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Product name: **Telzir**
Procedure No. **EMEA/H/C/000534/II/0018**

SCIENTIFIC DISCUSSION

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SCIENTIFIC DISCUSSION

1 Introduction

Telzir tablet and oral suspension contains fosamprenavir (FPV) which is the phosphate ester pro-drug of the protease inhibitor (PI) amprenavir (APV) and was developed to reduce the large pill burden and pill size associated with the amprenavir (Agenerase) soft gelatin capsule formulation. Telzir is approved for use in combination with low dose ritonavir (RTV) for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products. The recommended dose for adults is 700 mg twice daily, combined with 100 mg ritonavir twice daily.

At the time of approval of the initial Marketing Authorisation (MA) (indication for use of Telzir in adults; 12 July 2004), no paediatric data were available. The MAH had committed to provide paediatric data by 31 December 2006. The present variation was submitted to extend the indication to include the use of Telzir tablet and oral suspension in paediatric patients. Hence, this Type II variation was submitted to address the post-authorisation commitment undertaken by the MAH in their letter of undertaking dated 24 March 2004.

It is relevant to mention that Agenerase (amprenavir) is already approved in the EU for use in combination therapy for paediatric patients aged 4 years and above (dose 17 mg/kg oral solution three times daily). Because of the potential risk of toxicity from the large amount of the excipient, propylene glycol in Agenerase oral solution, it is contraindicated in infants and children below 4 years of age. Telzir oral suspension represents a significant improvement in that respect as it contains significantly lower concentrations of propylene glycol (10.2 mg/ml compared with 550 mg/ml); this extends the potential option of fosamprenavir treatment to children below the age of 4 years. In addition, the fosamprenavir oral suspension contains no Vitamin E (compared with 46 IU/ml for Agenerase) and is more concentrated (50 mg/ml compared with 15 mg/ml), reducing the volume required per dose.

The MAH performed three dose finding open Phase II studies (still ongoing) in paediatric patients of which 2 studies, namely Study APV29005 and Study APV20003, are considered most relevant for establishing the current dosing recommendation. In study APV29005, twice daily doses of fosamprenavir (with or without ritonavir) were administered to 75 children aged 2-18 years for 48-weeks. Dosing and analysis were performed by age groups (2-5, 6-11 and 12-18 years). In study APV20003, a once daily regimen was investigated in children aged 2-18 years, and in Study APV 20002, fosamprenavir oral solution + ritonavir were administered to 10 children aged < 2 years old. The MAH considered Study APV29005 as pivotal, and the other two studies (the one with the once daily regimen (APV20003) and the other in the very young (APV20002)) as supplementary.

Based on the study outcomes regarding safety and PK simulation data (compared to reference adult plasma levels), the MAH proposed the following posology for children:

- For children aged 2-5 years old: fosamprenavir/ritonavir 20/3 mg/kg twice daily
- For patients aged ≥ 6 years old: fosamprenavir/ritonavir 18/3 mg/kg twice daily, up to the standard adult fixed dose regimen of 700/100 mg twice daily for children and adolescents > 39 kg

As a reminder, for a 70 kg adult, the dose is 10 mg/kg fosamprenavir twice daily in combination with ritonavir 100mg twice daily.
Due to few participants in study APV20002 and insufficient plasma exposure achieved after even 4.5-fold higher doses/kg than in adults, no dosing recommendations could be made for the very young (children < 2 years old).

For this application the CPMP HIV guideline “Guideline on the clinical development of medicinal products for the treatment of HIV infection” is applicable (November 2005 CPMP/EWP/633/02, Rev. 1).

2 Non-Clinical

No new non-clinical data were submitted in support of this variation application. The juvenile toxicity studies submitted in the framework of the original Marketing Authorisation Application for Telzir and in the framework of post-marketing follow-up indicate that the safety profile of fosamprenavir in children ≥2 years of age is unlikely to be different to that seen in adult patients and support the safe clinical use of fosamprenavir in HIV-infected paediatric patients 2 to 18 years of age at the proposed recommend doses.

3 Clinical pharmacology – Pharmacokinetics

Due to the different dosage regimens employed within both studies (twice daily vs. once daily, boosted vs. unboosted, different mg/kg doses), evaluable plasma amprenavir pharmacokinetic (PK) data for fosamprenavir/ritonavir regimens in APV20003 and APV29005 are very limited; especially for the proposed twice daily regimen, only a very limited amount of plasma amprenavir data is presented (table 1).

Table 1 Number of 2 to 18 Year Old Subjects Contributing Plasma Amprenavir PK Data for Fosamprenavir Regimens

Fosamprenavir/ritonavir Regimens (N=106)[1]						
FPV/RTV BID	**PK Profile[2]**			**Cτ[2]**		
	6 to 11y		**12 to 18y**	**6 to 11y**		**12 to 18y**
FPV/RTV 15/3mg/kg BID	10		4	16		9
FPV/RTV 18/3mg/kg BID	9		0	17		2
FPV/RTV 700/100mg BID	3		8	4		24
FPV/RTV QD	**PK Profile**			**Cτ**		
	2 to 5y	**6 to 11y**	**12 to 18y**	**2 to 5y**	**6 to 11y**	**12 to 18y**
FPV/RTV 30/6mg/kg QD	10	10	3	15	15	10
FPV/RTV 1400/200mg QD	NA	0	3	NA	1	19

1. A total of 106 patients provided evaluable plasma APV PK data for FPV/RTV regimens in Studies APV20003 and APV29005; some patients provided data for more than one regimen.
2. For FPV/RTV 20/4mg/kg BID, one 5 year old and one 6 year old provided a PK profile and three 2 to 5year olds and one 6 year old patient provided Cτ data

Main Study APV29005

Study Design

Study APV29005 is a Phase II, open-label, 48-week study designed to evaluate plasma amprenavir pharmacokinetics, safety, and antiviral activity of fosamprenavir twice daily in HIV-1 infected, PI-naïve patients 2 to 5 years old and of fosamprenavir/ritonavir twice daily in PI-naïve and PI-experienced patients 2 to 18 years old. Subjects receiving fosamprenavir/ritonavir twice daily were enrolled into age-defined cohorts of 2 to 5 years, 6 to 11 years, and 12 to 18 years. At the time of submission, insufficient PK data in the 2 to 5 year old cohort was available; therefore, this group is not discussed within this report.

Subjects received concurrent NRTIs and patients older than 6 years of age could receive enfuvirtide; NNRTIs and other PIs were not allowed during the study. Subjects and/or their parents/legal guardians were instructed to administer the fosamprenavir oral suspension with food in order to accommodate the frequent eating schedule of children, to enhance adherence through taste masking with food, and to improve tolerability. For patients in each age cohort, serial PK sampling was conducted at Week 2 and trough sampling was conducted at all subsequent visits.

Pharmacokinetic Population

Seventy-five (75) patients were enrolled, 67 patients provided plasma amprenavir Cτ data and 51 patients provided full plasma amprenavir PK profiles.

Pharmacokinetic Results

Fosamprenavir/ritonavir twice daily in Patients 6 to 11 Years Old

Compared to the historical adult population receiving fosamprenavir/ritonavir 700/100mg twice daily, paediatric patients 6 to 11 years old, receiving fosamprenavir/ritonavir 15/3 mg/kg twice daily had 13% lower plasma amprenavir AUC(0-τ) and 23% lower Cmax values, but similar Cτ values; whereas, patients receiving fosamprenavir/ritonavir 18/3 mg/kg twice daily had 26% higher AUC(0-τ) and similar Cmax and Cτ values (table 2). Three 6 to 11 year old patients who weighed at least 39kg and received the adult tablet regimen of fosamprenavir/ritonavir 700/100mg twice daily had similar plasma amprenavir AUC(0-τ) and Cmax values, but 17% lower Cτ values compared to adult values (table 2).

Paediatric patients 6 to 11 years old who received fosamprenavir 15 mg/kg or fosamprenavir 18 mg/kg in combination with ritonavir 3 mg/kg twice daily had 51% higher plasma ritonavir AUC(0-τ), similar Cmax, and 2.58-fold higher Cτ values than observed in the historical adult population. Similarly, paediatric patients 6 to 11 years old who weighed at least 33 kg and received ritonavir 100 mg capsules had 43% higher plasma ritonavir AUC(0-τ), similar Cmax, and 3.04-fold higher Cτ values than observed in the historical adult population.

