (39)
Week 72	11/32 (34)	8/37 (22)	19/69 (28)
Week 96	11/32 (34)	8/37 (22)	19/69 (28)
Week 120	11/32(34)	8/37 (22)	19/69 (28)
Week 144	11/32 (34)	8/37 (22)	19/69 (28)
Week 168	11/32 (34)	8/37 (22)	19/69 (28)

Rapporteur's comment:
Apparently, there should be a mistake in the table for the PI-experienced patients with 8/37 of patients with VL<50 cp/mL whereas 7/37 of patients had VL<400 cp/mL in table 21.

Subgroup analyses

Antiviral response by age

Table 37 Summary of Proportion of Subjects with Plasma HIV-1 RNA Less Than 400 copies/mL in APV20003 ITT(E) Population by Age Group and Visit (TLOVR)

Actual Relative Time	2 - 5 Years (N=17) n/N (%)	6 - 11 Years (N=17) n/N (%)	12 - 18 Years (N=35) n/N (%)
Baseline	1 / 17 (6)	0 / 17	1 / 35 (3)
Week 12	15 / 17 (88)	7 / 17 (41)	20 / 35 (57)
Week 24	15 / 17 (88)	9 / 17 (53)	18 / 35 (51)
Week 48	11 / 17 (65)	8 / 17 (47)	13 / 35 (37)
Week 72	9 / 17 (53)	5 / 17 (29)	11 / 35 (31)
Week 96	9 / 17 (53)	5 / 17 (29)	10 / 35 (29)
Week 120	8 / 17 (47)	5 / 17 (29)	8 / 35 (23)
Week 144	7 / 17 (41)	5 / 17 (29)	7 / 35 (20)
Week 168	7 / 17 (41)	4 / 17 (24)	7 / 35 (20)

The response rates varied across the groups by age and by PI experience (see table below). When considering antiviral response by age and the cohort sample sizes, the differences in baseline resistance profile and treatment experience should be taken into account as previously explored in Week 48 analysis report for APV20003. Indeed, **a greater proportion of subjects in the 12 to 18 year group had >3 reverse transcriptase (RT) mutations (43%)** when compared to the other cohorts (23% and 13% for 2 to 5 and 6 to 11 year age groups, respectively).

Table 38 Proportion of Subjects with Quantitative Plasma HIV-1 RNA <400copies/mL by Visit, Age Group, and PI Status at Entry (TLOVR)

Actual Relative Time	2-5 Years		6-11 Years		12-18 Years	
	PI-naïve N=6 n/N	PI-experienced N=11 n/N	PI-naïve N=7 n/N	PI-experienced N=10 n/N	PI-naïve N=19 n/N	PI-experienced N=16 n/N
Baseline	0/6	1/11	0/7	0/10	1/19	0/16
Week 12	5/6	10/11	4/7	3/10	13/19	7/16
Week 24	5/6	10/11	5/7	4/10	11/19	7/16
Week 48	3/6	8/11	5/7	3/10	8/19	5/16
Week 72	3/6	6/11	4/7	1/10	7/19	4/16
Week 96	3/6	6/11	4/7	1/10	6/19	4/16
Week 120	3/6	5/11	4/7	1/10	5/19	3/16
Week 144	3/6	4/11	4/7	1/10	4/19	3/16
Week 168	3/6	4/11	4/7	0/10	4/19	3/16

The 2 to 5 years of age group consistently demonstrates the greatest response to FPV/RTV regimen.

Rapporteur's comment:
This trend of a lower rate of responders in the older children was already underlined by the Rapporteur during the assessment of the 48-week data and was related to the accumulation of resistance with longer treatment exposure.

Antiviral response by gender and by race
No apparent differences in antiviral response for race or gender were observed, although the number of subjects in each subgroup was small.

Safety results

Treatment emergent AEs

Adverse Events Regardless of Causality

Ninety-six percent (66/69) of subjects reported at least one AE. The most common AEs were vomiting (41%), diarrhea (26%), headache (26%), upper respiratory tract infection (25%), nausea (23%), and cough (23%).

There were no apparent differences in overall AE frequency for age group, gender or race at entry.

This overall AE pattern is similar to that reported in the Week 48 report (cut-off date 16 February 2005).

