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ASSESSMENT REPORT FOR APTIVUS

International Nonproprietary Name:
Tipranavir

Procedure No. EMEA/H/C/000631/II/29

Marketing Authorisation Holder (MAH):
Boehringer Ingelheim International GmbH

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

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1. Introduction

Aptivus (tipranavir – TPV) was developed for treatment-experienced patients who have Human Immunodeficiency Virus type 1 (HIV-1) strains with Protease Inhibitor (PI) resistance associated mutations. On 25 October 2005, TPV 250 mg soft capsules were authorised in the European Union (EU) under exceptional circumstances for combination antiretroviral (ARV) treatment of HIV-1 infected adult patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one PI. The recommended dose is 500 mg TPV, co-administered with 200 mg ritonavir (RTV; if used as booster =/r), twice daily (b.i.d.). In February 2008, following the 2nd annual reassessment of Aptivus, the CHMP recommended that the exceptional circumstances be lifted since all specific obligations had been fulfilled.

At the time of the initial marketing authorisation application (MAA) for Aptivus, the company submitted the interim results of a phase I/IIa (1182.14) study conducted in treatment naïve and experienced children using an oral solution formulation. Patients were stratified according to age (i.e. 2 to <6 years, 6 to <12 years and 12 to 18 years) and randomised into one of 2 different dose regimens: high dose group (TPV 375 mg/m^2 with RTV 150 mg/m^2) and low dose group (TPV 290 mg/m^2 with RTV 115 mg/m^2).

Only limited data from 37 children were available at the time of the initial opinion. Out of these 37 children, 33 received TPV with RTV for 4 weeks. The mean trough concentration was approximately 30% higher with the higher dose as compared to the lower dose. Considering the very limited clinical data available and the lack of bioequivalence between the oral solution and the capsules, the CHMP concluded at the time that TPV should not be used in children and that further data were needed before a marketing authorisation for the oral solution could be granted. The provision of the final reports from Study 1182.14 was part of the follow-up measures to be fulfilled in the post-authorisation setting.

The MAH submitted the 48-week results from Study 1182.14 in July 2006 in the framework of FUM 021. Following the review of these data, the CHMP requested additional information in December 2006 and responses were submitted by the MAH in February 2007. Although the duration of Study 1182.14 was 48 weeks, an optional safety extension was planned, for which 100-week results have now become available.

Based on these data, the MAH has now applied for an extension of the therapeutic indication to include HIV-infected paediatric patients aged 2 years and older. The proposed Body Surface Area (BSA) based dose for children (age 2 to 18 years) is 375 mg/m² TPV co-administered with 150 mg/m² RTV, b.i.d.. The paediatric dose should not exceed the adult dose.

In parallel to this variation application, the MAH also submitted an extension application for a new pharmaceutical form of TPV, i.e. a 100 mg/ml oral solution intended for use in paediatric and adult patients. This line extension application is assessed in parallel within the procedure EMEA/H/C/631/X/30.

In this variation application, the MAH proposed to update sections 4.1 “Therapeutic indications”, 4.2 “Posology and method of administration”, 4.4 “Special warnings and precautions for use”, 4.8 “Undesirable effects”, 5.1 “Pharmacodynamic properties” and 5.2 “Pharmacokinetic properties” of the Summary of Product Characteristics (SPC) to include information on the treatment of paediatric patients. The Package Leaflet (PL) is revised accordingly. In addition, a user testing has been performed on the proposed PL for the oral solution. This readability testing is discussed within procedure X/30. Consequential changes were proposed for the PL of the soft capsules.

2. Non-clinical aspects

Toxicology

At the time of initial MAA, a complete toxicological programme was performed with TPV. It included single dose studies (mice, rats and dogs), repeated dose studies (TPV alone in mice, rats and dogs and TPV + RTV in rats and dogs), genotoxicity and reproductive and developmental toxicity studies (rats and rabbits). Effects of TPV in repeat-dose toxicity studies with TPV were observed primarily in the liver, the gastrointestinal tract, the coagulation system and the testes. Liver was a target organ of TPV in all tested species: rats, mice and dogs. Hepatic effects of TPV common to all species included increased liver weights and hepatocellular hypertrophy. Testicular effects consisted of decreased weights and bilateral seminiferous tubule degeneration and/or atrophy observed in a 26-week TPV/r study in rats at a dose level of 1200/320 mg/kg/day TPV/r and in the 39-week study in dogs after administration of 320 mg/kg/day TPV alone. Further review of these findings led to the conclusion that the testicular effects were not attributable to TPV. Lymphocytolysis was also observed. An immunotoxicity study has been conducted in mice treated for 28 days to TPV/r the highest dose being 300/80 mg/kg. TPV/r had no effect on the antibody response following immunisation with a T-cell dependent antigen.

When assessing the need for additional toxicity studies in juvenile animals, differences between children and adults in the structure and function of organ systems resulting from growth and development should be considered to determine if the standard battery of toxicology studies is sufficient. Several organ systems are not of concern in children aged 2 years and older due to their maturation at an earlier time point (e.g. pulmonary and renal systems), or the lack of effects on these systems in the standard battery of repeat dose toxicology studies (e.g. skeletal system). Although the nervous system continues to develop until puberty, safety pharmacology studies and repeated dose toxicity studies did not raise any safety concern related to nervous central system in adults, and therefore this organ system was not considered to be potentially affected in the juvenile population.

Safety concerns pertaining to the immune and reproductive systems could be expected in the juvenile population. However, additional data provided during the initial MAA evaluation were reassuring. Finally, since liver is in a mature state in children aged 2 years, no difference was expected in hepatotoxicity in children compared to adults. Therefore, in accordance with the "Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications" (EMEA/CHMP/SWP/169215/2005), the CHMP agreed that there was no need to perform any further study in juvenile animals.

Since the initial MAA, two investigative studies in male rats were performed to evaluate the effects of TPV on the coagulation cascade and to determine if vitamin E-TPGS, an esterified derivative of vitamin E present in TPV oral solution, would modulate the changes induced by TPV. Bleeding events were observed, associated with prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT) and a decrease in some vitamin K dependent factors. Coadministration of TPV with vitamin E-TPGS resulted in an exacerbation of the anticoagulant effects of TPV, specifically causing increases in PT, aPTT, and Thrombotest levels and decreases in vitamin K dependent factors. Co-administration of TPV with vitamin E should be used with caution and at doses not higher than 1200 IU vitamin E per day. This information was included in the SPC (Variation II/23 – Commission Decision on 7 July 2008). Co-administration of TPV with vitamin E-TPGS, an esterified derivative of vitamin E, resulted in an exacerbation of the anti-coagulant effects of TPV in male rats, specifically causing increases in PT, aPTT, and Thrombotest levels and decreases in vitamin K dependent factors.

3 Clinical aspects

3.1 Pharmacokinetics/pharmacodynamics

The Bioavailability (BA) of TPV oral solution was evaluated through two studies:

- a Phase I study (1182.45) to assess the relative BA of TPV from capsule and oral solution formulations at 500 mg b.i.d., each co-administered with RTV 200 mg b.i.d (TPV/r 500/200).
- a Phase I study (1182.100) to assess the relative BA of TPV/r 500 mg/200 mg at steady state when TPV and RTV are administered as oral solutions versus capsules in the fed and fasted state.

These studies are discussed within procedure X/30.

In support of this application for a paediatric indication, the MAH submitted data from Study 1182.14, a multicentre, open-label, randomised Phase I/IIa study of two doses of TPV oral solution with low dose RTV in HIV-infected children and adolescents 2 to 18 years of age. The design, efficacy and safety findings from this study are presented in sections 3.3.2 and 3.3.3 of this report. Efficacy aspects include the issues of viral load dynamics, TPV concentrations, baseline viral resistance and viral response. The main pharmacokinetic (PK) results from Study 1182.14 are presented hereafter.

Model-based pharmacokinetic analyses in Study 1182.14 (4-week interim analysis)

In model-based analyses of steady-state population PK among 52 children in Trial 1182.14, during the first 28 days of TPV/r oral solution administration, low and high dose TPV/r were evaluated and stratified according to age group. Dosing for this trial was determined by allometric scaling of the adult dose, with TPV/r 290/115 mg/m^2 b.i.d. (the low dose) projected to be approximately equivalent to the adult dose and 375/150 mg/m^2 b.i.d. projected to be a 30% increase in the adult dose. The main PK results are shown in Table 1.

Higher concentrations for TPV $Cp_{0,12h}$, C_{max} and AUC_{0-12h} were observed in the 375/150 mg/m^2 dose group in the two lower age groups (2 to <6 and 6 to <12 years) compared to the lower TPV/r dose. Values were approximately equal in the 12 to 18 year age stratum. It should be noted that the dose was limited to 500/200 mg and that more patients in the TPV/r high dose in the 12 to 18 age group reached that limit.

Table 1: Steady state tipranavir pharmacokinetic parameters (mean ± SD) following twice-daily dosing in paediatric patients

Parameter	Dose Regimen	2 to <6 years	6 to <12 years	12 to 18 years
Oral Clearance (L/h)	Low Dose	0.45 ± 0.16	0.55 ± 0.30	0.78 ± 0.44
	High Dose	0.34 ± 0.11	0.45 ± 0.08	0.99 ± 0.96
Elimination Half-Life (h)	Low Dose	7.6 ± 5.1	7.5 ± 3.7	8.3 ± 9.0
	High Dose	8.1 ± 3.3	7.1 ± 2.1	5.2 ± 2.3
Predicted AUC_{0-12h} (µM•h)	Low Dose	710 ± 223	971 ± 469	1102 ± 526
	High Dose	1190 ± 332	1354 ± 256	1194 ± 517
Geometric mean observed concentrations (µM)	Low Dose	28.2	43.8	35.3
	High Dose	48.7	63.9	46.1

As illustrated in Table 2, a comparison of paediatric and adult data showed that TPV systemic exposure (AUC), trough and maximum concentrations obtained in children receiving the low dose were closer to those observed in adults. For both doses, the largest variability (approximately 70%) was observed in trough concentrations.