Table 2 Summary of Steady State Plasma amprenavir PK Parameters and Statistical Comparisons for fosamprenavir/ritonavir twice daily in Paediatric Subjects 6 to 11 Years Old in APV29005 and Historical Adults

Plasma APV PK Parameter	6 to 11 Years[1]			Historical Adult 700/100mg BID N=159[1,3,5]	6 to 11 Years vs Historical Adult[2,5]		
	15/3mg/kg BID N=10[3,4]	18/3mg/kg BID N=9[3,4]	700/100mg BID N=3[4]		15/3mg/kg BID	18/3mg/kg BID	700/100mg BID
AUC(0-τ) (h.µg/ml)	32.2 (23.0, 45.0) [46]	46.7 (33.9, 64.3) [44]	37.7 (22.1, 64.1) [22]	37.0 (35.1, 38.9) [33]	0.871 (0.718, 1.06)	1.26 (1.04, 1.53)	1.02 (0.734, 1.42)
Cmax (µg/ml)	4.34 (3.16, 5.96) [47]	6.07 (4.40, 8.38) [44]	5.85 (3.94, 8.70) [16]	5.62 (5.35, 5.92) [33]	0.772 (0.642, 0.928)	1.08 (0.890, 1.31)	1.04 (0.749, 1.45)
Cτ (µg/ml)	2.08 (1.47, 2.94) [59]	2.69 (2.15, 3.36) [45]	1.79 (0.340, 9.42) [140]	2.17 (2.05, 2.30) [38]	0.952 (0.743, 1.22)	1.03 (0.849, 1.25)	0.835 (0.605, 1.15)
CL/F (ml/min/kg)	6.50 (4.70, 8.99) [44]	5.42 (3.94, 7.46) [43]	5.92 (2.58, 13.6) [34]	3.52 (3.33, 3.71) [35]	1.85 (1.51, 2.26)	1.54 (1.26, 1.88)	1.68 (1.20, 2.37)
CL/F (ml/min)	195 (137, 279) [49]	160 (99.2, 259) [69]	265 (156, 452) [22]	270 (257, 284) [33]	0.723 (0.591, 0.885)	0.594 (0.485, 0.726)	0.983 (0.698, 1.38)
tmax (h)	2.00 (1.00, 6.00)	1.00 (0.50, 4.00)	3.92 (1.00, 4.02)	1.50 (0.50, 6.00)	ND	ND	ND

ND = not determined

1. Geometric Mean (95% CI) [CVb%], except tmax is presented as median (range)
2. GLS Mean Ratio (90% CI)
3. N=9 for 15/3mg/kg BID AUC(0-τ) and CL/F, N=158 for historical adult AUC(0-τ) and N=157 for historical adult CL/F
4. N=12 for 15/3mg/kg BID Cτ, N=17 for 18/3mg/kg BID Cτ,and N=4 for 700/100mg BID Cτ
5. Healthy Adults from Studies APV10010, APV10011, APV10012, APV10013, APV10018, APV10022, APV10026, APV10028, and APV10031

Fosamprenavir/ritonavir twice daily in Patients 12 to 18 Years Old

The majority of patients in the 12 to 18 year old age group received the adult tablet regimen of fosamprenavir/ritonavir 700/100mg twice daily. Compared to the historical adult population receiving fosamprenavir/ritonavir 700/100mg twice daily, 12 to 18 year old patients had 20% lower plasma amprenavir AUC(0-τ), 23% lower Cmax, and 20% lower Cτ values (table 3). Four patients in the 12 to 18 year old age group received fosamprenavir oral suspension at a dose of fosamprenavir/ritonavir

15/3 mg/kg twice daily and plasma amprenavir AUC(0-τ) was 41% lower, Cmax 30% lower, and Cτ 33% lower than observed in the historical adult population (table 3).

All of the 12 to 18 year old patients, except two patients who turned 12 years old during the study, received ritonavir 100 mg capsules. Compared to the historical adult population receiving fosamprenavir/ritonavir 700/100 mg twice daily, 12 to 18 year old patients had 20% higher plasma ritonavir AUC(0-τ), similar Cmax, and 33% higher Cτ values.

Table 3 Summary of Steady State Plasma amprenavir PK Parameters and Statistical Comparisons for Fosamprenavir/ritonavir in Patients 12 to 18 Years Old in APV29005 and Historical Adults

Plasma APV PK Parameter	12 to 18 Years[1]		Historical Adult	12 to 18 Years vs Historical Adult[2,5]	
	700/100mg BID N=8[4]	15/3mg/kg BID N=4[4]	700/100mg BID N=159[1,3,5]	700/100mg BID	15/3mg/kg BID
AUC(0, τ) (h.µg/ml)	29.4 (19.4, 44.5) [53]	21.8 (18.0, 26.3) [12]	37.0 (35.1, 38.9) [33]	0.795 (0.648, 0.974)	0.589 (0.443, 0.782)
Cmax (µg/ml)	4.33 (2.82, 6.65) [55]	3.92 (2.44, 6.29) [30]	5.62 (5.35, 5.92) [33]	0.770 (0.628, 0.945)	0.697 (0.524, 0.927)
Cτ (µg/ml)	1.61 (1.21, 2.15) [77]	1.29 (0.619, 2.71) [94]	2.17 (2.05, 2.30) [38]	0.803 (0.693, 0.931)	0.673 (0.509, 0.890)
CL/F (ml/min/kg)	6.06 (3.87, 9.48) [58]	10.0 (8.07, 12.5) [14]	3.52 (3.33, 3.71) [35]	1.72 (1.39, 2.13)	2.85 (2.12, 3.84)
Plasma APV PK Parameter	**12 to 18 Years[1]**		**Historical Adult**	**12 to 18 Years vs Historical Adult[2,5]**	
	700/100mg BID N=8[4]	**15/3mg/kg BID N=4[4]**	**700/100mg BID N=159[1,3,5]**	**700/100mg BID**	**15/3mg/kg BID**
CL/F (ml/min)	340 (225, 515) [53]	392 (356, 431) [6]	270 (257, 284) [33]	1.26 (1.02, 1.56)	1.45 (1.08, 1.95)
tmax (h)	2.00 (0.00, 4.00)	1.00 (1.00, 2.00)	1.50 (0.50, 6.00)	ND	ND

ND = not determined

1. Geometric Mean (95% CI) [CVb], except tmax is presented as median (range)
2. GLS Mean Ratio (90% CI)
3. N=158 for historical adult AUC(0-τ) and N=157 for historical adult CL/F
4. N=24 for 700/100mg BID Cτ, N=7 for 15/3mg/kg BID Cτ
5. Healthy Adults from Studies APV10010, APV10011, APV10012, APV10013, APV10018, APV10022, APV10026, APV10028, and APV10031

First Supportive Study APV20003 – once daily regimen

Study Design

Study APV20003 is a Phase II, open-label, 48-week study designed to evaluate plasma amprenavir pharmacokinetics, safety, and antiviral activity of fosamprenavir/ritonavir once daily in antiretroviral-naïve and -experienced patients 2 to 18 years of age. Patients were enrolled into three age-defined strata of 2 to 5, 6 to 11, and 12 to 18 years. Per protocol amendment ten patients (six in the 2 to 5, three in the 6 to 11, and one in the 12 to 18 year old age groups) switched to fosamprenavir/ritonavir twice daily regimens.

Patients received concurrent NRTIs. NNRTIs and other PIs were not allowed during the study. Patients and/or their parents/legal guardians were instructed to administer the fosamprenavir oral suspension with food in order to accommodate the frequent eating schedule of children, to enhance adherence through taste masking with food, and to improve tolerability. For patients in each age

stratum, serial PK sampling was conducted at Week 4 and trough sampling was conducted at all subsequent visits.

Pharmacokinetic Population
Sixty-nine (69) patients were enrolled, 55 patients provided plasma amprenavir Cτ data and 26 patients provided full plasma amprenavir PK profiles for the fosamprenavir/ritonavir 30/6 mg/kg once daily regimen. Two additional patients provided plasma amprenavir Cτ data for fosamprenavir/ritonavir twice daily only.

Pharmacokinetic Results
For 12 to 18 year old patients receiving either the fosamprenavir/ritonavir 30/6 mg/kg once daily or the fosamprenavir/ritonavir 1400/200 mg once daily regimen, plasma amprenavir AUC(0-τ) and Cmax appeared similar to and Cτ appeared approximately 20% lower than values historically observed for adult patients receiving fosamprenavir/ritonavir 1400/200 mg once daily.

For 6 to 11 year old patients receiving the fosamprenavir/ritonavir 30/6 mg/kg once daily regimen, on average, plasma amprenavir AUC(0-τ) was 27% lower and Cmax was 30% lower; whereas, Cτ appeared similar to values historically observed for adult patients receiving fosamprenavir/ritonavir 1400/200 mg once daily.

For 2 to 5 year old patients receiving the fosamprenavir/ritonavir 30/6 mg/kg once daily regimen, on average, plasma amprenavir AUC(0-τ) was 30% lower, Cmax was 34% lower, and Cτ was 30% lower than values historically observed for adult patients receiving fosamprenavir/ritonavir 1400/200 mg once daily.

Second Supportive Study APV20002 – very young children (< 2 years)

Study Design
Study APV20002 is a Phase II, open-label, 48-week study designed to evaluate plasma amprenavir pharmacokinetics, safety, and antiviral activity of Fosamprenavir alone twice daily in HIV-1 infected, PI-naïve, paediatric patients and of Fosamprenavir/ritonavir twice daily in PI-naïve and PI-experienced paediatric patients 4 weeks to <2 years old.
Data from patients below the age of two are presented although currently no dosing recommendation can be given for this age group. Patients received concurrent NRTIs. NNRTIs and other PIs were not allowed. Parents/legal guardians were instructed to administer the study drugs with food in order to accommodate the frequent eating schedule of children, to enhance adherence through taste masking with food, and to improve tolerability.

Pharmacokinetic Population
All 13 enrolled patients underwent PK sampling during the study and 12 patients provided evaluable data. Eleven patients provided plasma amprenavir PK profiles after administration of a single dose of fosamprenavir 30mg/kg. Nine patients provided steady-state plasma amprenavir and ritonavir PK profiles at Week 2 and Cτ data at subsequent visits.
Pharmacokinetic Results
Nine 6 to <24-month old paediatric patients receiving fosamprenavir/ritonavir twice daily regimens ranging from 29.4/5.6 to 51.1/8.2 mg/kg twice daily had steady-state plasma CL/F values that were markedly higher than those observed in the historical adult population (table 4).

Table 4 Steady-State Plasma amprenavir and ritonavir CL/F Estimates for Fosamprenavir/ritonavir twice daily in Paediatric Subjects 6 to <24 Months Old in APV20002 and Statistical Comparisons to Historical Adult Data

Steady-State Plasma APV CL/F (ml/min/kg)			Steady-State Plasma RTV CL/F (ml/min/kg)		
Paediatric Subjects 6 to <24 months N=9[1]	**Historical Adult Population N=157[1,3]**	**Paediatric Vs Historical Adult[2,3]**	**Paediatric Subjects 6 to <24 months N=9[1]**	**Historical Adult Population N=78[1,3]**	**Paediatric Vs Historical Adult[2,3]**
24.8 (11.9, 51.7) [122]	3.52 (3.33, 3.71) [35]	7.05 (5.64, 8.80)	20.2 (9.89, 41.2) [117]	4.76 (4.24, 5.34) [55]	4.24 (3.05-5.90)

1. Geometric Mean (95% CI) [CVb%]
2. GLS Mean Ratio (90% CI)
3. Healthy Adults from Studies APV10010, APV10011, APV10012, APV10013, APV10018, APV10022, APV10026, APV10028, and APV10031

PK parameter values were highly variable (CVb% ranging from 113 to 165% across the PK parameters) for the paediatric patients 6 to <24 months old. Co-administration of fosamprenavir with ritonavir in paediatric patients 6 to <24 months significantly reduced plasma amprenavir CL/F by approximately 60%.

Compared to the historical adult population, a subset of five paediatric patients ages 6 to <24 months receiving fosamprenavir/ritonavir 45/7 mg/kg twice daily demonstrated that despite an approximate 5-fold increase in fosamprenavir and ritonavir doses on a mg/kg basis, plasma amprenavir AUC(0-τ) was approximately 48% lower, Cmax 26% lower, and Cτ 29% lower in the paediatric patients.

Population PK model

The MAH developed a PPK model using pooled data from all three paediatric studies. The advantage of population modelling is that plasma samples from studies with different dosing regimens (once daily and twice daily) and sparse and rich sampling could be integrated in one model. From the model, exposure data for different dosing regimens and different age groups were simulated, in search of an optimal dosing schedule.

Population characteristics

The dataset was comprised of 137 patients aged 0.72-18 years, contributing 1322 plasma amprenavir concentrations. The median age was 10 years. Body weight ranged form 5.9-102.8 kg. Baseline alpha-1 acid glycoprotein (AAG) concentrations ranged from 0.41-2.69 g/l. Only 18 patients received no ritonavir. In 33 cases, fosamprenavir was administered in fasted state.

Structural model

Data were analysed using nonlinear mixed-effect modelling (NONMEM version V 1.1). Data were fitted to a two-compartment model plus an absorption compartment. The chosen parameters were Ka (absorption constant), V2/F (central compartment), CL/F (clearance from central compartment), V3/F (peripheral compartment) and Q (inter-compartmental clearance). CL and V were modelled as a function of weight (allometric scaling with 0.75 exponent).

In the base model, food, ritonavir intake and fosamprenavir formulation (tablet or oral suspension) were taken into account.

Inter-individual variability (IIV, symbolised by η) could be estimated for V2/F, CL/F and Q, but not for Ka. A co-variance term was defined for V2/F and CL/F (meaning that during estimating of IIV for CL and V2, co-variance between these two parameters is accounted for). Inter-occasion variability (IOV) was estimated for CL/F. The error model was described by proportional + additive error. The FOCE-INTERACTION method was used throughout model development.

Final model

Co-variates race, gender and AAG level were included. Despite the fact that weight was included in the basic model, still a part of the variability of CL and V could be explained by gender and age.

Population PK estimates

PPK parameter estimates are presenting a male child 10 years (35 kg), treated with suspension and food. CL without ritonavir was estimated as 84 l/hr, versus 34 l/hr when booster ritonavir was administered. For comparison, in an adult model, the unboosted CL/F was estimated as 91.8 l/hr and boosted CL/F as 21.5 l/hr. Weight-adjusted CL/F is expected to be 1.4 point greater in younger children (age 1.09 year) compared to children aged > 4 years. The negative relationships between CL or V2 and AAG were reported before for adults (table 5).

Bioavailability (F) for oral solution was estimated to be 13% lower with food. When fosamprenavir was administered as tablet, F is 9% higher compared to oral solution. F was 15% lower for girls, and 6% lower for African children. However, the 95% CI of these categorical co-variates include 1, indicating that the effect could not be reliably estimated.

Table 5 Population PK model parameters for amprenavir

Parameter[2]	**Population Estimate**	**%RSE**	**95%CI**
CL/F[3]	34.1 (l/hr)	7%	(28.9, 39.7)
V2/F	288 (l)	23%	(160, 421)
Q	63.5 (l/hr)	15%	(41.3, 91.2)
V3	1630 (l)	28%	(882, 3110)
K_a	1.13 (hr^{-1})	30%	(0.759, 1.74)
CL/F[4]	84.4 (l/hr)	11%	(59.1, 109)
Ftab	1.09	8%	(0.906, 1.28)
Ffood,sus	0.870	8%	(0.699, 1.1)
AMAX	0.790	65%	(0.521, 2.4)
AG50	2.05	26%	(1.41, 2.99)
SEX	0.846	7%	(0.744, 0.971)
$RACE_{black}$	0.940	8%	(0.782, 1.12)
$RACE_{other}$	1.06	13%	(0.863, 1.25)
AAG_{CL}	-0.626	9%	(-0.787, -0.489)
AAG_{V2}	-0.369	92%	(-0.845, 0.199)
Intersubject variances			
η_{CL} variance	0.0901 (30%)	17%	(0.0391, 0.145)
$\eta_{CL} - \eta_{V2}$ correlation	0.0945	40%	(-0.0374, 0.218)
η_{V2} variance	0.438 (66%)	27%	(0.0276, 0.968)
$\eta_{IOV,CL}$ variance	0.114 (34%)		(0.0679, 0.153)
η_{Q} variance	0.536 (73%)	36%	(0.222, 1.02)
Residual Errors			
Prop error	0.0827	7%	(0.0528, 0.125)
Additive error (µg/ml)	0.0760	12%	(0.035, 0.119)

1. Population parameter point-estimates and %SE for the full two compartment model and 95% CI from a non-parametric bootstrap are presented.
2. Body weight was included in the final model using fixed allometric relationships on clearance and volume parameters.
3. CL/F when ritonavir dose > 0
4. CL/F when ritonavir dose = 0

Ka = absorption rate constant; Ftab=bioavailability of tablet formulation relative to suspension; Ffood,sus= bioavailability of fasted suspension dose relative to fed suspension dose; AMAX=maximal age effect on CL/F; AG50=age at half-maximal age effect on CL/F; SEX = fraction of CL/F for females relative to males; RACEblack = fraction of CL/F for Black patients relative to Caucasians; RACEother=fraction of CL/F for patients of non-Black ethnic origin relative to Caucasians; AAG_{CL}=exponential effect of AAG values on CL/F; AAG_{V2}= exponential effect of AAG on V2/F

Validation
The posterior predictive check, evaluation of residual distributions and goodness-of-fit plots indicated that the model described the data reasonably well.

Simulation
Using the final population PK model, simulations were completed to predict twice daily dosage regimens that would deliver target plasma amprenavir AUC and Cτ levels in adults (AUC: 37.0 (mean)-64(max) µg/ml*hr, Cτ (=Cmin): 1.55 (minimal)-3.52 (maximal) µg/ml). For the simulations, doses were not to exceed the adult tablet dosing regimen and doses were administered under fed conditions. Based on the simulations, the following fosamprenavir/ritonavir dosage regimens and age-stratifications were predicted:

- 2 to 5 years: Fosamprenavir/ritonavir 23/3 mg/kg twice daily,
- ≤6 years: Fosamprenavir /ritonavir 18/3 mg/kg twice daily, up to adult tablet dosage regimen of
  Fosamprenavir /ritonavir 700/100 mg twice daily.

With these dosage regimens, the predicted plasma amprenavir plasma exposure values met the target for 2 to 11 year olds; for 12 to 18 year olds, the predicted geometric mean AUC(0-τ) and Cmin values were approximately 20% lower than the targeted adult exposure.

Results
The main predictors of plasma amprenavir exposure, as determined by change in CL/F, were:
- The presence or absence of ritonavir, where co-administration of ritonavir was estimated to decrease plasma amprenavir CL/F by approximately 60%.
- Age, where weight adjusted CL/F was estimated to be 1.4-fold greater in the youngest children (1.09 years) as compared to children ≥5 years of age.
- Body weight, with a range of typical population CL/F estimates of 6.6 to 46.2L/hr across the weight range in the dataset.
- AAG, with a range of typical population CL/F estimates of 22.5 to 55.6 l/hr across the AAG range of 0.4 to 1.5g/l.

The main predictors of plasma amprenavir V2/F were:
- Body weight, with a range of typical population V2/F estimates of 32.1 to 432L across the weight range in the dataset.
- AAG, with a range of typical population V2/F estimates of 189 to 367L across the AAG range of 0.4 to 1.5g/l.

Discussion on pharmacokinetics

The dose recommendation derived from the PPK model for children above the age of six is in line with the doses used in study APV29005 for this age group. The fact that for 12 to 18 year olds, the predicted geometric mean AUC(0-τ) and Cmin values were approximately 20% lower than the targeted adult exposure in the PPK model are to some extent balanced by the efficacy data for this age group. Nevertheless, this positive clinical outcome needs to be further substantiated in the ongoing studies. Concerns, however, remain with the age group of children below the age of six.

The PPK model arrived at dosage recommendation for children that are based on kg BW and stratified into two age groups with the age of 6 years being the limit between the two. A drawback of the currently proposed doses based on these age-classes is that on the 6th birthday, doses should be abruptly lowered.

In addition, according to the PPK model, higher doses (23/3 mg/kg fosamprenavir/ritonavir) were predicted for children 2 to 5 years of age than currently recommended (namely 20/3 mg/kg) and used in study APV29005. Assuming the validity of the PPK model, there is a risk of under-dosing when the study is continued with the lower dose. Therefore, this study design should be amended to either include a high-dose study arm (parallel-design) where children are treated with 23/3 mg/kg or an

interim analysis at an early stage to evaluate the adequacy of the 20/3 mg/kg dosing in order to avoid sub-optimal plasma levels. The MAH has addressed this need by committing to amend the study protocol to include a high-dose study arm (see also attached Letter of Undertaking).

Given the current absence of data in children aged 2 to 5 years in the recommended dosage regimen, questions raised in regards to the feasibility of the dose change at 6 years of age as well as the critical issue of potential under dosing identified by the PPK model remain unsolved. Therefore, no conclusion on the adequacy of the dose recommendation in children below the age of six can currently be reached. This will have to await the results of this age group from study APV 29005, once the above amendments have been incorporated in an amendment of the study protocol (see also attached Letter of Undertaking).

The fact that in study APV20002 (very young children of 6 to 24 months of age) no sufficient plasma levels could be achieved even after administration of fosamprenavir/ritonavir doses up to 4.5-fold the adult ones raises major concerns. This may not only be explained by the relatively higher CL in this age group, but may be due to an insufficient absorption of the oral solution, possibly because of a short gastrointestinal transit time in small children, or because of frequent vomiting and diarrhoea in HIV-infected children. The MAH should further research the underlying cause of this effect in the ongoing study (see also attached Letter of Undertaking).

Even though no dosing recommendations could be made for this age group of very young children (<2 years old) due to the small number of participants in study APV20002, the CHMP recommended that a warning should be included in the SPC that even with doses of fosamprenavir/ritonavir 45/7 mg/kg twice daily no sufficient plasma exposure levels were achieved in a number of patients.

4 Clinical efficacy

Main study APV29005 and First Supportive Study APV 20003

In Study APV29005 and Study APV20003, 126 paediatric patients above the age of two received at least one dose of fosamprenavir/ritonavir (table 6).

Table 6 Number of patients in Studies APV29005 and APV20003 by Age Group at Entry Receiving Fosamprenavir/ritonavir

	Number of patients			
	2 to 5 years	**6 to 11 years**	**12 to 18 years**	**All Subjects (2 to 18 years)**
APV29005 (FPV/RTV BID)	3	25	29	*57*
APV20003 (FPV/RTV QD)	17	17	35	*69*
Total	20	42	64	*126*

Ten patients in APV20003 switched to BID dosing; six in the 2 to 5 year age group, three in the 6 to 11 year age group, and one in the 12 to 18 year age group

Methods

The main inclusion criterion for Studies APV29005 and APV20003 studies was similar:

- Patients for whom, following resistance testing where appropriate, an active NRTI backbone regimen consisting of two NRTIs could be constructed.

Patients must have also met one of the following criteria:

- ART-naïve patients who have not received any length of therapy with NRTIs and/or NNRTIs in study APV29005. APV20003 included patients with ≤4 weeks (28 days) therapy with an NRTI, no previous therapy with an NNRTI and less than one week therapy with a PI.
- ART-experienced patients (with NRTIs NNRTIs and/or a PI).
- PI-naïve patients: defined as having received less than 1 week of any PI.

- PI-experienced patients: defined as having prior experience with no more than three PIs excluding Agenerase. Prior ritonavir boosted PI therapy was considered as only one PI as long as the ritonavir dose was lower than that recommended for use of ritonavir as an antiretroviral agent.

The main exclusion criteria for both studies were similar and were:

- The patient had a prior history of having received amprenavir.
- The patient had NNRTI therapy within 14 days prior to study drug administration or anticipated need for concurrent NNRTI therapy during the study period.
- The patient had a malabsorption syndrome or other gastrointestinal dysfunction which might interfere with drug absorption or render the patient unable to take oral medication.
- The patient had any serious medical condition (e.g., haemoglobinopathy, chronic anaemia, diabetes, cardiac dysfunction, and hepatitis) which, in the opinion of the investigator, might compromise the safety of the patient.
- The patient had current Grade 2 or higher serum lipase within 28 days prior to study drug administration and/or history of clinically relevant pancreatitis within the previous 6 months.
- The patient had Grade 3 or 4 transaminase levels (alanine aminotransferase and/or aspartate aminotransferase within 28 days prior to study drug administration and/or clinically relevant hepatitis within the previous 6 months.
- Treatment with protocol-excluded medications within 28 days prior to receiving study medication or the anticipated need during the study.

Demographics and disease characteristics

Age groups, with the exception of FPV/RTV recipients in the 2 to 5 year age group (APV29005, 3 patients vs. 17 in APV20003), were similarly represented across the two studies. The median age was 12.0 years in both studies. Overall there were slightly more female patients than males, and patients were predominantly Caucasian.

The majority of paediatric patients were either mildly (Class A) or moderately (Class B) symptomatic at baseline according to the CDC Classification for children <13 years. Likewise, the majority of adolescents were CDC Class A or B at baseline.

The baseline plasma HIV-1 RNA levels, median CD4+ cell counts and CD4+ percentages were similar among PI-naïve and PI-experienced patients (table 7).

Table 7 Distribution of Plasma HIV-1 RNA Values and CD4+ Cell Counts and CD4+ Percentages at baseline by PI Status (ITT[E] Population)

Clinical Characteristic	**Number of patients (%)**			
	Study APV29005		**Study APV20003**	
	PI-Naïve N=27	**PI-Experienced N=30**	**PI-Naïve N=32**	**PI-Experienced N=37**
baseline HIV-1 RNA	n=27	n=29	n=27	n=37
Median plasma HIV-1 RNA log_{10} copies/ml, (IQR)	4.6 (4.1, 5.2)	4.5 (4.1, 4.9)	4.7 (4.3, 5.2)	4.9 (4.3, 5.2)
HIV-1 RNA copies/ml, n (%)				
<400	0	0	1 (3)	1 (3)
400 to <5000	3 (11)	5 (17)	2 (6)	4 (11)
5000 to <100,000	14 (52)	17 (59)	17 (53)	17 (46)
100,000 to 250,000	7 (26)	6 (21)	6 (19)	9 (24)
>250,000 to 500,000	1 (4)	1 (3)	3 (9)	2 (5)
≥500,000	2 (7)	0	3 (9)	4 (11)
baseline CD4+ cell counts	n=27	n=26	n=32	n=37
Median CD4+ cells/mm^3 (IQR)	262 (134, 484)	418 (247, 682)	357 (258, 500)	379 (260, 848)

Clinical Characteristic	Number of patients (%)			
	Study APV29005		Study APV20003	
	PI-Naïve N=27	PI-Experienced N=30	PI-Naïve N=32	PI-Experienced N=37
CD4+ cells/mm^3, n (%)				
<100	6 (22)	1 (3)	4 (13)	5 (14)
100 to <200	4 (15)	6 (20)	3 (9)	2 (5)
200 to <350	7 (26)	4 (13)	8 (25)	9 (24)
350 to <500	4 (15)	6 (20)	9 (28)	5 (14)
≥500	6 (22)	13 (43)	8 (25)	16 (43)
baseline % CD4+ cells	n=27	n=30	n=32	n=37
Median % CD4+ cells (IQR)	19 (10, 31)	21 (11, 29)	20 (13, 28)	21 (14, 28)
% CD4+ cells, n (%)				
<15	9 (33)	12 (40)	9 (28)	10 (27)
15 to <25	8 (30)	6 (20)	12 (38)	12 (32)
25 to <50	10 (37)	10 (33)	11 (34)	15 (41)
≥50	0	2 (7)	0	0

There were differences between the studies with regard to the median duration of prior exposure to NRTIs and NNRTIs for patients in the fosamprenavir/ritonavir group; this was substantially longer in study APV29005 compared to study APV20003 (table 8).

Table 8 Summary of Prior NNRTI and NRTI Antiretroviral Therapy in ITT(E) Population by PI Status

	Number of patients (%)			
	Study APV29005		Study APV20003	
	PI-Naïve N=27	PI-Experienced N=30	PI-Naïve N=32	PI-Experienced N=37
Median duration of all prior NRTI exposure in weeks (range)	421 (1, 749)	385 (50, 638)	281 (56, 611)	256 (37, 633)
Median duration of all prior NNRTI exposure in weeks (range)	213 (8, 304)	106 (24, 269)	135 (12, 279)	77 (13, 226)

Abacavir/lamivudine was the most common NRTI initial combination, used by 44% (55/126) of patients. Most PI-experienced patients enrolled had one prior PI exposure only (predominantly nelfinavir).

Antiviral response endpoints

Antiviral responses endpoints for studies APV29005 and APV20003 were secondary and included the proportion of patients with plasma HIV-1 RNA <400 and <50copies/ml over time, changes from baseline in HIV-1 RNA over time, changes from baseline in helper-inducer T-lymphocyte surface antigen (CD4+) cell counts and CD4+ cell percentages over time. In both studies, HIV Genotypic Resistance testing (Geneseq, Monogram Biosciences Inc) was to be performed at baseline and at the time of protocol-defined virologic failure. Due to the open-label, non-comparative design of the paediatric studies, no formal statistical hypothesis testing was performed. Descriptive methods were thus used in analysis of the data obtained from these studies. Intent-to-Treat Exposed ITT(E) Population was the primary population for the antiviral response analysis in these two studies, and consisted of all patients with documented evidence of having received at least one dose of investigational product. Analyses of antiviral response for the ITT(E) Population included the TLOVR algorithm and Observed analysis.

Results

Patient disposition

The proportion of premature discontinuation was higher in APV20003 (43% versus 18%) in the fosamprenavir/ritonavir treatment groups. Patients listed as discontinued for "Other" reasons were mainly due to being unable to adhere to or tolerate the taste of fosamprenavir/ritonavir, too low plasma amprenavir concentration at the end of the dosing interval, very bad compliance for all antiretroviral drugs generally and a pregnancy (table 9).

Table 9 Summary of Treatment Discontinuation (ITT[E] Population) as of the cut-off date for each study

	Number of Patients (%)	
	Study APV29005 24-Week (N=57)	**Study APV20003 48-Week(N=69)**
Enrolled and treated	57	69
Ongoing at the time of data cut-off	47 (82)	39 (57)
Prematurely discontinued	10 (18)	30 (43)
AE	2 (4)	10 (14)
Subject decided to withdraw	2 (4)	4 (6)
Lost to follow-up	0 (0)	0 (0)
Protocol violation	0 (0)	1 (1)
Insufficient viral load response	0 (0)	5 (7)
Insufficient CD4+ response	0 (0)	0 (0)
Disease progression	0 (0)	0 (0)
Other	6 (11)	10 (14)

Antiviral response

The majority of patients in both studies had greater than 48 weeks of exposure to study treatment. However, the initially submitted interim study reports do not present antiviral response data beyond Week 24 for Study APV29005 because 3 patients in this study receiving fosamprenavir/ritonavir twice daily did not reach their Week 24 visit evaluation but were still on therapy as of the data cut-off date. They were therefore classified as virologic failures in the TLOVR algorithm. Across the two studies, similar proportions of PI-naïve patients and of PI-experienced patients achieved HIV-1 RNA <400copies/ml at Week 24 (table 10).

Table 10 Summary of Proportion of patients with Plasma HIV-1 RNA less than 400 copies/ml by Visit and PI Status (ITT[E] Population) (TLOVR)

Week	**Number of Patients n/N (%)**			
	Study APV29005		**Study APV20003**	
	PI-Naïve[1] N=27	**PI-Experienced N=30**	**PI-Naïve[2] N=32**	**PI-Experienced N=37**
Week 4	11 / 27 (41)	9 / 30 (30)	14 / 32 (44)	12 / 37 (32)
Week 8	17 / 27 (63)	14 / 30 (47)	24 / 32 (75)	19 / 37 (51)
Week 12	22 / 27 (81)	15 / 30 (50)	22 / 32 (69)	20 / 37 (54)
Week 24	19 / 27 (70)	17 / 30 (57)	21 / 32 (66)	21 / 37 (57)
Week 48			15 / 32 (47)	16 / 37 (43)

1. Nine patients were ART-naïve (Study APV29005)
2. Fifteen patients were ART-naive (Study APV20003)

The ITT (E) TLOVR analysis of the response by visit and PI status based on the plasma HIV-1 RNA <50 copies/ml is summarised in the following table (table 11). The response rates were lower than those based on the analysis of the plasma HIV-1 RNA <400 copies/ml.

Table 11 Summary of Proportion of patients with Plasma HIV-1 RNA less than 50 copies/ml by Visit and PI Status in ITT(E) Population (TLOVR)

Week	Number of patients n/N (%)			
	Study APV29005		Study APV20003	
	PI-Naive N=27	PI-Experienced N=30	PI-Naive N=32	PI-Experienced N=37
Week 4	1 / 27 (4)	3 / 30 (10)	4 / 32 (13)	4 / 37 (11)
Week 8	2 / 27 (7)	6 / 30 (20)	7 / 32 (22)	9 / 37 (24)
Week 12	7 / 27 (26)	8 / 30 (27)	15 / 32 (47)	13 / 37 (35)
Week 24	12 / 27 (44)	10 / 30 (33)	15 / 32 (47)	15 / 37 (41)
Week 48			13 / 32 (41)	13 / 37 (35)

The reasons for non-response was primarily due to virological failure (mainly due to viral level rebound in the PI-naïve patients versus never reaching viral load suppression in the PI-experienced patients) followed by adverse events (with a higher rate in the fosamprenavir/ritonavir once daily dosing regimen in study APV20003). In both studies, the median plasma HIV-1 RNA level decreased over time.

There were differences in antiviral response across the age groups, although the differences were not consistent between studies (table 12).

Table 12 Proportion of patients with Quantitative Plasma HIV-1 RNA less than 400copies/ml by Age in the ITT(E) Population (TLOVR)

Age	Number of patients n/N (%)					
	Study APV29005			Study APV20003		
	2 to 5 years N=3	6 to 11 years N=25	12 to 18 years N=29	2 to 5 years N=17	6 to 11 years N=17	12 to 18 years N=35
baseline	0 / 3	0 / 25	0 / 29	1/17 (6)	0/17	1/35 (3)
Week 4	1 / 3 (33)	6 / 25 (24)	13 / 29 (45)	9/17 (53)	5/17 (29)	12/35 (34)
Week 8	2 / 3 (67)	9 / 25 (36)	20 / 29 (69)	14/17 (82)	7/17 (41)	22/35 (63)
Week 12	2 / 3 (67)	11 / 25 (44)	24 / 29 (83)	15/17 (88)	7/17 (41)	20/35 (57)
Week 24	2 / 3 (67)	11 / 25 (44)	23 / 29 (79)	15/17 (88)	9/17 (53)	18/35 (51)
Week 48				11/17 (65)	8/17 (47)	12/35 (34)

The groups are too heterogeneous with regard to sample size, baseline antiretroviral experience, resistance profile and differences in fosamprenavir/ritonavir exposure and dosing regimens to derive meaningful conclusions by age category.

Antiviral response in adolescents at week 48

In answer to the request for supplementary information, the MAH performed a preliminary Week 48 efficacy analysis of the 12-18 years old age group in APV29005 based upon laboratory data currently available. Tables 13 and 14 below present the Week 48 antiviral response for adolescents in APV290005.

Table 13 Proportion of Subjects with Quantitative Plasma HIV-1 RNA <400 copies/ml by Visit and PI Status for 12-18yr Age Group – TLOVR ITT (E) Population

Visit	PI-naïve (N=19)	PI-exp. (N=10)	Total (N=29)
Baseline	0/19	1/10	0/29
Week 24	16/19 (84%)	8/10 (80%)	24/29 (83%)
Week 36	15/19 (79%)	8/10 (80%)	23/29 (79%)
Week 48	14/19 (74%)	7/10 (70%)	21/29 (72%)

Compared to Week 24, the two additional PI-naïve patients classified as failure in the Week 48 TLOVR analysis comprised one virological rebound and one discontinuation while suppressed due to 'other' reasons captured as 'poor medical compliance' for the IP discontinuation data. The one additional PI-experienced patient classified as failure post Week 24 in the Week 48 TLOVR analysis was a virological failure at Week 48 due to plasma HIV-1 RNA rebound.

Table 14 Proportion of Subjects with Quantitative Plasma HIV-1 RNA <50 copies/ml by Visit and PI Status for 12-18yr Age Group – TLOVR ITT (E) Population

Visit	PI-naïve (N=19)	PI-exp. (N=10)	Total (N=29)
Baseline	0/19	0/10	0/29
Week 24	9/19 (47%)	4/10 (40%)	13/29 (45%)
Week 36	12/19 (63%)	6/10 (60%)	18/29 (62%)
Week 48	14/19 (74%)	6/10 (60%)	20/29 (69%)

Study outcomes at Week 48 using the <50 copies/ml TLOVR analysis in the ITT(E) Population for PI-naïve and PI-experienced adolescents respectively were as follows: 14/19 (74%) and 6/10 (60%) of were responders, 3/19 (16%) and 3/10 (40%) experienced virological failure. In addition, three PI-naïve adolescents discontinued study drug before achieving suppression (n=2) or while suppressed (n=1), one for adverse events and two for 'other' reasons.
Overall, the data show that the efficacy observed at Week 24 is generally sustained through Week 48, and that the majority of patients achieving viral suppression to <400 plasma HIV-1 RNA copies/ml also achieved maximal suppression to <50 copies/ml, especially in the group of PI-naïve patients.

Immunological response
In the ITT(E) Observed analysis of the median change from baseline in CD4+ cells, increases (114 to 149 cells/mm^3) were observed at Week 24 and were similar between the PI-naïve and the PI-experienced groups in Studies APV29005 and APV20003 (table 15).

Table 15 Median baseline CD4+ Cells/mm^3 and Median Change from baseline by Visit and PI Status in ITT(E) (Observed)

Week	Median (IQR) baseline CD4+ Cell Count and Median Change from baseline (cells/mm^3)							
	Study APV29005				Study APV20003			
	PI-Naïve N=27	n	PI-Experienced N=30	n	PI-Naive N=32	n	PI-Experienced N=37	n
baseline	262 (134, 484)	27	418 (247, 682)	30	357 (258, 500)	32	379 (260, 848)	37
Week 4	83 (33, 128)	21	33 (-29, 132)	25	77 (19, 132)	25	63 (1, 117)	32
Week 8	79 (38, 151)	24	125 (0, 247)	26	86 (19, 256)	28	56 (-49, 142)	32
Week 12	120 (59, 236)	24	199 (118, 317)	21	96 (15, 145)	23	43 (-31, 108)	28
Week 24	131 (71, 275)	21	149 (-3, 241)	24	127 (71, 227)	26	114 (30, 210)	31
Week 48					163 (81, 302)	21	145 (2, 251)	34

Improvements were also observed in Week 24 CD4+ immune category results for patients who had both baseline and Week 24 data in studies APV29005 and APV20003 (table 16). Similar improvements were seen across the PI-naïve and PI-experienced groups in both studies. Roughly 1/3 of the patients showed improvement and 2/3 maintained their status. Week 48 results (not shown for study APV20003) showed a similar pattern.