Rash was reported in 23% of subjects, and described under a variety of terms. The majority of these treatment emergent rash AEs were of Grade 1 intensity.

Treatment Emergent Adverse Events Attributable to Study Drug

Fifty-seven percent (57%, 39/69) of subjects reported at least one drug-related AE. The most common drug-related AEs reported were vomiting (26%, 18/69), nausea (20%, 14/69), and diarrhea (12%, 8/69).

Subjects in the 6 to 11 year old age group reported fewer drug-related AEs (29%, 5/17) than subjects in the 2 to 5 year old (71%, 12/17) or 12 to 18 year old (63%, 22/35) age groups, although the numbers in each group are small. This is a similar pattern to that described in the Week 48 report.

Serious AEs

There were no fatal events reported in this study.

SAEs occurring in more than one subject were drug hypersensitivity (4%, 3/69), measles (3%, 2/69) and pyrexia (3%, 2/69).

Four of the SAEs were considered by the investigator to be drug-related comprising blood alkaline phosphatase increased, Benign salivary gland neoplasm, hemoptysis and hyperglycemia.

AEs leading to discontinuation

Twelve subjects (17%, 12/69) (2 to 5 years: n=3; 6 to 11 years: n=2, 12 to 18 years: n=7) reported an AE leading to permanent discontinuation of study drug and withdrawal from the study. Of these 12, two are new withdrawals since the Week 48 report. Events included vomiting (3), nausea (3), stomach discomfort (1), hyperglycemia (1), hypertriglyceridemia (1), Hodgkin's disease (1), elevated blood alkaline phosphatase (1), elevated eosinophil count (1) and hemoptysis (1).

Clinical laboratory evaluations

Overall, the incidence of treatment-emergent Grade 3-4 clinical chemistry laboratory abnormalities was low (9%, 6/66), and represented increases in liver transaminases and triglycerides

Overall, there were median increases in triglycerides, total cholesterol, HDL and LDL through Week 168. Of these parameters, only one subject experienced a Grade 3 laboratory abnormality of elevated triglycerides.

Rapporteur's comment:
No new safety signals have emerged since the Week 48 report

Pharmacokinetic results

The PK results were assessed in the setting of Telzir II-18 variation and will not be detailed in the present report.

In the Telzir II-18 AR, it was concluded that:
- When children 2-12 years old were treated with 30/6 mg/kg FPV/RTV QD, underdosing of approximately 30% occurred.
- For adolescents treated with 1400/200 mg single tablet dose, similar AUCs were achieved as the adult reference population but Ctrough were 30% lower than in adults (the sample size was limited to 3 patients).

Viral genotyping and phenotyping results

Post-Week 48 genotypes are available for twelve subjects and post-Week 48 phenotypes are available for eleven subjects.

Mutations in Reverse Transcriptase
Twelve subjects have genotypes post-Week 48 available.
Of these 12 subjects, three have post-Week 48 RT genotypes identical to what was observed at Week 48.

Table 64 Genotypic Analysis; Mutations in Reverse Transcriptase (RT)

Week	RT Mutations
Day 1	*K103K/N*
Week 24	*K103K/N*
Week 60	M184V
Day 1	
Week 72	G190A
Day 1	*K103N, L100I/L,L210W, M41L/M, V108I/V*
Week 8	*K103N, L210W, M41L/M, V108I*
Week 24	*K103N, L210W, M41L/M, V108I/V*
Week 48	K103N, L1210W, V108I
Week 204	L210W
Day 1	*L210L/R/W, m184V, T215Y*
Week 24	*L210L/R/W, M184M/V, T215Y, V106A/V*
Week 48	L210LR/W, T215Y
Week 96	L210L/R/W, T215Y
Day 1	
Week 84	
Week 132	
Week 180	
Day 1	
Week 48	
Week 108	
Week 120	
Week 156	
Week 180	
Day 1	
Week 60	K103K/N
Week 96	K103N, M184V
Week 108	D67D/N, K103N, M184V
Week 144	K103N, M184V
Week 156	K103N, M184V
Day 1	
Week 96	
Day 1	
Week 4	*M184V, M41L, T215Y*
Week 24	*M184V, M41L, T215Y*
Week 240	M184V, M41L, T215Y