Table 2: Overall statistical analysis for the relevant pharmacokinetic parameters at the two dose levels studied compared to adult patients receiving TPV/r 500/200 mg capsules BID

Dose	Statistic	C_{trough} (µM)	C_{max} (µM)	AUC (h•µM)	CL/F (L/h)	V/F (L)
290 mg/m^2	Geometric Mean	34.4	91.2	794	0.49	4.4
n=25	gCV %	76	42	46	48	56
375 mg/m^2	Geometric Mean	53.7	133.1	1172	0.44	4.1
n=26	gCV %	65	38	41	56	49
500 mg	Geometric Mean	35.6	77.6	710	1.3	10.2
N=106 males	gCV %	54	22	30	30	5
500 mg	Geometric Mean	41.6	94.8	851	1.2	7.7
N=14 females	gCV %	153	24	44	44	5

Further analyses showed that the higher variability may be mainly driven by the 12-18 year group, which may reflect a limited compliance in these patients. When considering the individual demographic and PK parameters, it was noted that in the low dose group the youngest patients were most frequently under-dosed (difference of more than 10 mg less between dose actually administered and dose calculated according to BSA) as compared to the older age groups. The opposite trend was observed for the high dose group (older age groups more frequently under-dosed). However patient numbers in each age group were too small to allow for a reliable comparison.

In conclusion, both the low and high doses met protocol-defined PK criteria for dose selection: geometric mean TPV C_{min} >16 µM and geometric mean TPV $AUC_{0\text{-}12h}$ >483 h•µM. However, PK results at Week 4 suggested that the low dose (290 mg TPV) was the most comparable to the adult dose.

Steady-state trough concentrations in Study 1182.14

Plasma TPV and RTV trough concentrations collected 10-14 hours after administration were evaluated by patient age group (2 - <6 years, 6 - <12 years and 12-18 years) and TPV/r dose group (290/115 mg/m^2 and 375/150 mg/m^2). Table 3 summarises the individual plasma concentrations collected from patients over 8 to 100 weeks of study and includes the 25% of patients (N = 23 patients of the total 93 patients) where the TPV/r dose was changed over those weeks of study.

Table 3: Summary of steady-state plasma TPV and RTV trough concentrations collected 10-14 hours after dosing

Plasma tipranavir concentrations				
		TPV/r dose (mg/m^2)		
Age (years)	Summary Statistic	290/115	375/150	Ratio[1]
2 to <6	N samples (N patients)	102 (17)	48 (11)	
	N samples BLQ	3	4	
	N samples for Geometric Mean	99	44	
	Geometric Mean (µM)	32.69	46.91	1.4
	Geometric CV (%)	99.2	66.8	
6 to <12	N samples (N patients)	136 (37)	90 (16)	
	N samples BLQ	16	6	
	N samples for Geometric Mean	120	84	
	Geometric Mean (µM)	33.08	61.32	1.9
	Geometric CV (%)	91.9	86.1	
12 to 18+	N samples (N patients)	135 (27)	104 (23)	
	N samples BLQ	29	22	
	N samples for Geometric Mean	106	82	
	Geometric Mean (µM)	49.79	55.06	1.1
	Geometric CV (%)	115.0	124.5	
Plasma ritonavir concentrations				
		TPV/r dose (mg/m^2)		
Age (years)	Summary Statistic	290/115	375/150	Ratio[1]
2 to <6	N samples (N patients)	102 (17)	48 (11)	
	N samples BLQ	17	6	
	N samples for Geometric Mean	85	42	
	Geometric Mean (µg/mL)	0.11	0.14	1.2
	Geometric CV (%)	113.2	114.3	
6 to <12	N samples (N patients)	136 (37)	90 (16)	
	N samples BLQ	28	11	
	N samples for Geometric Mean	108	79	
	Geometric Mean (µg/mL)	0.12	0.22	1.8
	Geometric CV (%)	116.6	111.3	
12 to 18+	N samples (N patients)	135 (27)	104 (23)	
	N samples BLQ	36	24	
	N samples for Geometric Mean	99	80	
	Geometric Mean (µg/mL)	0.23	0.44	1.9
	Geometric CV (%)	152.4	164.7	

Note: [1]High Dose (375/150) : Low Dose (290/115)

For the TPV/r low dose group, the geometric mean plasma TPV trough concentrations were approximately 33 µM for patients 2 to <6 years and 6 to <12 years old and were approximately 50 µM for patients 12 years and older. For those patients receiving TPV/r high dose, the geometric mean plasma TPV trough concentrations were approximately 47, 61 and 55 µM for the age groups 2 to <6, 6 to <12 and 12-18 years, respectively. For the TPV/r low dose group, the geometric mean plasma RTV trough concentrations were 0.11, 0.12 and 0.23 µg/ml for patients in the age groups 2- <6, 6- <12 and 12-18 years, respectively. For the high dose group, geometric mean plasma RTV trough concentrations were 0.14, 0.22 and 0.44 µg/ml for patients in the age groups 2- <6, 6- <12 and 12-18 years, respectively. The CHMP questioned the relevance of these PK data in the lower dose group as well as the comparison of the TPV trough levels for the two doses, since data from patients having switched doses after 48 weeks were included in the analysis and their proportion per age group is unknown.

3.2 Clinical efficacy

Design of Study 1182.14

Study 1182.14 is a multicentre, open-label, randomised Phase I/IIa study of two doses of TPV oral solution with low dose RTV in HIV-infected children and adolescents 2 to 18 years of age.

Objectives
The primary objective of this study was to determine the safety and tolerability of TPV oral solution and soft-gel capsules each with low-dose RTV in HIV-1 infected children and adolescents and to provide information regarding the PK-PD characteristics of two dose levels of TPV and RTV in this age group. The secondary objective of this study was to determine the dose of TPV/r in children and adolescents between 2 and 18 years of age required for an adult equivalent systemic exposure of TPV/r 500/200 mg. Based on these objectives, an optimal treatment dose of TPV/r in children was to be selected and the benefits of formulation options were to be determined.

Inclusion and exclusion criteria
HIV-infected (viral load >1500 RNA copies/ml) patients 2 to 18 years of age could be included regardless of prior ARV therapy or HIV resistance status. This approach was considered questionable by the CHMP, in view of the safety profile of TPV; however, only 3 treatment- naïve patients were enrolled in the trial. To be included, children had to have acceptable screening laboratory values i.e. severity not higher than Grade 1 for all tests defined by the DAIDS (>3 months of age) Table for Grading Severity of Paediatric Adverse Experiences with the following exceptions: Grade 2 GGT, Grade 2 cholesterol, Grade 2 triglycerides. Active hepatitis B or C disease defined as HBsAg positivity or HCV antibody or RNA positivity with AST/ALT above Grade 2 were among exclusion criteria.

Study design and treatment arms
Following the screening period, eligible patients were randomised to one of two doses of TPV/r:

- TPV/r low dose group: TPV 290 mg/m^2 + RTV 115 mg/m^2 b.i.d.
- TPV/r high dose group: TPV 375 mg/m^2 + RTV 150 mg/m^2 b.i.d.

Patients were stratified according to age (i.e., 2 to <6 years, 6 to <12 years, and 12 to 18 years). All patients started treatment with TPV oral solution. Children who were 12 years or older and reached TPV/r 500/200 mg dose were eligible to switch to TPV soft capsules after Week 4. HIV genotype testing was performed at the screening visit, but was not part of the inclusion/exclusion criteria, and was used to guide investigators in selecting optimal background antiretroviral regimen. At least two background antiretroviral agents were required in addition to TPV/r. No other PIs were allowed in the trial.

Dose selection
The two TPV/r doses used in this trial are allometrically scaled doses of the adult recommended TPV/r 500/200 mg dose. The low dose (TPV 290 mg/m^2 + RTV 115 mg/m^2) is BSA-equivalent of the adult dose, derived by dividing the adult dose with mean adult BSA of 1.73 m^2. The high dose (TPV 375 mg/m^2 + RTV 150 mg/m^2) was calculated by dividing the adult dose with 1.33 m^2 (12 year old male BSA). Actual dosing of TPV and RTV was based on the BSA to reduce potential inter-individual pharmacokinetic variability. BSA was calculated at randomisation and at each study visit and TPV/r dosing was adjusted as needed. The maximum TPV/r dose allowed was 500/200 mg b.i.d. regardless of the patient's BSA.

A protocol defined interim analysis for optimal dose selection was performed on a subset of 52 patients who completed 4 weeks of treatment and pseudorandom/intensive PK sampling. The following criteria were applied to select the optimal dose: <20% severe AEs; <20% DAIDS Grade 3 or 4 laboratory abnormalities; median viral load (VL) decrease greater than 0.5 $\log_{10}$ copies/ml; geometric mean TPV C_{min} >16 μM and geometric mean TPV $AUC_{0\text{-}12h}$ >483 h•μM.

Number of patients
Planned: 100; Enrolled: 132, Randomised: 115

- TPV 290 mg/m^2 + RTV 115 mg/m^2 b.i.d.:
  Entered: 58; treated: 58; analysed (for primary endpoint): 58
- TPV 375 mg/m^2 + RTV 150 mg/m^2 b.i.d.:
  Entered: 57; treated: 57; analysed (for primary endpoint): 57

The interim analysis subset (IAS) dataset included 52 patients who completed intensive/pseudorandom pharmacokinetic evaluation at Week 2 and completed 4 weeks of treatment. The full analysis set (FAS) population through 48 and 100 weeks of study treatment exposure consisted of 115 randomised and treated patients.