Table 16 Change from baseline to Week 24 in Immune Category by PI Status (ITT[E] Population)

	Study APV29005			Study APV20003		
FPV/RTV PI-Naive	**Week 24 CD4+ Immune Category Value n(%)**			**Week 24 CD4+ Immune Category Value n(%)**		
baseline CD4+ Category	<15%	15 to <25%	≥25%	<15%	15 to <25%	≥25%
<15%	3 (33)	6 (67)	0	2 (29)	5 (71)	0
15% to <25%	1 (20)	2 (40)	2 (40)	1 (11)	3 (33)	5 (56)
≥25%	0	1 (14)	6 (86)	0	0	10 (100)
FPV/RTV PI-Experienced	**Week 24 CD4+ Immune Category Value n(%)**			**Week 24 CD4+ Immune Category Value n(%)**		
baseline CD4+ Category	<15%	15 to <25%	≥25%	<15%	15 to <25%	≥25%
<15%	5 (45)	6 (55)	0	6 (67)	2 (22)	1 (11)
15% to <25%	0	2 (40)	3 (60)	0	4 (44)	5 (56)
≥25%	0	1 (13)	7 (88)	0	1 (8)	12 (92)

Disease progression

There was no disease progression or HIV-associated conditions reported in Study APV29005. HIV disease progression during Study APV20003 occurred in one patient in the PI-experienced group, who developed a mycobacterial infection.

Resistance data

Both genotype and phenotype analyses were performed in studies APV29005 and APV20003.

APV29005

In this study, the majority of the ITT-exposed population was included in the Virology population at baseline, comprising 82% (47/57) of patients and including 87% (26/30) of the PI-experienced patients. Nine of the 12 patients classified as virological failures at Week 24 (ITT[E] TLOVR, ≥400 copies/ml) provided on-therapy analysis. An additional seven patients were analysed for clinical management purposes following the investigator's request, but four of these were after only 4 weeks therapy.

In the group of ART experienced patients without significant phenotypic resistance to fosamprenavir/ritonavir baseline (N=40), 38 were lacking amprenavir-associated mutations at baseline. In the PI-experienced group (N=26), 2 patients had HIV virus with >4-fold reduced susceptibility to amprenavir at baseline. Both experienced virologic failure.

Three of nine patients with virological failure at Week 24 with on-therapy genotypes showed significant PRO mutation selection on-therapy. Amprenavir resistance associated mutations selected were I54M/l (n=2), I50V (n=2), and I84V (n=2) (total number of patients: n=3) and these were always associated with phenotypic resistance to fosamprenavir/ritonavir. There was relatively little change in the genomes of the viruses from the other six patients. Of the seven patients analysed at the investigator's request, only one showed changes from baseline in protease.

APV20003

Two virology populations were analysed: the NRTI-experienced population, and the Virology Failure Population. Genotypic analyses were performed in the NRTI experienced subpopulation at screening (N=53) to help construct an active background regimen of two NRTIs, and both genotypic and phenotypic analyses were performed for patients with plasma HIV-1 RNA >400 copies/ml at Week 24 or 48 or at the investigator's request (N=30).

Of the seven patients with virological failure who developed amprenavir resistance associated mutations, six were in the PI-experienced group; one of these patients had an amprenavir mutation at baseline and selected I54L on therapy. Six of the patients also had one or more TAMs at baseline, four of these with M184V; one patient did not have NRTI resistance-associated mutations. Thus in six of these seven cases, it is likely that the NRTI had impact on the success of the regimen.

On treatment analysis has shown that the highest absolute fold-changes in amprenavir resistance were observed when amprenavir resistance mutations were selected into a background of other PI mutations. Of a total of 11 patients with virus showing phenotypic resistance to amprenavir on-treatment, 10/11 were previously PI-experienced patients and were infected with virus containing multiple PI-mutations at baseline, and 3/11 patients harboured viruses with phenotypic resistance to amprenavir at baseline. Such isolates showed cross-resistance to other PIs except for LPV where 73% (8/11) remained below the clinical cut-off.

Treatment Adherence in Study APV29005

The adherence was planned to be explored in this study:

- by the pill count and the visual assessment of full, partial or empty bottle
- by the Paediatric AIDS Clinical Trials Group (PACTG) adherence questionnaire exploring the potential reasons for non-adherence (including taste, refusal, interference with lifestyle etc.)

Fosamprenavir adherence behaviour assessment was only available for 51% of patients. The reasons for non-adherence were obtained for only 59% of patients at weeks 24. The lower rate of adherence was observed for patients aged 12-18 years (73% at week 24). The rate of adherence decreased between week 24 and week 48 for all cohorts; comprised between 86 % and 60% at week 48. By week 24, the major reason for non-adherence was "taste, can't get it down, spits up, amounts of pills or liquid" in children less than 13 years and "made me sick to my stomach; threw-up; it tasted badly". Of note, the reporting of these events decreased over the course of the study.

Discussion on clinical efficacy

Overall, the clinical efficacy data submitted in support of this type II variation are limited. Those derived from study APV29005, which evaluated the efficacy of the recommended fosamprenavir/ritonavir twice daily regimen when used in combination with two NRTIs are only supportive for the use of fosamprenavir/ritonavir twice daily in paediatric patients above the age of six, due to the lack of children evaluated for the lower age group. The MAH agreed to this restriction as compared to the initially proposed age group of children above the age of two (see also attachment 8 to this assessment report). In the supported age group, however, both antiviral and immunological responses were acceptable.

The studies were designed to evaluate primarily the PK and safety of fosamprenavir/ritonavir in children of all ages, who were antiretroviral therapy naïve or experienced, PI-naïve or experienced, and had variable baseline viral resistance. Antiviral activity was a secondary endpoint only, which is consistent with ICH E11 guidance. The observed variability in antiviral response by age group was most likely due to differences in underlying baseline viral resistance or treatment experience of each individual patient rather than due to age per se. In APV29005, the majority of patients with any (one or two) primary protease mutations were in the 6 to 11 age group. The most prevalent primary protease mutations present in the 6 to 11 year old age group was L90M, associated with broad cross-class resistance, while the most prevalent in the 12 to 18 year old age group was D30N, associated specifically with resistance to NFV only. Thus, the 6 to 11 year age group appeared to have the most extensive PI genotypic resistance, and also had the lowest antiviral response to fosamprenavir/ ritonavir therapy in APV29005. In separate analyses, the number of active NRTI drugs in the regimens was estimated based on both genotype and phenotype scoring (GSS and PSS). Of the 17 patients with fully active backbones (both GSS and PSS =2), three (18%) experienced virologic failure. In contrast, five of 12 patients (42%) identified with GSS and PSS $\leq$2 experienced failure. Thus, as expected, there appeared to be an association between the activity of both the fosamprenavir/ritonavir as well as the background therapy with response.

The antiviral responses observed in APV29005 and APV20003 are comparable to those with lopinavir/ritonavir in the paediatric population, as shown in a cross-study comparison. Such a comparison has limitations due to differences in study population, differences in baseline susceptibility to the PI and the active background regimen. Noting these limitations, virologic and immunologic responses observed in APV29005 are comparable to those seen with the

lopinavir/ritonavir liquid formulation, which was examined in 100 antiretroviral therapy-naïve and experienced patients (aged 6 months to 12 years) in combination with 2 to 3 N(N)RTIs (Saez Llorens, 2003). The similar antiviral and immunologic responses between APV29005 and the lopinavir/ritonavir study were seen despite differences in patient population and study design.

It is widely acknowledged that PI liquid formulations in general have a relatively poor taste (Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection, October 2006). The guidelines also list poor palatability as a disadvantage of other PI liquid formulations (Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection, October 2006; Sharland M. et al, 2004). The data from questionnaires indicated that in children less than 13 years old, the most commonly reported issues that could be associated with non-adherence to fosamprenavir were "Taste, can't get it down, spits up, amount of pills or liquid" (reported by 27% at Week 2) and "Child refuses" (reported by 24% at Week 2). However, the reporting of these issues decreased substantially over the course of the study, indicating that children may have become used to the taste of fosamprenavir after repeated administration.

Only one patient was reported to have discontinued APV29005 clearly due to palatability related issues. Four other patients receiving fosamprenavir oral solution discontinued the study due to reasons that potentially could have been related to palatability. The antiviral response obtained by patients receiving fosamprenavir oral suspension and/or tablets during studies APV20003 and APV29005 is indicative of a relatively good level of adherence. If palatability were a major obstacle, a worse antiviral response and a higher rate of discontinuations would be expected, particularly in the youngest age group where all patients were receiving fosamprenavir oral suspension.

While the presented data suggest a durability of the virologic response for adolescents (12 to 18 years), they remain currently limited. For PI experienced adolescents, the use of fosamprenavir/ritonavir should be guided by current clinically validated resistance algorithms; TDM may be a useful tool to ensure appropriate fosamprenavir exposure in an individual patient. In order to substantiate the current efficacy data in this age group, 8 additional patients will be recruited in Study APV29005 (see also attached Letter of Undertaking).

The paediatric studies APV29005 and APV20002 are still ongoing, actively enrolling additional children. Antiviral activity will continue to be monitored in these trials, as well as post-marketing data on the use of fosamprenavir/ritonavir in HIV infected children gathered (see also attached Letter of Undertaking). Once these data are available, a further extension of indication to include children below the age of six should be submitted for assessment. In addition, these data will be essential in further substantiating the long-term efficacy of fosamprenavir/ritonavir in children.

5 Clinical safety

Patient exposure

Studies APV29005 and APV20003 include so far 20 patients who were 2-5 years of age, 42 patients who were 6-11 years of age and 64 patients who were 12-18 years of age. The majority of patients had more than 48 weeks of exposure. The numbers comprise patients treated with both once and twice a day regimens, so the numbers of patients treated for each individual dosing regimen is small.

Study APV20002 is assessing use of fosamprenavir and fosamprenavir/ritonavir in patients less than 2 years of age. Limited data has been collected to date in this study population. Further study of fosamprenavir/ritonavir in this group of patients is expected.

Safety was assessed by both laboratory and clinical evaluations. Clinical adverse events (AEs) and laboratory AEs were graded according to the modified Division of AIDS (DAIDS) toxicity grading guidelines. Although 1994 DAIDS guidelines were originally specified in the protocol, laboratory AEs were re-graded according to the 2004 revised guidelines, which were published during the time of the study.

Adverse events

Rash
Rash is a known side effect of therapy with fosamprenavir; rash occurred in 9-17% of patients in studies of HIV-infected adults (APV30002, APV30003, ESS100732), with drug-related grade 2-4 rashes occurring in 3% of patients in each study. In studies of adults, rash has been described as erythematous or maculopapular eruptions (with or without pruritus). Rash occurred in 23/126 (18%) of patients in the paediatric clinical trial programme. Most rash events were grade 1-2 in severity and no patients discontinued treatment due to rash. The cumulative incidence of rash AEs over time shows that rash generally occurred early.

Gastrointestinal events
In the paediatric clinical development programme, gastrointestinal events were generally the most frequently reported AEs, occurring in 72/126 (57%) of patients receiving fosamprenavir/ritonavir. The most common gastrointestinal events were vomiting, diarrhoea, and nausea. The majority of gastrointestinal events were grade 1-2 in severity (two Grade 3-4 events of nausea and stomach discomfort were reported in the same patient).

Vomiting	34% (all grades), 6% (grade 2-4)
Diarrhoea	22% (all grades), 4% (grade 2-4)
Nausea	16% (all grades), 3% (grade 2-4)

Laboratory Findings
Hepatobiliary events observed in these trials were single cases of severe elevations in AST/ALT, bilirubin remained with normal ranges.

Upward shifts in lipid parameters were recorded, with a few (3 cases) grade 3 or higher toxicity grades.

Glucose did not show clinical significant patterns.

Neutropenia
Grade 3/4 neutropenia was documented significantly more frequently in patients in APV20003 (13/66, 20%) than in APV29005 (2/53; 4%). The reason for the frequency of neutropenia seen in APV20003 is unclear. Neutropenia has been identified as a potential risk.

Potential for overdose
Experience with fosamprenavir or amprenavir overdose is very limited; it is not known whether amprenavir can be removed by haemodialysis. It is notable that high-dose fosamprenavir/ritonavir (fosamprenavir/ritonavir 1400/100mg twice daily) is currently being studied in treatment-experienced, HIV-infected adults in APV102002; analysis of interim data has not revealed safety concerns with this regimen. The proposed product information for fosamprenavir/ritonavir in children is based upon weight and age based dosing recommendations, in order to minimise the risk of overdose.

Potential for off-label paediatric use
Within the HIV indication, there is a possibility of unboosted fosamprenavir use (in patients who cannot tolerate ritonavir) or once daily dosing (if compliance is an issue). These regimens have been studied within the paediatric clinical programme and no specific safety concerns have been identified with unboosted or once daily dosing regimens. At present there are currently no dosage recommendations for children aged below the age of 6 years; thus, there is the potential for off-label use in this age group.

6 Risk management plan

Pharmacovigilance plan

The MAH declared to having-

- established processes for the collection and, as required, notification of any adverse events occurring anywhere in the world, including the European Union.
- established processes for the regular and systematic review of ongoing safety data relating to its pharmaceutical products.
- permanently and continuously at its disposal the services of a Qualified Person responsible for pharmacovigilance.

The MAH submitted both the summary of safety concerns and planned pharmacovigilance actions (table 15) as well as the overview of study protocols for the pharmacovigilance plan (table 16).

Table 15 Summary of Safety Concerns and Planned Pharmacovigilance Actions

Safety Concern	Planned action(s)
Important identified risks:	-
Important potential risks:	
Neutropenia	Safety data from future and current enrolees in APV29005, APV20002 and APV20003 to be reviewed in-stream on a quarterly basis until studies complete. Quarterly reviews of clinical SAEs, spontaneous reports and published literature for 2 years post approval of the paediatric indication (then subject to review at the end of 2 years to see if still required).
Off label use of unboosted fosamprenavir	Under development Action plan to be included in the next EU RMP Update, which will be submitted with the Telzir PSUR in December 2007
Important missing information:	
Lack of safety data in children aged under 2 years	Collect information from ongoing clinical study APV20002 which is evaluating PK, safety and antiviral response in children under 2 year and review in-stream on a quarterly basis until study complete.
Additional information regarding long term use in children under 18 years	Collect additional safety data from ongoing paediatric studies APV29005 and APV20003 and review in-stream on a quarterly basis until studies complete
Further characterise safety profile in paediatrics post-marketing	Conduct quarterly reviews of post-marketing data (clinical SAEs, spontaneous reports and published literature) in children under 18 years for 2 years following approval of the paediatric indication (then subject to review at the end of 2 years to see if still required).

Table 16 Overview of Study Protocols for the Pharmacovigilance Plan

Study	Titles of protocols	Protocol Version	Protocol status	Planned submission date of interim data	Planned date for submission of final data
APV20003	Evaluating the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Fosamprenavir + Ritonavir when Administered to HIV-1 infected, Antiretroviral Naïve and Experienced, Paediatric Subjects, 2 to 18 Years Old	Protocol amendment 6 of Jan06	Ongoing	48wk CSR already submitted in Dec 06	No further recruitment planned; TBC
APV29005	Evaluating the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Fosamprenavir + Ritonavir when Administered to HIV-1 infected, PI- Naïve and Experienced, Paediatric Subjects 2 to 18 Years Old and of Fosamprenavir Administered to PI-Naïve, Paediatric Subjects 2 to <6 Years Old	Protocol amendment 2 of Jan 06	Ongoing	24 wk data Q4 2009 48 wk data, Q2 2010	TBC

Study	Titles of protocols	Protocol Version	Protocol status	Planned submission date of interim data	Planned date for submission of final data
APV20002	Evaluating the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of Fosamprenavir and Fosamprenavir + Ritonavir when Administered to HIV-1 infected Protease Inhibitor (PI) Naïve and PI Experienced, Paediatric Subjects aged 4 weeks to < 2 years	Protocol amendment 4 of Aug 05	Ongoing	24 wk data Q4 2009 48 wk data, Q2 2010	TBC
WEUSRTP 2427	Feasibility of using observational cohorts and drug utilisation databases to monitor drug safety.	Concept protocol being drafted	Planned	31 Aug 2007	Dependent on feasibility assessment

Risk Minimisation Plan

The MAH stated that no additional concerns with fosamprenavir were identified during the paediatric clinical development programme which would necessitate an update to the product information or additional risk management activities.

Table 17 Summary of the EU Risk Management Plan, version 02

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Measures
Identified Risks		
Lack of safety data in children aged under 2 years	Study APV20002 evaluating use in children under 2 years	-
Additional information regarding long term use in children under 18 years	Additional experience from ongoing paediatric studies APV20003, APV29005	-
Further characterise safety profile in paediatrics post-marketing	Quarterly post-marketing reviews (subject to review at the end of 2y to see if still required) Explore feasibility of using observational cohorts and healthcare claims databases to assess real world use of FPV in paediatrics.	-
Potential Risks		
Neutropenia	Monitor current and future enrolees in APV29005, APV20002 and APV20003 Quarterly post-marketing reviews (subject to review at the end of 2y to see if still required) Routine pharmacovigilance using specific targeted safety questionnaires.	-
Off label use of unboosted fosamprenavir	Under development Action plan to be included in the next EU RMP Update, which will be submitted with the Telzir PSUR in December 2007	-

Discussion on Clinical Safety, the PhV System and the RMP

Two clinical studies (APV29005 and APV20003) provided safety data on HIV-infected children between the age of 2 to 18 years. However, the number of patients receiving fosamprenavir/ritonavir twice daily in the age group 2 to 5 years is too small to reach a conclusion on the safety profile in this age group. For patients < 2 years of age, only very limited data has been collected from study APV20002. Further data in this age group are awaited; this study so far could therefore not be used in evaluating the safety profile of fosamprenavir in the very young.

Although the key study in this program is APV29005, in which patients received fosamprenavir/ritonavir twice daily, APV20003 (once daily regimen) provided additional safety data as it included paediatric patients from the same age range who achieved comparable plasma amprenavir PK exposures. Overall cumulative exposure was 151 patient-years, and the majority (70%) of patients received fosamprenavir/ritonavir for >48 weeks.

With regards to dose level, a substantial proportion of overall exposure to fosamprenavir/ritonavir in Study APV29005 occurred at or above the proposed recommended doses: in total, 52 of the 57 patients (91%) treated with fosamprenavir/ritonavir twice daily in APV29005 received doses at or higher than those proposed in the PPK model.

The five most frequently reported AEs, regardless of causality (excluding AEs likely associated with a concurrent illness) included vomiting, diarrhoea, headache, nausea, and rash. Laboratory parameters which were examined were total cholesterol, LDL cholesterol, triglycerides, absolute neutrophil count, and ALT. Plasma amprenavir PK did not generally correlate with observed AEs or the clinical laboratory parameters tested.

Neutropenia was a potential new safety concern detected in one of the two paediatric studies (APV20003). The observed rate of neutropenia in APV20003 was considered to have been specific to that study and to have been at least partially confounded by concomitant medications and spurious laboratory results. Nevertheless, neutropenia is considered as a potential risk that will be monitored within the ongoing clinical studies and post-marketing surveillance.

In addition, off-label use of unboosted fosamprenavir (in patients who cannot tolerate ritonavir) is a potential risk.. The MAH has proposed to provide an action plan to address possible off-label use (see also attached Letter of Undertaking).

Pharmacological class effects of PIs observed in adults, gastrointestinal events, lipid abnormalities, AST/ALT elevations and blood glucose elevations should be considered as identified risk also for the paediatric population. Rash is also an identified risk in adults population and in paediatric population.

Overall, due to the limited database on safety in paediatric patients, further experience with the fosamprenavir/ritonavir twice daily regimen is required, particularly for 2 to 5 year old patients. Study APV29005 is ongoing, and has been amended to evaluate the proposed dose (fosamprenavir/ritonavir 23/3 mg/kg twice daily) in the 2 to 5 year old age group. In addition, up to 8 patients in the age group of 6 to 18 years will be added to the study, further substantiating the safety profile (see also attached Letter of Undertaking).

In addition, the MAH is currently assessing the feasibility of using observational cohorts and drug utilisation databases to provide information on usage of fosamprenavir in children within the real world population (see also attached Letter of Undertaking). To further characterise the safety profile in paediatrics post-marketing, the MAH will perform quarterly safety reviews and revert back to a 6-monthly PSUR cycle as of the next data lock point.

The MAH has committed to update the RMP in the light of the above identified issues in parallel to the submission of the next PSUR. In this update, the inclusion of the adult population in the EU RMP will be done (see attached Letter of Undertaking).

Taking the above limitations of available data into consideration, the safety profile of fosamprenavir/ritonavir twice daily is acceptable in the added paediatric population of children above the age of six, subject to the pharmacovigilance activities undertaken.

7 Overall discussion and benefit/risk assessment

Given the availability of Telzir oral suspension, the extension of indication to include the treatment of paediatric patients is of interest, especially in view of the limited available boosted PI regimens available in this population in contrast to adult patients.

In the target population Telzir is expected to be a preferable option as compared to the current oral solution formulation of amprenavir with regards to the excipients content (lower propylene glycol concentration) and the higher concentration of active, allowing the administration of lower volumes.

Pharmacokinetics

The dose recommendation derived from the PPK model for children above the age of six is in line with the doses used in study APV29005 for this age group. The fact that for 12 to 18 year olds, the predicted geometric mean AUC(0-τ) and Cmin values were approximately 20% lower than the targeted adult exposure in the PPK model are to some extent balanced by the efficacy data for this age group. Nevertheless, this positive clinical outcome needs to be further substantiated in the ongoing studies. Concerns, however, remain with the age group of children below the age of six.

The fact that in study APV20002 (very young children of 6 to 24 months of age) no sufficient plasma levels could be achieved even after administration of fosamprenavir/ritonavir doses up to 4.5-fold the adult ones raises major concerns. This may not only be explained by the relatively higher CL in this age group, but may also be due to an insufficient absorption of the oral solution, possibly because of a short gastrointestinal transit time in small children, or because of frequent vomiting and diarrhoea in HIV-infected children. The MAH should further research the underlying cause of this effect in the ongoing study. In addition, theses findings were reflected in the SPC.

Clinical efficacy
Overall, the clinical efficacy data submitted in support of this type II variation are limited. Those derived from study APV29005, which evaluated the efficacy of the recommended fosamprenavir/ritonavir twice daily regimen when used in combination with two NRTIs are only supportive for the use of fosamprenavir/ritonavir twice daily in paediatric patients above the age of six, due to the lack of children evaluated for the lower age group. In the supported age group, however, both antiviral and immunological responses were acceptable.

The observed variability in antiviral response was most likely due to differences in underlying baseline viral resistance or treatment experience of each individual patient. The antiviral responses observed in APV29005 and APV20003 are comparable to those with lopinavir/ritonavir in the paediatric population, as shown in a cross-study comparison. The similar antiviral and immunologic responses between APV29005 and the lopinavir/ritonavir study were seen despite differences in the patient populations and in the study designs.

The antiviral response obtained by patients receiving fosamprenavir oral suspension and/or tablets during studies APV20003 and APV29005 is indicative of a relatively good level of adherence, even though palatability is a common problem in antiretroviral therapy with oral solutions.

While the presented data suggest a durability of the virologic response for adolescents (12 to 18 years), they remain limited. For PI experienced adolescents, the use of fosamprenavir/ritonavir should be guided by current clinically validated resistance algorithms; TDM may be a useful tool to ensure appropriate fosamprenavir exposure in an individual patient. Efficacy of fosamprenavir/ritonavir in all age groups will further be evaluated in the ongoing clinical trials.

Clinical safety
Two clinical studies (APV29005 and APV20003) provided safety data on HIV-infected children between the age of 2 to 18 years. However, in the age group 2 to 5 years the number of patients receiving fosamprenavir/ritonavir twice daily is too small to reach a conclusion on the safety profile in this age group. For patients <2 years of age, only very limited data has been collected from study APV20002. Further data in this age group are awaited; this study so far could therefore not be used in evaluating the safety profile of fosamprenavir in the very young.

Neutropenia was a potential new safety concern detected in one of the two paediatric studies (APV20003). However, this signal may have been at least partially confounded. Neutropenia is considered as a potential risk that will be monitored within the ongoing clinical studies and post-marketing surveillance.

In addition, off-label use of unboosted fosamprenavir is a potential identified risk (in patients who cannot tolerate ritonavir).

Overall, due to the limited database on safety in paediatric patients, further experience with the fosamprenavir/ritonavir twice daily regimen is required, particularly for 2 to 5 year old patients. Study APV29005 is ongoing, and has been amended to evaluate the proposed dose (fosamprenavir/ritonavir 23/3 mg/kg twice daily) in the 2 to 5 year old age group. In addition, up to 8 patients in the age group of 6 to 18 years will be added to the study, further substantiating the safety profile.

In addition, the MAH is currently assessing the feasibility of using observational cohorts and drug utilisation databases to provide information on usage of fosamprenavir in children within the real world population (see also attached letter of undertaking). To further characterise the safety profile in paediatrics post-marketing, the MAH will perform quarterly safety reviews and revert back to a 6-montly PSUR cycle as of the next data lock point.

The MAH has committed to update the RMP in the light of the above identified issues in parallel to the submission of the next PSUR. In this update, the inclusion of the adult population in the EU RMP will be done (see attached Letter of Undertaking).

Taking the above limitations of available data into consideration, the safety profile of fosamprenavir/ritonavir twice daily is acceptable in the added paediatric population of children above the age of six, subject to the pharmacovigilance activities undertaken.

Benefit/risk assessment

Overall, the pharmacokinetic, efficacy and safety data provided within this variation application are adequate to support the extension of indication to include the children and adolescents between the ages of 6 to 18 years. This is founded in the validity of the dose recommendation, the durability of the virologic and immunologic response and the safety profile for this age group.

In the light of the above, the CHMP considered the benefit/risk balance for the extension of indication of fosamprenavir/ritonavir in combination with other antiretroviral medicines to include children and adolescents of the age of six years or above to be positive.

8 Product information

Further to the assessment of the initial (see attachment 8) and additional proposals of the MAH to amend the Product Information and in the light of the assessment of the submitted data, the CHMP requested the following amendments in the Summary of Product Characteristics (SPC), Annex II and Package Leaflet (PL). The MAH was in agreement with this and withdrew the request for an extension of indication below the age of six years.

SPC

Section 4.1 "Therapeutic indication"

The MAH's initial proposed changes to section 4.1 were discussed and not agreeable by the CHMP. Telzir oral suspension should be indicated in children and adolescents above the age of six years, mainly due to the fact that for the paediatric population below the age of six pharmacokinetic and efficacy data as well as long-term safety experience is limited.

Section 4.2 "Posology and method of administration"

The MAH's initial proposal was amended to reflect the fact that the extension of indication was only agreed for children above the age of six years. In addition, a warning about the lack of data in the younger children was added, together with a cross-reference to section 5.2.

Section 4.8 "Undesirable Effects"

The adverse event profile in children and adolescents was updated based on the integrated safety data from studies APV29005 and APV20003. The initial proposal by the MAH to add warnings about the non-recommendation of the once-daily regimen was deleted as this is duly reflected in section 4.2.

Section 5.1 "Pharmacodynamic properties"

Results of study APV29005 are presented. The initial proposal by the MAH to reflect all age groups was not agreed, and the data was recalculated to represent only the results obtained in the newly added paediatric population. As APV20003 employed the once daily regimen, the initially proposed full description of its results was reduced.

Section 5.2 "Pharmacokinetic properties"

Pharmacokinetic results of study APV29005 are reflected for the relevant age group. In addition, upon request by the CHMP, the findings of study APV20002 are shortly given, i.e. that even with dose increases up to 4.75 fold no satisfactory plasma exposure in this age group was achieved. This information was thought to be pertinent in order to further discourage the off-label use of fosamprenavir/ritonavir in this age group.

Section 5.3 "Preclinical safety data"
As the nature of hyaline droplets in the kidneys of juvenile rats had been clarified to be α2μ globulin within a post-authorisation commitment, the relevance of the renal findings in juvenile animals during the assessment of the initial MA was addressed as such: *"Toxicity was not aggravated when juvenile animals were treated as compared with adult animals, but the data did indicate a steeper dose response."*

PL
The PL was updated in accordance to the changes proposed to the SPC. The CHMP agreed with the MAH proposed wording.

Annex II
Annex II was updated to include the conditions or restrictions with regards to the safe and effective use of fosamprenavir.

The MAH agreed with the above amendments and submitted a revised Product Information.