Week	RT Mutations
Week 252	M184V, M41L, T215Y
Day 1	
Week 84	K70R, M184V
Day 1	
Week 48	A62V, K103N, L100I, M184V, T215F
Week 96	A62V, K103N, L100I/I, M184V, T215F
Day 1	*D67D/N, K103N, K70R, L100I*
Week 48	D67N, K103N, K70R, L100I, M184V
Week 180	D67D/N, K103N, L100I, L74L/V, M184V, V75G/I/S/V, Y115F

Mutations in Protease

Twelve subjects have genotypes post-Week 48 available.
None of the subjects with Week 48 genotypes had protease (PRO) resistance mutations post-Week 48 that were identical to the PRO resistance mutations observed at Week 48.

Table 65 Genotypic Analysis; Mutations in Protease (PRO)

Time	PRO Mutations[a]
Day 1	*G16E/G, V77I*
Week 24	*G16E/G, I93I/M, V77I*
Week 60	G16E/G, V77I
Week 72	I62V, L10I/L, L63P
Day 1	*I93L, K20K/R, L63L/P, **L90L/M**, V77I*
Week 8	*I93L, K20K/R, L10I/L, L63L/P, **L90L/M**, V77I*
Week 24	*I93L, K20K/R, I63L/P, **L90L/M**, V77I*
Week 48	I93L, K20K/R, L63L/P, **L90L/M**, V77I
Week 204	I93L, K20R, L63L/P, V77I
Day 1	*G16E/G, K20R, M36I*
Week 24	*G16E, K20R, L10L/V, M36I*
Week 48	G16E, **I54I/L**, K20R, L10L/ V, **L33F/L**, M36I
Week 96	G16E, **I54L**, K20R, L10V, **L33F**, M36I
Day 1	
Week 84	G16E, M36I/M, V77I
Week 132	G16E, M36I/M, V77I
Week 180	G16E, M36I/M, V77I/V
Day 1	*I64I/M, L63F/L/P/S*
Week 48	
Week 108	I13I/V, L10I/L
Week 120	I13V
Week 156	G16E/G, I13V
Week 180	I13V
Day 1	*I93L, L63P*
Week 60	I93L, L63P
Week 96	I93L, L63P
Week 108	I93L, L63P
Week 144	I93L, L63P, M36I/M
Week 156	I93L, L63P, M36I/M
Day 1	
Week 96	I13V, L63P
Day 1	
Week 240	G16E, I13V, **I54L**, **I84V**, K20R, K43T, L10V, **L33F**, **V32I**
Week 252	G16E, I13V, **I54L**, **I84V**, K20R, K43K/T, L10V, **L33F**, **V32I**
Day 1	

Time	PRO Mutations[a]
Week 84	A71T, L63P, V77I/V
Day 1	
Week 48	**I54L**, I62V, **I84V**, I93L, L10F/L, V77I
Week 96	D60D/E, **I54L**, I62V, **I84V**, I93L, L10F, **L33F**, V77I
Day 1	*D60E, H69K, I13V, I62I/V, L10I, **L90M**, M36I*
Week 48	D60E, H69K, I13V, **L10I**, **L90M**, M36I
Week 180	D60E, G16A/E, H69K, L10I/V, M36I

Phenotypic analysis for NRTIs

Eleven subjects have phenotypes post-Week 48 available.

- Two subjects had ABC FC above the clinical cut-off (4.5 FC ABC).
- Five subjects had 3TC FC above the clinical cut-off (3.5 FC 3TC).
- Three subjects had ddI FC above the cut-off (1.3 FC ddI).
- Two subjects had d4T FC above the cut-off (1.7 FC d4T).

Six of eight subjects with NRTI-associated resistance mutations post-Week 48 had phenotypic resistance above the cutoff to ABC, 3TC, ddI and/or d4T

Phenotypic analysis for amprenavir

Eleven subjects have APV phenotypes post-Week 48 available.
Of these eleven subjects, only subjects and had APV FC above the clinical cut-off for APV (cut-off FC = 4).
Subject had primary PRO resistance mutations I54L and L33F; Subject had primary PRO resistance mutations I54L, I84V, L33F and V32I. Neither subject was PI-experienced prior to entering the study and these mutations were not present in either subject at Day 1.