Endpoints
The primary endpoint was the assessment of the safety and tolerability of TPV/r oral formulation. Efficacy and pharmacokinetic endpoints were assessed as secondary endpoints.

Efficacy endpoints:
- Proportion of patients reaching and maintaining a VL <400 copies/ml at Week 48;
- Change in mean CD4 count from baseline to Week 48;
- Assessment of patient compliance with administration of study medication;
- Time to treatment failure.

Safety endpoints:
Adverse events and laboratory measurements using the DAIDS standardised Toxicity Table for Grading Severity of Paediatric (>3 months) Adverse Experiences

Pharmacokinetic endpoints:
- TPV and RTV pharmacokinetic parameters at steady-state (C_{max}, Cp_0, Cp_{10h}, Cp_{12h}, $AUC_{0\text{-}10h}$, $AUC_{0\text{-}12h}$, t_{max}, CL, V, $t_{1/2}$;
- Relative bioavailability of TPV oral solution and TPV soft-gel capsules.

Statistical methods and definitions
Descriptive statistics were used to summarise and evaluate the safety, pharmacokinetic, and virologic parameters. Most analyses were stratified for age (2 to <6, 6 to <12, and 12 to 18 years of age) and evaluated with respect to TPV/r treatment.

Study populations:
- FAS: The complete set of patients that included all randomised and non-randomised patients who took at least one dose of TPV/r.
- On treatment (OT): Missing data in these analyses were not replaced. This approach was used for all endpoints. On treatment was a method to derive a valid measurement as close to the planned visit as possible within a "window" around a planned visit.
- Non-completer considered failure (NCF): Missing values replaced by an indicator for failure. This approach was applicable only for binary endpoints (e.g., VL reduction <400 copies/ml). If a rebound was immediately preceded by consecutive missing values the NCF approach considered them as failures.

The time to treatment failure was analysed using standard Kaplan-Meier (KM) statistical methods. The NCF method of dealing with missing data, utilising the FAS population was used.

Compliance:
Compliance with the study intake regimen was defined as a treatment adherence rate between 95% and 120%. Treatment adherence was measured at each study visit by measuring the amount of oral solution or capsules that were returned.

Virologic parameters:
For all analyses of HIV RNA, values were expressed as $\log_{10}$ copies/ml. The baseline was defined as the mean of the last two observations after $\log_{10}$ transformation, prior to the start of treatment with TPV/r. Sensitivity analyses used both the last observation carried forward (LOCF) and OT approaches to investigate the influence of missing data. The median and mean baseline VL and the median and mean change in VL from baseline were derived. Additionally, the proportion of patients who achieved an RNA level below the limit of quantification (e.g., <400 and <50 copies/ml) and the proportion of patients who had ≥1 $\log_{10}$ reduction were presented in a descriptive fashion and analysed separately for each of the two dose groups at Week 48.

Immunologic parameters:
For the CD4 cell count and CD4 percentage (CD4%) analysis, the median and mean baseline value for each treatment group were derived. The CD4% is defined as the percent of total lymphocytes that express the CD4 marker. The change in CD4 cell counts from baseline through Week 100 was assessed using descriptive statistics. Both the LOCF and OT methods, utilising the FAS populations were used.

Resistance parameters:
The measures of resistance included the following scores:

- TPV score: number of mutations present in any of the following protease gene codons L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V;
- FDA score: number of protease gene mutations at codons 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, and 90;
- IAS score: number of protease gene mutations at any of the following codons: 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 63, 71, 73, 77, 82, 84, 88, and 90;
- "Lamivudine (3TC) and/or tenofovir (TDF) mutations" include reverse transcriptase gene mutations K65R, M184I/V, and Q151M as well as any insertion at codon 69;
- "Thymidine analog mutations (TAMs)" which include reverse transcriptase mutations 41L, 67N/G, 70R, 210W, 215F/Y, 219Q/E/N'

Phenotypic susceptibility was expressed as "x"-fold-change from wild-type control 50% inhibitory concentration (FC in IC50) for the individual medicinal products tested (i.e., TPV, lopinavir).
A genotypic sensitivity score (GSS) was derived as a measure of sensitivity to the ARV background regimen. Each background ARV medication was assigned a value of 0, 0.25, or 1 based on defined criteria. The GSS was the sum of these values for each patient.
The genotypic inhibitory quotient (GIQ) is defined as the geometric mean TPV concentration divided by the number of TPV mutations at baseline.

Study duration
The planned duration of the study was 48 weeks. However, continued TPV/r treatment was permitted for patients who achieved a viral load <400 copies/ml or a viral load reduction of 0.5 $\log_{10}$ from baseline at the 48-week visit, or who had not fulfilled the criteria and rules for stopping treatment, in the optional safety extension (OSE). The study is ongoing.

Discussion on the design
The following deficiencies, which may hamper the validity of the results, were identified by the CHMP:

- the study was conducted in an "open-label" manner;
- no (external) comparator group was included;
- the study was not powered for a comparison of the efficacy of the different dosing/formulation groups;
- the switch to TPV capsules in the 12-18 year-old patients was not conducted in a randomised manner.

Efficacy results from the 4-week interim analysis
A more pronounced decrease in VL was observed in the TPV/r low dose group. Furthermore a lower virological response was observed in the 12-18 year group when compared to other age groups in both TPV dose groups. The defined criteria of median VL decrease >0.5 log_{10} copies/ml was not met in the 12-18 year group receiving high dose TPV/r.

Interim analysis conclusions
With the exception of the efficacy criterion for the 12-18 year/high dose group, both doses met the five protocol defined criteria for dose selection *(PK and safety results are presented in sections 3.3.1 and 3.3.3 of this report, respectively)*. However, the TPV low dose provided TPV trough concentrations closer to those in adults while allowing an overall better safety profile with no loss of efficacy. Even if no statistical analysis was performed, a general trend for higher early virological response was reported in the low dose group. These results in favour of the low dose group were mainly apparent for the two youngest age groups (2 to <6 age and 6 to <12). Based on these results, the low dose (TPV/r 290/115 mg/m^2 b.i.d.) was selected and patients were switched to this dose. However, at the time the switch was implemented, all but 4 patients had already reached Week 48.

Efficacy results at Week 48
A total of 115 randomised patients were included in the 48-week analysis, 58 in the TPV/r low dose and 57 in the TPV/r high dose group.

Baseline data
The population mostly consisted of male children of white race. The baseline HIV characteristics of patients showed that immunologic and virologic parameters were comparable between the two treatment groups overall, with a median baseline HIV RNA of 4.7 log_{10} copies/ml, CD4 cell counts of 379 cells/mm^3, and CD4% of 20%. Twelve patients (10.4%) had positive clinical markers for hepatitis B co-infection. There were no patients with HCV co-infection. The majority of the patients (93%, 107/115) acquired the HIV infection through mother-to-child transmission.

The CHMP highlighted that based on the demographic and HIV-related baseline characteristics, the 12-18 years old patients continuing the oral solution differed from those switching to the soft capsules. Patients switching were older and came more often from European study sites. Moreover, in "switchers", number of PI resistance mutations and VL were lower, CD4 cells (absolute count as well as percentage) were higher. These differences indicate that the "non-randomised" option to switch the formulation may have led to imbalances impacting the validity of the comparison of the performance of the two formulations.

Median number of previously used ARVs was 3 in the 2 to <6 age group, 8 in the 6 to <12 age group and 10 in the 12 to 18 age group. Assessment of the mutations related to TPV showed higher resistance patterns in the older age groups. Resistance to all PIs was 20.0% (5/25) in the 2 to <6 age group compared to 47.4% (18/38) in 6 to <12 age group and 65.4% (34/52) in the 12 to 18 age group. The same pattern was present for individual PIs, as well as for ARVs from other classes. Efavirenz (EFV) was the most frequently used NNRTI (17.4%, 20/115). Enfuvirtide (ENF) was used by 13% (15/115) patients, 10.5% (4/38) in the 6 to <12 age group and 21.2% (11/52) in the 12 to 18 age group.

Treatment compliance
Despite the unpleasant taste of RTV and TPV oral solutions, the overall compliance was comparable between TPV/r high dose and low dose. The compliance was significantly higher in younger children (92% in low dose group vs. 67% in high dose group) than in older age groups (29-33% in low dose group and 50-53% in high dose group). The difference in favour of the higher dose group may be explained by the fact that more patients in this group were allowed to switch to capsules as they reached per BSA-based calculation the maximum dose of TPV/r 500/200 mg. Moreover, many (24) of the patients who were supposed to take RTV oral solution switched to RTV capsules because of bad taste.

Patient disposition
There were more patient discontinuations in the TPV/r low dose group than in the TPV/r high dose group at both Weeks 24 and 48. The frequency of other reasons (virological failure) was notably higher in the TPV/r low dose group 10.3% (6/58) than in the TPV/r high dose group 5.3% (3/57) at Week 48.

Results
Overall, 45.6% (26/57) patients achieved VL <400 copies/ml in the TPV/r high dose compared to 39.7 % (23/58) in the TPV/r low dose, but the difference was not statistically significant (p=0.57). A total of 34.5% (20/58) patients in the TPV/r low dose group vs. 35.1% (20/57) patients in the TPV/r high dose group achieved <50 copies/ml. Median VL decrease was -0.80 log_{10} copies/ml in the TPV/r low dose group compared to -1.24 log_{10} copies/ml in the TPV/r high dose group. The difference between the two doses at Week 48 was not statistically significant. The overall proportion of patients achieving VL decrease ≥1 log_{10} copies/ml was 43.1% (25/58) in the TPV/r low dose and 45.6% (26/57) in the TPV/r high dose at Week 48 (p=0.85). Both dose groups showed overall increase in CD4 cell count and CD4% through Week 48.

Table 4: Summary of the Week 48 efficacy results

Age group	2 to <6		6 to <12		12 to 18	
Dose	TPV/r low	TPV/r high	TPV/r low	TPV/r high	TPV/r low	TPV/r high
Median VL change log_{10} copies/mL	-2.74	-2.38	-0.57	-1.24	-0.26	-0.62
VL < 400 copies/mL	76.9%	66.7%	31.6%	42.1%	26.9%	38.5%
VL < 50 copies/mL	53.8%	50.0%	31.6%	42.1%	26.9%	23.1%
VL decrease ≥1 log_{10} copies/mL	84.6%	66.7%	36.6%	42.1%	26.9%	38.5%
Median CD4 increase	504	140	143	141	25	31
Median CD4% increase	10	6	5	3	2	0

As shown in Table 4 above, a higher proportion of patients achieved VL<400 copies/ml in the 2 to <6 age group than in the 6 to <12 age group and the 12 to 18 age group. Likewise, the proportion of patients with virologic response was higher in younger children (e.g. 50% of patients in the 2- <6 year group achieved VL <50 copies/ml vs. 25% in the 12-18 year group). Although there was an overall trend towards better virological response with the TPV/r high dose, no statistically significant difference was observed. This trend for higher response with the high dose was mainly due to the better results observed in the 6 to <12 years old and 12 to 18 years old age cohorts. In the 2 to <6 year group there was on the contrary a trend for higher virological response with the TPV/r low dose group.

A logistic regression was performed modelling the effects of treatment group, genotypic inhibitory quotient (GIQ), baseline viral load, age group, TPV adherence, and genotypic sensitivity score (GSS) on the outcome at Week 48 for the three virologic endpoints of HIV RNA <400 copies/ml, HIV RNA <50 copies/ml, and ≥1 log_{10} reduction of HIV RNA from baseline.

Greater baseline resistance tended to result in a lower proportion of virologic responders. Increasing TPV mutation scores were associated with decreased rates of virologic response, particularly for the low dose patients. In those patients with more baseline resistance, the high dose groups had higher viral response rates, especially in the group with ≥5 TPV mutations.

Table 5: Proportions of patients with virologic response (<400 copies/ml) at Week 48 by baseline TPV mutation score (FAS 48)

Baseline TPV Mutation Score	Low Dose n (%) N	High Dose n (%) N
0	6 (85.7) 7	4 (33.3) 12
1 to 4	16 (44.4) 36	17 (51.5) 33
5 or more	1 (6.7) 15	5 (41.7) 12
Total	23 (39.7) 58	26 (45.6) 57

The GIQ is a reflection of TPV concentration and baseline resistance to TPV. It was determined for each patient by dividing the geometric mean of TPV C_{trough} obtained at steady state by the number of TPV mutations present at baseline. Patients with the largest number of TPV mutations (i.e. patients with more advanced infections and more extensive prior treatment) had the lowest GIQ values.

However, this baseline resistance was countered in the high dose group by the achievement of higher concentrations of TPV. Overall, the median GIQ values were larger among TPV/r high dose-treated patients (12.33 for low dose vs. 19.04 for high dose), a trend that was observed within each age group as well. Moreover, among the age groups, the 2 to <6 year-olds exhibited the largest median GIQ score, with the 6 to <12 year-olds given high dose TPV/r having a lower score, followed by 12 to 18 year-olds having the lowest score, reflecting that the younger children had fewer baseline mutations, which translated into higher GIQ and thus better virologic response rates.

Table 6: Virologic response at Week 48 based on the GIQ quartiles

GIQ quartiles	<400 copies/mL n (%) N	<50 copies/mL n (%) N	≥1 $\log_{10}$ copies/mL n (%) N
Q1 (0.56-7.19)	2 (8.0) 25	1 (4.0) 25	2 (8.0) 25
Q2 (7.23-13.50)	13 (52.0) 25	11 (44.0) 25	14 (56.0) 25
Q3 (13.68-38.61)	15 (57.7) 26	13 (50.0) 26	16 (61.5) 26
Q4 (39.29-215.38)	17 (68.0) 25	14 (56.0) 25	17 (68.0) 25

Multivariate analyses revealed that GIQ level and adherence to treatment were each statistically significant predictors of viral load response. When these parameters were included in the model, age was no longer an important factor. Overall, higher GIQ scores led to higher odds ratios for response compared to the lowest GIQ quartile. This suggests that treatment response can be improved by using the higher dose of TPV/r, resulting in an increase in TPV concentration and a higher GIQ.

Four (4) patients, all in the TPV/r low dose group, developed an AIDS defined illness. Kaplan-Meier probability of reaching an AIDS defining illness up to Week 48 was 7.8% in the TPV/r low dose group vs. 0.0% in the TPV/r high dose group (p = 0.04).

Discussion on the 48-week results

The MAH concluded that TPV/r high dose, TPV 375 mg/m^2 + RTV 150mg/m^2, is the appropriate dose for paediatric patients aged 2 to 18 years as it provided a higher and more durable response with an acceptable safety profile *(safety results are presented in section 3.3.3)*. Therefore, although the interim analysis results at 24-week led to selection of the TPV/r low dose, all patients were switched to the TPV/r high dose following analysis of the 48-week results.

Theses changes highlight the difficulty of identifying the appropriate dosing based on a rational argument as overall the results were not consistent across the different age groups: the low dose gave better response rate in the 2-6 and in the 12-18 age groups whereas the high dose gave better response rate in the 6-12 age group.

However, when analysing the efficacy results for both dose groups by 48 weeks for all age groups, the percentage of patients with VL <50 copies/ml, results were similar for the low dose and the high dose

(34.5% and 35.1%, respectively). This inconclusiveness of findings, not giving a clear picture on the effective dose within a good safety margin, highlights the paucity of the available data.

Specifically for the 12-18 year-old patients, only a small virologic impact was observed, i.e. -0.26 in TPV/r low dose group to -0.62 log_{10} copies/ml in the TPV/r high dose group (-0.2 in the oral solution group and -0.4 in the capsule group). Nevertheless, comparison with other clinical trials of RTV boosted PIs show similar results. For all of them, efficacy results markedly decreased for adolescents when compared to children.

GIQ and adherence were shown to be significant predictors of Week 48 response rates while the age group was not a significant predictor. For this reason, the MAH believes that the higher dose of TPV/r is appropriate, especially for children who fulfil the current indication for TPV/r, and are infected with HIV that has failed prior therapy. In principle, the CHMP considered the use of the dose that provides the higher GIQ in this target population with viral strains harbouring multi-resistance reasonable. However, clinical data to substantiate this dose in children remain limited.

In addition, regarding the use of the capsule formulation in children, it is important to note that:

- the clinical experience gained with the capsule formulation is only derived from the use in children above 12 years of age,
- the capsule formulation is not suitable for the recommended BSA based dosing regimen in children less than 12 years of age

Taking into account on the one hand the effect on viral load and on the other the above limitations, TPV/r may have a place, even if very limited, in the treatment strategy for HIV infected children harbouring a multi resistant virus. In view of the limitations of clinical data in children with the recommended dose, TPV/r as capsules could be considered for the treatment of children above 12 years of age when no other therapeutic options are available.

During the procedure the MAH agreed to restrict the paediatric indication to children from 12 years of age and proposed a new wording for an indication in this age group for the capsule formulation.

Efficacy results at Week 100

As discussed above, based on the 48-week data, the MAH selected the TPV/r high dose for the continuation of the study, i.e. patients who were on low dose from the beginning of the trial and those who were on high dose and switched to low dose after the first interim analysis received the TPV/r high dose after Week 48.

Disposition of patients

The rate of discontinuation during the extension phase was similar to that during the first 48 weeks of the study (around 25%). More patients in the 12-18 year group discontinued prior to Week 100 as compared to the younger groups (43% vs. 32%), mainly for non-adherence, adverse events and “other reasons”. The discontinuation rate was the highest in the 12-18 years old children still receiving the oral solution, in particular during the first 48 weeks (44%). Only 6 patients in this subgroup were still in the study at week 100.

Treatment compliance

The compliance was not assessed at Week 100. The CHMP highlighted that data on long-term compliance would have been of interest.

Results

The 100-week efficacy analyses were mainly focussed on the comparison of the two formulations (oral solution and soft capsules) but not on the different dose regimens investigated in the first 48 weeks of the study. Changes from baseline in viral load, CD4 and CD4% and virological response rates are summarised in Tables 7 and 8 respectively.

Table 7: Median change from baseline for virologic and immunologic parameters for TPV/r treated patients, by age group and formulation

	TPV OS			TPV SEDDS
	2-<6 yrs N (%)	6-<12 yrs N (%)	12-18 yrs N (%)	12-18 yrs N (%)
Total treated	25 (100.0)	37 (100.0)	24 (100.0)	29 (100.0)
Median VL log_{10} copies/mL change from baseline - (LOCF)				
Baseline [1]	5.0	4.6	5.1	4.6
Week 24	-2.5	-1.7 [2]	-0.4	-1.2
Week 48	-2.7	-1.0 [2]	-0.4	-0.8
Week 100	-2.7	-1.2 [2]	-0.2	-0.4
Median CD4+ cell count (cells/mm^3) change from baseline - (LOCF)				
Baseline [1]	795	398	208	330
Week 24	293	133	24	56
Week 48	323	143	21	39
Week 100	294	121	12	45
Median CD4% change from baseline - (LOCF)				
Baseline [1]	26	19	12	19
Week 24	7	4	1	2
Week 48	7	5	1	3
Week 100	6	4	1	0

1 Represents baseline values and not a change from baseline
2 ANOVA p≤0.05 comparing OS treated 2 - <6 and 6 - <12 year old patients

Table 8: Proportion of TPV/r treated patients with viral response, by age group and formulation

	TPV OS			TPV SEDDS
	2-<6 yrs N (%)	6-<12 yrs N (%)	12-18 yrs N (%)	12-18 yrs N (%)
Total treated	25 (100.0)	37 (100.0)	24 (100.0)	29 (100.0)
Number of patients with at least 1 log_{10} VL reduction - (NCF)[1]				
Week 24	20 (80.0)	18 (48.6) [2]	9 (37.5)	13 (44.8)
Week 48	19 (76.0)	14 (37.8) [2]	8 (33.3)	9 (31.0)
Week 100	14 (56.0)	13 (35.1)	6 (25.0)	7 (24.1)
Number of patients <400 copies/mL - (NCF) [1]				
Week 24	16 (64.0)	15 (40.5)	8 (33.3)	10 (34.5)
Week 48	18 (72.0)	13 (35.1) [1]	8 (33.3)	9 (31.0)
Week 100	14 (56.0)	11 (29.7) [2]	6 (25.0)	7 (24.1)
Number of patients <50 copies/mL - (NCF) [1]				
Week 24	10 (40.0)	12 (32.4)	6 (25.0)	8 (27.6)
Week 48	13 (52.0)	31 (35.1)	6 (25.0)	8 (27.6)
Week 100	12 (48.0)	11 (29.7)	5 (20.8)	6 (20.7)

1 NCF = Non-Completers considered Failures
2 Fisher's exact p≤ 0.05 comparing OS treated 2-<6 and 6-<12 year old patients
3 Fisher's exact p=0.06 comparing OS treated 2-<6 and 6-<12 year old patients

Discussion on the 100-week results

According to the MAH, these results suggest a comparable efficacy between the two TPV formulation treatment groups based on the NCF analysis of the number of patients with VL reduction <400, <50 copies/ml and at least 1 $\log_{10}$ sustained VL reduction from baseline virologic endpoints. The results also showed an advantage among capsule treated patients over oral solution treated patients LOCF median changes from baseline in virologic and CD4-cell endpoints.

Due to the design of study, in particular in view of the "non-randomised" switch of formulations in the 12-18 year group, a valid comparison is difficult. Therefore, the CHMP could not conclude on the therapeutic equivalence of the two formulations based on the above results. Overall, the response rate in this study was significantly low. In both formulation groups, only approximately 20% of the 12-18 year-old patients had VL <50 copies/ml at week 100 (NCF), which is considered worrying. The 100-week efficacy data confirmed a lower virologic response in the12-18 year group compared to younger groups.

A Kaplan-Meier analysis of time to treatment failure (VL >50 copies/ml) among patients 12-18 years of age per formulation showed that the rate of patients never achieving VL<50 copies/ml was important, especially for the OS formulation (70.8% vs. 58.6%). The analysis indicates that over the whole study period of 100 weeks the patients on TPV capsules had a consistently lower probability for virologic failure as compared to the group treated with OS. The difference became less pronounced towards the end of the observational period, but was still noticeable despite all patients being treated with the higher TPV/r dose after 48 weeks. This is essential, as not only patients with a loss of virological response are counted as failures, but also patients discontinuing study treatment for any reason (i.e. also side effects). Since the switch from oral solution to soft-gelatin capsule was conducted in a non-randomised manner, patients staying on oral solution can be considered as pre-selected in terms of tolerability of the liquid formulation. Nevertheless, globally the capsule compares favourable to the oral solution.

Resistance analyses

Patient population included in the resistance analyses

Thirty-six (36) paediatric HIV-infected patients who experienced virologic rebound or failure in Study 1182.14 were selected for on-treatment resistance testing. Among these patients, 5 (13.9%) patients were 2 to <6 years old, 7 (19.4%) were 6 to <12 years old, and 24 (66.7%) were 12 to 18 years old.

Out of 115 patients randomised in Study 1182.14, three were treatment-naïve, one in each age group. In the Rebound subgroup, only 1 patient was treatment-naïve. Prior treatment with the three main classes of ARVs (NRTIs, NNRTIs, and PIs) was extensive and 8 patients had been treated with enfuvirtide.

Protease gene mutations associated with nelfinavir, lopinavir, and amprenavir use commonly present at baseline included: D30N (9.6%), M46I/L (39.1%), I47V (9.6%), V82A (29.6%), I84V (14.8%), and L90M (44.3%). More than half of the study population had 3 or more TAMs present at baseline and had resistance mutations associated with lamivudine and tenofovir use.

Analyses of response by genotype
As expected, the overall response decreased as the number of mutations increased (see Table 9).

Table 9: Virologic response (<400 copies/ml) at Week 48 by TPV and FDA Score Mutations and Age Group (NCF)

	Age Group (years)									Total		
	2 - <6			6 - <12			12 - 18					
	n	N	%	n	N	%	n	N	%	n	N	%
Overall	17	25	**68.0**	16	37	**43.2**	16	53	**30.2**	49	115	**42.6**
TPV score*												
0	7	8	87.5	1	4	25.0	2	7	28.6	10	19	52.6
1-2	6	11	54.5	9	14	64.3	5	12	41.7	20	37	54.1
3-4	3	4	75.0	6	13	46.2	4	15	26.7	13	32	40.6
5-9	1	2	50.0	0	6	0.0	5	19	26.3	6	27	22.2
FDA score**												
0	5	7	71.4	2	7	28.6	0	6	0.0	7	20	35.0
1-2	9	13	69.2	7	12	58.3	7	12	50.0	23	37	56.8
3-4	3	4	75.0	2	3	66.7	4	6	66.7	9	13	61.5
5-8	0	1	0.0	5	15	33.3	5	29	17.2	10	45	22.2

* TPV score mutations include 10V,13V,20M/R/V,33F,35G,36I,43T,46L,47V,54A/M/V,58E,69K,74P,82L/T,83D,84V
** FDA mutations include any at 30,32,36,46,47,48,50,53,54,73,82,84,88,90

The median GSS for the paediatric population was 0.5. Forty-three (43) patients (37.4% of 115) had a GSS of 0.00, indicating resistance to all background ARVs (see Table 10).

Table 10: Virologic response (<400 HIV RNA copies/ml) at Week 48 by Genotypic Sensitivity Score and Age Group

GSS, Dose Group	Age Group (years)									Total		
	2 - <6			6 - <12			12 - 18					
	n	N	%	n	N	%	n	N	%	n	N	%
0.00												
Low dose	2	5	40.0	3	8	37.5	2	10	20.0	7	23	30.4
High dose	2	3	66.7	4	8	50.0	0	9	0.0	6	20	30.0
0.25-1.00												
Low dose	2	2	100.0	4	8	50.0	3	8	37.5	9	18	50.0
High dose	3	5	60.0	2	5	40.0	7	12	58.3	12	22	54.5
1.25-2.25												
Low dose	5	6	83.3	0	3	0.0	2	8	25.0	7	17	41.2
High dose	3	4	75.0	3	5	60.0	2	6	33.3	8	15	53.3

The CHMP noted that the above results were too conflicting and the sample sizes by age strata too limited to allow drawing any conclusion on the optimal dose in children.

Emergence of protease gene mutations
Paired genotype results (at baseline and on-treatment) were available for 28 patients among the 36 with virologic failure or rebound. To evaluate the mutations emerging with TPV treatment, the 28 paired genotypes were compared and each codon of the protease gene was evaluated for any amino-acid shifts and corresponding shifts in TPV IC_{50} fold-change from baseline.

Numerous protease gene mutation gains and losses were observed. Mutations emerged at 26 codon positions (14, 16, 18, 20, 23, 33, 34, 35, 36, 45, 47, 55, 57, 58, 61, 66, 70, 71, 77, 82, 84, 85, 89, 92, 93, and 95). The largest net gain of mutations with TPV/r exposure was seen at codons 33, 36, 82 and 84, each with a net gain of 4 mutations. At codon 54, the I54V mutation was selected with TPV/r

treatment whereas the I54L mutation was de-selected. The previously reported emergence of the V82L mutation in patients with wild-type (WT) virus and the shift from pre-existing V82A to T was confirmed in these paediatric patients. The predominant emerging mutations with TPV treatment currently described in the SPC are L33F/I/V, V82T/L and I84V. Therefore, the emerging mutations observed in paediatric patients are consistent with those observed in adults.

Phenotypic data
Phenotype could not be determined for 6 of the isolates; thus, results for 30 of the patients were available. As illustrated in Table 11, the median TPV baseline phenotypic susceptibility was 1.2-fold WT IC_{50} with 75% of isolates having susceptibility below 2.6-fold WT IC_{50}. This is within the susceptible range for TPV as established in adult patients (0-3 FC IC_{50} susceptible, >3-10 decreased susceptibility, and >10 resistant). All isolates were at least partially susceptible to TPV (max 6.6-fold WT IC_{50}). Baseline phenotype analysis for other proteases showed reduced susceptibility according to the clinical cut-offs reported in the product information of these medicinal products: lopinavir <10 susceptible, 10-40 partially susceptible, >40 resistant; saquinavir 2.5, amprenavir 2.5, indinavir 3.0, nelfinavir 4.0, atazanavir 4.0, and darunavir 10.0.

Table 11: Baseline phenotypic susceptibility (Anitvirogram) of Rebound patient isolates for TPV and existing protease inhibitors in Trial 1182.14

	Antiretroviral Drug Tested/Fold WT IC_{50}							
	Tipranavir	**Lopinavir**	**Saquinavir**	**Amprenavir**	**Indinavir**	**Nelfinavir**	**Atazanavir**	**Darunavir**
N	30	30	30	29	30	30	30	30
Min	0.5	0.2	0.4	0.4	0.3	0.6	0.3	0.2
Q25	0.9	1.2	1.1	1.8	1.9	9.7	2.4	0.5
Median	**1.2**	**39.6**	**9.6**	**8.3**	**6.8**	**27.1**	**18.3**	**1.5**
Q75	2.6	52.6	56.4	17.3	15.5	72.1	63.0	5.1
Max	6.6	55.2	70.8	100.0	84.5	95.5	169.9	44.3
n (%) R	**6 (20.0)**	**18 (60.0)**	**17 (56.7)**	**19 (65.5)**	**20 (66.7)**	**25 (83.3)**	**21 (72.4)**	**3 (10.0)**

%R = Percent reduced susceptibility

In summary, with the exception of darunavir and TPV, the majority of isolates had reduced susceptibility to PIs. This supports the value of TPV/r in patients harbouring viral strains with reduced susceptibility to other PIs.

Considering that LPV/r is currently considered as the PI of choice in paediatric patients, it is expected that children that could receive TPV/r would have been previously treated by LPV/r. An analysis of response rates focussing on the subgroup of patients presenting a genotypic resistance to LPV/r showed that the virologic response in the group of patients with 0-2 LPV mutations had a VL decrease of more than 2 $\log_{10}$ copies/ml and more than 60% of patients achieving <400 copies/ml. Patients with 3-5 LPV mutations still showed strong virologic responses with median VL decrease of 1.14 copies/ml and 42.9% of patients achieving <400 and <50 copies/ml in the TPV/r high dose group.

The difference between the TPV/r low dose group and the TPV/r high dose group was not statistically significant; however, the study was not powered for efficacy analysis. Even in the group of patients with 6-9 LPV mutations, about 25% of patients showed virologic response. Patients with up to 5 LPV mutations at baseline showed a good response, particularly in the TPV/r high dose group. These data show that patients who developed resistance to LPV/r treatment would benefit from the TPV/r treatment. The CHMP concluded that these analyses, although based on very limited subgroup of patients, give support to the selection of the higher dose besides the PK/PD reasoning.

On-treatment TPV phenotypic susceptibility was reduced for 20 of 30 patients. This is due in large part to the acquisition of protease gene mutations since TPV phenotype correlated with the number of TPV score mutations. Paired genotype/phenotype data were available for 30 baseline samples and for 22 on-treatment samples. At baseline, reduced susceptibility (TPV FC IC_{50} >4) was noted only among

those isolates with 7 or more TPV score mutations. However, on-treatment, virus with 4 or more TPV score mutations showed reduced TPV susceptibility, with median TPV FC IC_{50} ranging from 10.2 to 37.7.

Conclusion on efficacy

Overall, as for the adult population, this medicinal product can be only considered as a last line therapy in highly pre-treated paediatric patient. Based on the data provided Aptivus capsule is only a treatment option in children above 12 years of age with virus resistant to multiple protease inhibitors and with no other therapeutic options. The age restriction is necessary as the experience gained with the capsule formulation is only derived from the use in children above 12 years of age. The capsule formulation is not suitable for the recommended BSA based dosing regimen in children less than 12 years of age. A deep salvage therapy is mainly expected to be observed in adolescents as compared to younger children (apart for the situation of transmission of multi-resistant strain from the mother). The use of TPV/r is expected to be marginal in children below 12 years. Indeed, the younger the children are, the less likely is the presence of HIV harbouring multiple PI resistance mutations. However, it is recognised that TPV/r could still potentially address a medical need in situations of last-line therapy for children of younger ages (see assessment report of EMEA/H/C/631/X/30).

3.3 Clinical safety

Safety results from Study 1182.14

Interim analysis

As shown in Table 12, there were slightly more patients with adverse events (AEs) in the TPV/r high dose group (69.2%, 18/26) than in the TPV/r low dose group (61.5%, 16/26).

Table 12: Summary of adverse events reported during the first 28 days of treatment

	TPV/r low dose N (%)	TPV/r high dose N (%)	Total N (%)
Total treated	26 (100.0)	26 (100.0)	52 (100.0)
Total with any AE	16 (61.5)	18 (69.2)	34 (65.4)
Total with any severe AE	2 (7.7)	0 (0.0)	2 (3.8)
Total with any study drug-related AE	8 (30.8)	11(42.3)	19 (36.5)
Serious AE	2 (7.7)	0 (0.0)	2 (3.8)
Significant AE	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

TPV/r low dose = TPV 290 mg/m^2 / RTV 115 mg/m^2
TPV/r high dose = TPV 375 mg/m^2 / RTV 150 mg/m^2

This difference was greater in the two youngest age groups (83.3% vs. 58.3% in the 2 to <6 age group and 62.5% vs. 50.0% in the 6 to <12 age group), while in the 12 to 18 age group there were more patients with adverse event in the TPV/r low dose group (83.3%, 5/6) than in the TPV/r high dose group (50.0%, 3/6).

There were also more patients with study treatment related AEs, i.e. Adverse Drug Report (ADRs) in TPV/r high dose group, 42.3% (11/26) compared to 30.8% (8/26) in TPV/r low dose group. In the 12 to 18 age group, there were more patients with ADRs in the TPV/r low dose group (66.7%, 4/6) than in the TPV/r high dose group (33.3%, 2/6).

Two patients experienced serious adverse events (SAEs), both in the TPV/r low dose group. However, in both cases events were considered not related to study treatment.

Laboratory evaluations showed 7 patients with DAIDS Grade 3 or 4 laboratory abnormalities, 2 in the TPV/r low dose group (7.7%) and 5 (19.2%) in the TPV/r high dose group. Only one of these events reached DAIDS Grade 4 severity, one case of increased amylase (TPV/r high dose group). Overall, both doses showed a similar early safety profile although there appeared to be more study treatment-related adverse events and Grade 3 or 4 laboratory abnormalities in the TPV/r high dose group.

Safety results up to 100 weeks

Exposure

The overall median exposure was 724 days for a total of 179.2 patient exposure years (PEY). For the 12-18 year group, median exposure and total patient exposure years were higher in the TPV capsule group as compared to the TPV oral solution group. More patients received study medication for at least 100 weeks in the younger groups.

Adverse events

A total of 93.9% patients reported at least one AE at 48 weeks and 96.5% patients at 100 weeks with a lower incidence in the 2- <6 year old patients receiving TPV oral solution (84.0%) at 48 weeks. SAEs were reported by 25.2% (29/115) of patients at 48 weeks and 30.4 % (35/115) of patients at 100 weeks, with the fewest events (16.0%) in the 2- <6 year group on TPV oral solution at 48 weeks and (20.0%) at 100 weeks as compared to 25%-37.5% in the other age groups and formulations. The lowest incidence of SAEs was seen in the 12–18 year-old patients on TPV capsule at both time points.

Vomiting was the most frequent AE reported overall by 37.4% (43/115) and 40.0% (46/115) of patients at 48 and 100 weeks, respectively, followed by cough (27.8%, 32/115 at 48 weeks and 33.0%, 38/115 at 100 weeks), diarrhoea (25.2%, 29/115 at 48 weeks and 29.6%, 34/115 at 100 weeks) and pyrexia (23.5% 27/115 at 48 weeks and 29.6%, 34/115 at 100 weeks). The events were observed with similar frequency among the age groups receiving TPV oral solution as well as the older age group receiving TPV capsules. Oral candidiasis and herpes simplex were among the more common events in the oldest age group receiving TPV capsules, at both time-points, reflecting the more advanced stage of HIV in these children.

Several events were present at 100 weeks that were not seen at 48 weeks of treatment, e.g., rhinorrhoea, rash papular, lymphadenopathy, influenza, back pain, epistaxis, and rash, with the incidence of rash papular (10.3%) and back pain (13.8%) both highest in the 12-18 year-old patients on TPV capsules.

Medically selected terms

Three medically selected terms (MSTs) for AEs (i.e., bleeding, hepatitis and skin rash) of special interest for children receiving TPV were evaluated and the results are presented in Table 13.

Table 13: Medically selected adverse events terms at week 48 and 100 for randomised patients (FAS) by age group and formulation

	TPV OS			TPV SEDDS	Total
	2-<6 yrs [1] N (%)	6-<12 yrs N (%)	12-18 yrs [2] N (%)	12-18 yrs N (%)	N (%)
Week 48					
Total treated	25 (100.0)	37 (100.0)	25 (100%)	28 (100.0)	115 (100.0)
• Bleeding	2 (8.0)	2 (5.4)	1 (4.0)	4 (14.3)	9 (7.8)
• Hepatitis	1 (4.0)	6 (16.2)	6 (24.0)	5 (17.9)	18 (15.7)
• Skin Rash	3 (12.0)	11 (29.7)	4 (16.0)	9 (32.1)	27 (23.5)

Week 100					
Total treated	25 (100.0)	37 (100.0)	24 (100.0)	29 (100.00)	115 (100.0)
• Bleeding	2 (8.0)	5 (13.5)	4 (16.7)	4 (13.8)	15 (13.0)
• Hepatitis	2 (8.0)	7 (18.9)	6 (25.0)	6 (20.7)	21 (18.3)
• Skin Rash	4 (16.0)	13 (35.1)	6 (25.0)	12 (41.4)	35 (30.4)

1 Percentages are calculated using total number of patients per treatment as the denominator.

2 Patient group of 12 to 18 year olds includes Patient No. 5406 who entered the trial at 11.5 years of age and switched from TPV OS to TPV SEDDS at 12 years of age.

The most frequently reported events within the Skin Rash MST were eruption, rash, rash papular, rash macular, rash maculo [papular], and urticaria. Skin rash MST events were almost twice as frequently reported in 12-18 year-old patients receiving TPV capsules than in those receiving the oral solution.

The most frequently reported events within the Hepatitis MST were GGT increased, ALT increased, hyperbilirubinemia, AST increased and liver function test abnormal. Overall there was an increase of three patients with Hepatitis MST events from 48 (15.7%) to 100 weeks (18.3%).

The most frequently reported events within the Bleeding MST were epistaxis, haematoma, gingival bleeding, haematochezia, menorrhagia, and diarrhoea hemorrhagic. Overall bleeding events increased from 48 to 100 weeks (7.8% to 13%). The frequency of Bleeding MST events was higher in children receiving TPV capsules than in those receiving the oral solution at 48 weeks. At 100 weeks the frequency of bleeding events was more uniform between age groups and formulation with the fewest events in the 2- <6 year group. There was one fatal case of gastrointestinal haemorrhage (17 year-old male receiving the oral solution).

Adverse events leading to discontinuation

A total of 13.9% (16/115) of patients permanently discontinued from the trial due to AEs through 100 weeks. Ten (8.7%) of these patients had already discontinued at 48 weeks. The most frequent events leading to discontinuation were gastrointestinal AEs, all in the 12–18 year group, as well as increased liver transaminase levels (all increases in GGT except one case of increased ALT). The highest frequency of permanent discontinuation was observed in the 6- <12 year and 12-18 year groups receiving the oral solution (6 interruptions in each group).

Deaths and serious adverse events

There were no deaths reported during the first 48 weeks of the study. There were 2 deaths as of the data cut-off for the 100-week analyses. Both of these patients had multiple underlying conditions contributing to these fatal events. One patient, a 17-year–old male treated with TPV oral solution, died of gastrointestinal bleeding. The other, a 10-year–old male, treated with TPV oral solution, died of renal failure, secondary to B-cell lymphoma. Both of these events were considered by the investigator unrelated to study medication.

Serious AEs were reported by 25.2% (29/115) patients at Week 48 and by 28.7% (33/115) patients at Week 100, with the most events experienced by the 12-18 year group of patients treated with TPV oral solution at both time points. Serious AEs in the Infestations and infections System Organ Class (SOC) were the most frequent overall, reported by 18.3% (21/115) of patients at 48 and 100 weeks, with the lowest incidence among the 12–18 year-old patients treated with TPV capsules. Serious AEs in the Gastrointestinal disorders SOC were the next most common (4.3%, 5/115 at 48 weeks and 7.0%, 8/115 at 100 weeks), predominantly in the youngest age groups (2 - <12 years of age) treated with TPV oral solution.

The most common SAE was pneumonia 5.2% (6/115) at Week 48 and 6.1% (7/115) at Week 100, followed by herpes zoster at 48 weeks and herpes zoster, diarrhoea, and pyrexia at 100 weeks. There was no pneumonia reported by the 12 – 18 year-olds at 48 or 100 weeks on TPV capsules. During the 100 weeks of study, 8 patients (all on TPV oral solution) experienced 10 serious AEs considered to be related to study medication (vomiting, abdominal pain, nausea, diarrhoea, urticaria, GGT increased, anaemia). Two of the 8 patients were 2- <6 years old, three were 6- <12 years old and three were 12-18 years old. Five of the patients required hospitalisation and all recovered.

Clinical laboratory evaluation
The most frequently reported Grade 3 or 4 laboratory abnormalities were increased GGT (10.7%, 12/112 at 48 weeks and 11.6%, 13/112 at 100 weeks) and increased creatinine phosphokinase (10.7%, 12/112 at 48 weeks and 15.2%, 17/112 at 100 weeks). The GGT increases were highest among the 12–18 year-old patients on TPV oral solution.

Two patients had Grade 4 ALT elevations. More patients in the 12-18 year group on TPV capsules at 48 weeks and at 100 weeks experienced increased levels of ALT (14.3% at 48 weeks and 17.2% at 100 weeks). Based on Kaplan-Meier analyses, by 48 weeks of treatment, 15.1% of 12-18 year-old patients on TPV capsules experienced Grade >2 ALT/AST elevations as compared to 5.6% of the 12-18 year old patients on TPV oral solution. No ALT/AST elevations above Grade 2 were observed in children 2 - <6 years on TPV oral solution and only two patients (6.0%) 6 - <12 years of age were observed with elevations.

By 100 weeks of treatment, 19.8% (5 patients) of the 12-18 years old on TPV capsules experienced Grade >2 ALT elevations compared to 5.6 % (1 patient) of the 12 - 18 years old on TPV oral solution, with no elevations seen in children 2 - <6 years on TPV oral solution and only two patients (6.0%) 6 - <12 years of age experiencing an elevation on TPV oral solution.

No patients experienced an increased cholesterol levels or increased triglyceride levels through 100 weeks of exposure with the exception of one patient in the 6 - <12 year group who experienced increased Grade 3 triglyceride levels at 100 weeks.

Discussion on safety results from Study 1182.14
Data from Study 1182.14 (especially long-term results) are considered too limited to draw reliable conclusions on the safety profiles of TPV oral solution and capsule formulation in paediatric patients. As previously discussed, the 'non-randomised' switch of formulations in the 12-18 year group further precludes the comparison of the two formulations. It can however be noted that patients receiving the oral solution in the 12-18 year group had a higher incidence of SAEs and permanent discontinuations than those receiving the capsules.

The frequency of some AEs and some laboratory findings were influenced by patient age, i.e. the 2-6 year group tended to experience fewer severe events, fewer MST events, fewer protocol-defined significant AEs, and none of these patients had Grade 3 or 4 elevations in ALT. The incidence of vomiting decreased with age in children receiving TPV oral solution, with the highest incidence observed in the 2–6 year group at both 48 and 100 weeks. In children aged 2-6 years, 52% of the children experienced vomiting and 24%, respectively, had diarrhoea and pyrexia. All these reactions have considerable impact on patients' daily activities. In the 12-18 year group, children taking TPV capsules experienced cough at a rate of 39.3%.

These examples indicate that the safety profile of TPV in children may overall be comparable to that in adults, but with marked variability depending on the age group. Therefore, the MAH, on the CHMP request, inserted a table in section 4.8 of the SPC of the TPV capsules describing the reported adverse events and laboratory abnormalities at 48 weeks of study 1182.14 in the group of paediatric patients aged 12-18 years (given the requested age restriction for the indication), together with the respective frequencies.

No new safety concerns emerged after 100 weeks of study medication, with the exception of bleeding events which increased from 48 to 100 weeks (7.8% vs. 13%). This reinforces the existing concerns about the safety profile of TPV and bleeding, in particular with respect to intracranial haemorrhages.

According to the result presented the safety profile of TPV/r in paediatrics seems to be comparable to that observed in adults. The CHMP re-emphasised that during the assessment of the initial MA of TPV/r in adults, the severe safety profile of TPV has been considered as a main issue, notably regarding its poor hepatic tolerability, which for example resulted in the premature closure of clinical

trials in ARV naïve adults. Therefore, when prescribing TPV/r to a paediatric patient, the same close safety monitoring (e.g. liver function) as in adults is recommended.

TPV/r oral solution was characterised by a high rate of vomiting. It was discussed that the high rate of vomiting may be related to the bad taste of the RTV oral solution. RTV oral solution presents a very bad taste which may induce nausea and vomiting. However, TPV oral solution has a very bad taste on its own, therefore it is difficult to judge which of the two oral solutions contribute more to the poor palatability. The poor palatability of ARV oral solutions is indeed a main issue in the treatment of HIV-infected children that does not only lead to a poor gastro-intestinal tolerance but also to a poor compliance with the related risks of treatment failure and emergence of resistance.

Safety data from other clinical trials

There were 25 paediatric patients from the Expanded Access Program/Emergency Use Program (EAP/EUP) (trials 1182.16, 1182.58, and 1182.67) and trials 1182.33 and 1182.48 for whom exposure data were available. Of these 25 patients, 18 (72%) had treatment exposure of ≥24 weeks, and of these 18, 12 (67%) had exposure of >48 weeks. The range of exposure was 8 days to approximately 2 years. Thirteen (52%) of the 25 patients were 18 years old and 12 (48%) were 11 to 17 years old; 14 (56%) were males and 11 (44%) were females. There were 12 (48%) patients with a baseline CD4 cell count of <50 cells/mm^3, and 7 (28%) had a CD4 cell count of 50 to 200 cells/mm^3. Thirteen (52%) had a VL of <100,000 copies/ml.

SAEs were reported among 9 (36%) of the 25 patients; SAEs were infections in 5 of these patients. Three patients discontinued due to AEs (all from EAP/EUP): 1 from Trial 1182.16, due to abdominal pain, diarrhoea, nausea, and vomiting; and 2 from 1182.58, 1 with incapacity to swallow TPV capsules, and the other with acute respiratory distress syndrome, which led to a fatal outcome. Significant medical history for this patient included recurring cerebral toxoplasmosis. Two patients in the EAP/EUP had SAEs relating to hepatic toxicity: 1 patient had hepatic failure and the other patient had cytolytic hepatitis. One patient in Trial 1182.16 experienced septic shock that led to a fatal outcome. This patient had multiple underlying conditions contributing to this fatal event, including cryptococcosis and atypical mycobacterial infection.

3.4 Risk management plan (RMP)

The MAH has submitted an updated RMP (version 4.2) which is summarised in Table 14.

Table 14: Summary of Risk Management Plan

Safety concern	**Important pharmacovigilance activities** (routine and additional)	**Important risk minimisation activities** (routine and additional)
Lipid metabolism disorders	n/a	Current state of knowledge adequately presented in CCDS and local labels
Hepatotoxicity	Ongoing study 1182.59 in HCV infected subjects, study 1182.99 in HBV/HCV co-infected patients, epidemiological database analyses	Intensive monitoring of hepatic cases, reports to Authorities in tight schedule
Rash	Study 1182.98 to deliver data about incidence in female patients	Current state of knowledge adequately presented in CCDS and local labels
Bleeding Intracranial haemorrhage	Coagulation parameters from ongoing studies 1182.98 ('SPRING') and 1182.71 ('POTENT'), healthy volunteer study 1182.117, further epidemiological database analyses	Current state of knowledge adequately presented in CCDS and local labels; paper for publication on epidemiological database analyses has been prepared and submitted

Safety concern	Important pharmacovigilance activities (routine and additional)	Important risk minimisation activities (routine and additional)
Safety in the elderly	Epidemiological database analyses	Advice to exercise caution included in the CCDS and SPC
Safety in black patients	Study 1182.98 ('SPRING') to enrol 200 non-white patients to examine non-white minority patients and gender effects, epidemiological database analyses	n/a
Safety in patients of Asian descent	Study 1182.71 to generate data in Asian patients, study 1182.98 to examine non-white minority patients and gender effects	n/a
Safety in pregnancy and during lactation	Continued participation in the international Antiretroviral Pregnancy Registry	Appropriate risk warning as regards use in pregnancy; Aptivus use should rule out breast-feeding
Safety in female patients	Study 1182.98 to generate data in 200 female patients and examine gender effects	n/a

The CHMP identified a number of insufficiencies in the initially submitted RMP. All concerns were satisfactorily addressed by the MAH. The following two points will require an update of the RMP that will be submitted together with the next PSUR number 7 in February 2010.

- It is agreed that the safety profile of TPV in paediatric population may possibly be comparable to adults, but available safety data remain still very limited. Further data to substantiate the safety of TPV in this target population is needed. On the CHMP request the MAH agreed on a surveillance with one of existing cohorts, e.g. Collaborative HIV Paediatric Study (CHIPS), to obtain more safety information on children exposed to TPV in real life settings and commit to review 12 months after Marketing Authorisation the feasibility of providing meaningful safety data and analyses from the Collaborative HIV Paediatric Study (CHIPS), and provide data and analyses where possible.
- On CHMP request the pharmacovigilance plan will include activities focusing on the safety in paediatric population. The target paediatric population who might receive TPV is actually limited, but still needs to be carefully monitored and followed to confirm the safety profile of TPV.

Activities focusing on the safety of the paediatric population will specifically include the following: If paediatric case reports are received, the team of safety reviewers will determine if additional information should be requested from the reporter, in order to improve the interpretability of the report, and evaluate the impact on the safety of TPV. Cases will be followed up accordingly with the reporter. Globally, all postmarketing adverse-event reports received over the year 2008 - there were 46 reports from sources spontaneous reporting and Health Authority - have been described and discussed individually in the pertaining TPV PSUR which contains a separate section about the use in children and adolescents, with three such cases reported in one year. The MAH will continue to monitor the use of TPV in children carefully and include all relevant information in the upcoming PSURs.

4. Overall conclusions, risk/benefit assessment and recommendation

In support to the extension of indication of TPV/r in paediatric patients from 2 years of age, the MAH has submitted a randomised, open-label trial to evaluate the pharmacokinetics, efficacy and safety of TPV/r in HIV-infected, treatment experienced paediatric patients aged 2-18 years. In this study performed in 115 children, two (low and high) dosing regimen were tested, 290 mg/m^2 TPV + 115 mg/m2 ritonavir b.i.d. and 375 mg/m2 TPV + 150 mg/m^2 ritonavir b.i.d.

The validity of the study results were hampered by several factors, possibly introducing bias:

- the study was conducted in 'open-label' manner
- no (external) comparator group was included
- the studied patients were more heterogeneous and overall less treatment-experienced as compared to the adult population, for which TPV/r has been approved.
- the study was not powered for a comparison of the efficacy of the different dosing/formulation groups
- the switch to TPV capsules in the 12-18 age group was not conducted in a randomised manner

The dose selection was not regarded as appropriately justified. The MAH concluded that TPV/r high dose, TPV 375 mg/m^2 + RTV 150mg/m^2, is the appropriate dose for paediatric patients aged 2 to 18 years as it provided a higher and more durable response with an acceptable safety profile. Therefore, although the interim analysis results at 24-week led to selection of the TPV/r low dose, all patients were switched to the TPV/r high dose following analysis of the 48-week results.

Theses changes highlight the difficulty of identifying the appropriate dosing based on a rational argument as overall the results were not consistent across the different age groups: the low dose gave better response rate in the 2-6 and in the 12-18 age groups whereas the high dose gave better response rate in the 6-12 age group. However, when analysing the efficacy results for both dose groups by 48 weeks for all age groups, the percentage of patients with VL <50 copies/ml, results were similar for the low dose and the high dose (34.5% and 35.1%, respectively). This inconclusiveness of findings, not giving a clear picture on the effective dose within a good safety margin, highlights the paucity of the available data.

Specifically for the 12-18 year-old patients, only a small virologic impact was observed, i.e. -0.26 in TPV/r low dose group to -0.62 $\log_{10}$ copies/ml in the TPV/r high dose group (-0.2 in the oral solution group and -0.4 in the capsule group). Nevertheless, comparison with other clinical trials of ritonavir boosted PIs show similar results. For all of them, efficacy results markedly decreased for adolescents when compared to children.

GIQ and adherence were shown to be significant predictors of Week 48 response rates while the age group was not a significant predictor. For this reason, the MAH believes that the higher dose of TPV/r is appropriate, especially for children who fulfil the current indication for TPV/r, i.e. those infected with HIV and having failed on prior therapy.

In principle, the CHMP considered the use of the dose that provides the higher GIQ in this target population with viral strains harbouring multi-resistance reasonable. However, clinical data to substantiate this dose in children remain limited.

Nevertheless, it was demonstrated that patients with up to 5 LPV mutations at baseline showed a good response, particularly in the TPV/r high dose group. These data show that patients who developed resistance to LPV/r treatment would benefit from the TPV/r treatment. The CHMP concluded that these analyses, although based on a very limited subgroup of patients, give support to the selection of the higher dose.

In addition, regarding the use of the capsule formulation in children, it is important to note that:

- the clinical experience gained with the capsule formulation is only derived from the use in children above 12 years of age,
- the capsule formulation is not suitable for the recommended BSA based dosing regimen in children less than 12 years of age

Taking into account on the one hand the effect on viral load and on the other hand the above limitations, TPV/r may have a place, even if very limited, in the treatment of HIV infected children harbouring a multi resistant virus. In view of the limitations of clinical data in children with the recommended dose, TPV/r as capsules could only be considered for the treatment of children from 12 years of age when no other therapeutic options are available.

Data from Study 1182.14 (especially long-term results) are considered too limited to draw reliable conclusions on the safety profiles of TPR oral solution and capsule formulation in paediatric patients. As previously discussed, the 'non-randomised' switch of formulations in the 12-18 year group further precludes the comparison of the two formulations. It can however be noted that patients receiving the oral solution in the 12-18 year group had a higher incidence of SAEs and permanent discontinuations than those receiving the capsules.

The frequency of some AEs and some laboratory findings were influenced by patient age, i.e. the 2 - <6 year group tended to experience fewer severe events, fewer MST events, fewer protocol-defined significant AEs, and none of these patients had Grade 3 or 4 elevations in ALT. The incidence of vomiting decreased with age in children receiving TPV oral solution, with the highest incidence observed in the 2– <6 year group at both 48 and 100 weeks. In children aged 2-6 years, 52% of the children experienced vomiting and 24%, respectively, had diarrhoea and pyrexia. All these reactions have considerable impact on patients' daily activities. In the 12-18 year group, children taking TPV capsules experienced cough at a rate of 39.3%.

These examples indicate that the safety profile of TPV in children may overall be comparable to that in adults, but with marked variability depending on the age group. Therefore, the MAH, on the CHMP request, inserted a table in section 4.8 of the SPC of the TPV capsules describing the reported adverse events and laboratory abnormalities at 48 weeks of study 1182.14 in the group of paediatric patients aged 12-18 years (given the requested age restriction for the indication), together with the respective frequencies.

No new safety concerns emerged after 100 weeks of study medication, with the exception of bleeding events which increased from 48 to 100 weeks (7.8% vs. 13%). This reinforces the existing concerns about the safety profile of TPV and bleeding, in particular with respect to intracranial haemorrhages.

According to the results presented with the capsule the safety profile of TPV/r in paediatrics, as, seems to be comparable to that observed in adults. The CHMP re-emphasised that during the assessment of the initial MA of TPV/r in adults, the grave safety profile of TPV has been considered as a main issue, notably its poor hepatic tolerability, which for example resulted in the premature closure of clinical trials in ARV naïve adults. Therefore, when prescribing TPV/r to a paediatric patient, the same close safety monitoring (e.g. liver function) as in adults is recommended.

Taking into account the efficacy and safety profile as demonstrated in the supportive data, the CHMP concluded that the benefit risk balance of TPV/r (500 mg/200 mg) capsules could be considered positive only in a very restricted indication of last line therapy in children and adolescents above the age of 12 with virus resistant to multiple protease inhibitors and for whom no other treatment options are available.

The final adopted indication reads as follows:

"APTIVUS, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adults and adolescents 12 years of age or older with virus resistant to multiple protease inhibitors. APTIVUS should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options.

This indication is based on the results of two phase III studies, performed in highly pre-treated adult patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors and of one phase II study investigating pharmacokinetics, safety and efficacy of APTIVUS in mostly treatment-experienced adolescent patients aged 12 to 18 years (see section 5.1) ”.