Relationship of genotypic and phenotypic results to virologic response
Eight of the 12 subjects had NRTI associated resistance mutations post Week 48 and all twelve subjects had PRO mutations post Week 48. Two of these 12 subjects never achieved virologic suppression by Week 48; the remaining subjects exhibited plasma HIV-1 RNA rebound. Change from baseline varied from +0.09 (Subject at Week 204) to -2.48 (subject at Week 60) log10 copies/mL HIV-1 RNA.

Of the eleven subjects with APV phenotypes post Week 48, only subjects and had APV FC above the clinical cut-off for APV. Subject had APV FC and d4T FC above the cut-off at week 96. This subject had 3.96 log10 copies/mL HIV-1 RNA at Week 96 (-1.02 log10 copies/mL change from baseline). Subject had APV, ABC, 3TC, ddI and d4T FCs above the cut-offs for each individual drug at Week 252. This subject had 3.46 log10 copies/mL HIV-1 RNA at Week 252 (-1.12 log10 copies/mL change from baseline).

Rapporteur's comment:
There is no relevant finding regarding the emergence of genotypic/phenotypic resistance.

3. Discussion on clinical aspects

The applicant discussed the results from study APV20003 in view of those derived from other paediatric studies.

Twice daily LPV/RTV fixed dose combination liquid formulation was examined in 100 ART-naïve and experienced subjects (aged 6 months to 12 years) in combination with 2 NRTIs. At Week 48, 84% (37/44) of the ART naïve subjects and 75% (42/56) of ART-experienced subjects had HIV-1 RNA <400 copies/mL (ITT M=F) with a response rate of 58% in the 24 PI-experienced children [Saez-Llorens et al, Pediatric Infect Dis J 2003; 22:216-23.].
The poor performance of FPV/RTV in this study over 168 Weeks may be partially attributable to the up front use of FPV/RTV once daily in this population, as this regimen has been shown to be inferior to LPV/RTV in treatment experienced adults in APV30003. Of note, higher treatment response rates were seen when FPV/RTV was given twice daily in APV29005: 70% (19/27) of PI-naïve and 57% (17/30) of PI-experienced subjects were responders by TLOVR (<400 copies/mL) through 24 Weeks in that study.
Given the higher antiviral response rates seen with FPV/RTV in APV29005, FPV/RTV given twice daily is currently recommended for children aged 6 and above.

Rapporteur's comment:
As previously observed in adult patients, the once daily regimen of FPV/RTV is not optimal to achieve virologic suppression in paediatric patients.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

Telzir in combination with low dose ritonavir is currently indicated **children from 6 years of age as a BID regimen as for adult patients.**

Study APV20003 was aimed to explore the FPV/RTV **once daily regimen** in paediatric patients aged **2 to 18 years.** The FPV/RTV QD regimen is currently not approved in the UE and the applicant does not intend to seek authorisation for a QD regimen of FPV/RTV. Therefore, the data derived from study APV20003 are regarded as simply informative.

The 48-week results of study APV20003 were already assessed by the CHMP in the setting of Telzir II18 variation for the extension of indication of Telzir to paediatric patients and the 168-week data currently submitted did not reveal any new relevant finding as regards efficacy or safety.

As a matter of fact, the results of this study were hampered by a **very high rate of discontinuation (77%).** Overall, this study in paediatric patients to some extent reinforces the previous assertion derived from adult patients that the once daily regimen of fosamprenavir/ritonavir is not optimal to achieve virologic suppression.

Additional data on the use of FPV/RTV in paediatric patients are awaited from studies APV20002 (for patients aged 6 weeks to <2 years of age) and APV29005 (for patients aged 2 to 18 years).

In this setting, the Rapporteur would like to be updated by the applicant on the planned dates of submission for these both studies. Indeed, **whereas the 24-week report for study APV290005 was submitted by Q4 2006, the 48-week final study report is only planned to be submitted by Q1 2014. The Rapporteur would like the applicant to discuss the reasons for such a long period between both submissions.** All the more that additional data for paediatric patients derived from both studies are awaited for 31 December 2009 according to the letter of undertakings dated 19 July 2007.

The applicant could provide his response to this request by a separate letter.

This procedure is considered as fulfilled.

- **Recommendation**

No further action required.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable.