22 June 2017
EMA/CHMP/443456/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kaletra

International non-proprietary name: lopinavir / ritonavir

Procedure No. EMEA/H/C/000368/II/0161/G

Note

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

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1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 30 September 2016 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	Annex A, I, IIIA and IIIB
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	Annex A, I, IIIA and IIIB

Extension of Indication to include children aged 14 days and older in the treatment of HIV-1; as a consequence, sections 4.1, 4.2, 4.3, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. The studies provided in support of the paediatric indication are part of the agreed PIP (decision P/0144/2012). In addition, the Marketing authorisation holder (MAH) further updated section 4.4 to add a warning regarding the use of Kaletra oral solution with feeding tubes. The updated RMP v.8 is provided accordingly.
IB-B.II.e.5.a.2-To add a new pack size of 120 ml (in 2X 60ml bottles) for Kaletra 80mg/ml/20 mg/ml oral solution (EU/1/01/172/009).
IA-B.IV.1.a.1-To add a new 2 ml oral dose syringe for the 120ml presentation.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	30 September 2016
Start of procedure:	29 October 2016
CHMP Rapporteur Assessment Report	27 December 2016
PRAC Rapporteur Assessment Report	3 January 2017
Updated PRAC Rapporteur Assessment Report	6 January 2017
PRAC Outcome	12 January 2017
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 January 2017
Request for supplementary information (RSI)	26 January 2017
CHMP Rapporteur Assessment Report	25 April 2017
PRAC Rapporteur Assessment Report	26 April 2017
PRAC members comments	26 April 2017
Updated PRAC Rapporteur Assessment Report	4 May 2017
PRAC Outcome	5 April 2017
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	12 May 2017
2nd Request for supplementary information (RSI)	18 May 2017
PRAC Rapporteur Assessment Report	2 June 2017
PRAC members comments	
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	9 June 2017
PRAC Outcome	9 June 2017
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	9 June 2017
Opinion	22 June 2017

2. Scientific discussion

2.1. Introduction

LPV/r demonstrated to be a safe and effective ARV agent while providing a high barrier to HIV resistance development. Determining the optimal timing for initiation of highly active ARV therapy (HAART) in children infected with HIV remains a challenge. For HIV-infected children, early initiation of HAART is needed, given its strong survival benefit, improved neurodevelopmental outcomes, and faster growth recovery. HAART initiation at younger ages is associated with better immunologic recovery.

Yin et al demonstrated that starting ARV treatment (ART) at higher CD4+ T lymphocyte (CD4+) percentage and younger ages maximizes the potential for immunologic recovery. PENTA guidelines recommend initiation of an ARV regimen as soon as HIV-1 status is diagnosed or as early as 14 days of life.

Kaletra (LPV/r) is a HIV protease inhibitor (PI) currently indicated in the EU in combination with other ARV for the treatment of HIV-1 infected adults, adolescents and children ≥ 2 years old. Kaletra is available in EU as oral solution and film-coated tablets.

The current recommended doses of Kaletra in EU are as follows:

- Oral solution (children ≥ 2 years old):

- 230/57.5 mg/m^2 twice daily (BID) with food (maximum 400/100 mg BID; the dose should be increased to 300/75 mg/m^2 when co-administered with nevirapine or efavirenz), OR
- 10/2.5 mg/kg BID with food for children weighing 15 to 40 kg (maximum 400/100 mg BID; without coadministration with nevirapine or efavirenz).

- Tablets:

- Adults and adolescents 400/100 mg BID with food Children≥ 2 years old (able to swallow tablets):
    - Weighing ≥ 40 kg or BSA ≥ 1.4 m²: 400/100 mg BID with or without food
    - Weighing 15 to < 40 kg:

Table 1. Paediatric dosing guidelines without concomitant efavirenz or nevirapine*

Weight (kg)	Body surface area (m^2)	Recommended number 0f 100/25 mg tablets twice-daily
15-25	≥0.5 to ≤0.9	2 tablets (200/50mg)
> 25-35	≥ 0.9 to < 1.4	3 tablets (300/75mg)
> 35	≥ 1.4	4 tablets (400/100mg)

*weight based dosing recommendations are based on limited data

Table 2. Paediatric dosing guidelines with concomitant efavirenz or nevirapine

Body surface area (m^2)	Recommended number 0f 100/25 mg tablets twice-daily
≥0.5 to ≤0.8	2 tablets (200/50mg)
≥ 0.8 to < 1.2	3 tablets (300/75mg)
≥ 1.2 to < 1.4	4 tablets (400/100mg)
≥ 1.4	5 tablets (500/125mg)

In the United States, LPV/r is licensed for paediatric patients **at least 2 weeks of age (since 2008)**:

- Oral solution:

Table 3. Paediatric dosing guidelines without concomitant efavirenz or nevirapine

Patient age	Based on weight (mg/kg)	Based on BSA (mg/m^2)	Frequency
14 days to 6 months	16/4	300/75	Given twice daily
6 months to 18 years	< 15 kg (12/3) ≥15 kg to 40 kg (10/2.5)	230/57.5	Given twice daily

- Co-administered with efavirenz or nevirapine or nelfinavir: for children ≥ 6 months old to < 18 years of age:
    - 300/75 mg/m^2 BID OR
    - 13/3.25 mg/kg BID for patients weighing <15 kg; 11/2.75 mg/kg for patients weighing 15 to 45 kg

- Tablets:

Table 4. Paediatric dosing guideline without co-administration with efavirenz or nevirapine or nelfinavir: for children ≥ 6 months old to < 18 years of age

Weight (kg)	Body surface area (m^2)*	Recommended number 0f 100/25 mg tablets twice-daily
15-25	≥0.6 to ≤0.9	2
> 25-35	≥ 0.9 to < 1.4	3
> 35	≥ 1.4	4 (or two 200/50mg)
*Kaletra oral solution is available for children with a BSA less than 0.6 m^2 or those who are unable to reliably swallow a tablet		

Table 5. Paediatric dosing guideline co-administered with efavirenz or nevirapine or nelfinavir: for children ≥ 6 months old to < 18 years of age:

Weight (kg)	Body surface area (m^2)*	Recommended number 0f 100/25 mg tablets twice-daily
15-20	≥0.6 to ≤0.8	2
> 20-30	≥ 0.8 to < 1.2	3
> 30 to 45	≥ 1.2 to < 1.7	4 (or two 200/50mg)
> 45	≥ 1.7	5
*Kaletra oral solution is available for children with a BSA less than 0.6 m^2 or those who are unable to reliably swallow a tablet. Please refer to the individual product labels for appropriate dosing in children		

European and WHO guidelines (PENTA 2016 WHO 2016) support the use of LPV/r in all patients < 1 year of age.

On 23 July 2012, the European Medicines Agency (EMA) provided a decision (P/0144/2012) to accept the modifications of the agreed pediatric investigation plan (PIP) for LPV/r (Kaletra) (EMEA-00100S-PIP01-10-M01). The accepted modifications included clarifications to the PK, efficacy, and safety endpoints, eligibility criteria, and study duration for the P1030, P1060, and Children with HIV Early Antiretroviral Therapy (CHER) studies that included data in the population ≤ 36 months of age. The data presented in this clinical overview reflect the modifications accepted in Decision P/0144/2012, as well as additional post-marketing safety data.

This application for a Type II variation for Kaletra (80 mg + 20 mg)/mL oral solution is being submitted in support the extension of the dosing of paediatric patients to those who are 2 weeks of age and older. The MAH's claim for the EU pediatric extension of indication is "Kaletra is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children aged 14 days and older". The proposed paediatric posology of Kaletra is

similar to the US posology, excepted for the lack of weight-based dosage for children from 14 days to 6 months of age in the proposed EU SmPC.

2.2. Quality aspects

Dosing Commodities – 2 mL Oral Dosing Syringe

The 2 mL polyethylene/polystyrene oral dosing syringe was selected for dosing Kaletra Oral Solution doses less than 2.0 mL. The oral dosing syringe is graduated with 0.1 mL markings from 0.2 mL to 2.0 mL, with volume labeled every 0.2 mL. The syringe has CE marking (Notified Body number 0373) and the materials are in compliance with REACH (EC 1907/2006).

In order to ensure dosing accuracy, the accuracy of the dosing syringe was evaluated according to Ph. Eur. 2.9.27 – Uniformity of mass of delivered doses from multi-dose containers. The dosing accuracy test was performed for target dosage volumes of 0.5 mL and 2.0 mL (selected target dosage volumes covered the low end and the high end of dosing). Twenty replicates were performed for each target dosage volume. The requirements are that not more than two individual masses deviate from the average mass by more than 10% and none of the individual masses deviate from the average mass by more than 20%.

Results are summarized in Table 6. No individuals were outside ± 10% from the average. No individuals were outside ± 20% from the average.

Table 6. Testing Result Summary from the Uniformity of Mass of Delivered Doses from the Syringe

Target Volume (mL)	Minimum Value (g)	Maximum Value (g)	Average of 20 Replicates (g)	± 10% Range of Average (g)	± 20% Range of Average (g)
0.5	0.51543	0.54747	0.52721	0.47449 to 0.57993	0.42177 to 0.63265
2.0	2.05788	2.10359	2.08069	1.87262 to 2.28876	1.66455 to 2.49683

Compatibility of Kaletra Oral Solution

The compatibility of lopinavir/ritonavir with the 2 mL oral dosing syringe was assessed at ambient temperature (25°C/60% RH) for the initial time-point, 2 hours and 12 hours; and at accelerated conditions 30°C/65% RH for 3 hours, each in triplicate. No significant change was observed in lopinavir and ritonavir potency and degradation products at ambient conditions and accelerated conditions during storage of Kaletra Oral Solution in the 2 mL oral dosing syringe. Also, physical inspection of the samples showed that the appearance, colour, and clarity specifications were met after storing the solutions at these storage conditions. The results are summarized in Table 7.

Table 7. Summary of Results for In-use Stability and Compatibility Study for Kaletra Oral Solution in 2 mL Syringe

Testing Interval	Lopinavir Assay (% Label Amount, Range)	Total Lopinavir Degradation Products (%w/w)	Ritonavir Assay (% Label Amount, Range)	Total Ritonavir Degradation Products (%w/w)
Acceptance Criteria	**90 to 110**	**≤ 0.5**	**90 to 110**	**≤ 3.0**
Initial	102.4 to 103.5	0.0	101.7 to 102.7	0.13 to 0.14
25°C/60% RH, 2 hours	99.1 to 100.5	0.0	100.8 to 102.1	0.14 to 0.15
25°C/60% RH, 12 hours	102.1 to 103.2	0.0	101.2 to 102.3	0.13 to 0.14
30°C/65%RH, 3 hours	99.9 to 100.6	0.0	101.5 to 102.2	0.13 to 0.14

2.2.1. Discussion on quality aspects

During assessment of the Kaletra PIP application, the Paediatric Committee (PDCO) commented that to minimize the risk of overdosage, an oral dosing syringe of 2 mL or 2.5 mL was recommended instead of the 5 mL oral dosing syringe included in the currently approved 300 mL (5 × 60 mL bottles) pack of Kaletra oral solution. In line with the PDCO recommendation, the marketing authorization holder (MAH) proposed to add a 2-mL oral dosing syringe for use with Kaletra oral solution when dosing paediatric patients who require a dosage of 2 mL or less. In addition, the MAH proposed to add a new pack size of two 60-mL bottles of Kaletra oral solution. The 120 mL pack size is a more appropriate size for the very young paediatric patients. The new pack size will include two 2-mL oral dosing syringes. The applications for the new administration device (2 ml syringe) and the 2-bottle pack have been grouped with this variation.

Of note the 2 ml syringe is different from that of 5 ml: polyethylene for both barrel and plunger for the 2 ml syringe and polypropylene for both barrel and plunger for that of 5 ml. The worst case compatability study found in section 3.2.P.2.6 under 12h/25°C-60%RH and 3h/30°C-65%RH largely mimicking the time of contact do not raise any particular issue.

The MAH has also performed compatibility studies with materials of feeding tube (polyvinyl chloride and silicone) to support recommendation of use via a feeding tube in the SmPC. However, those data were later removed from the application further to interaction with EMA, as the EMA has judged that this should be a new route of administration to be adequately validated.

The MAH has nevertheless maintained a statement in the SmPC as regards the incompatibility with polyurethane because of the ethanol content: “Because Kaletra oral solution contains alcohol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility.” This can be endorsed.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Indeed according to the CHMP in the initial MA and PDCO, to support an indication in paediatrics, the

toxicity of the combination was also evaluated in neonatal (3-4 days old at the start of treatment) or juvenile rats (16 days old at start of treatment) treated with oral doses up to 40/20 mg/kg/d and 100/50 mg/kg respectively. Similar to the manifestation in adult animals, target organ toxicity was most evident in the liver of juvenile rats but less so in neonatal rats.

Despite the fact that the combination altered pup viability at day 4 post-partum in rats at doses that were not toxic to the dams but not at weaning in the peri/post-natal development study, neonates (3-4 days old at the start of treatment) appear to be less sensitive to the toxicity produced by LPV/r when compared with adult rats.

No updated environmental risk assessment for lopinavir and ritonavir has been provided. However, as stated in the EPAR of KALETRA that the lack of environmental risk assessment was considered acceptable since lopinavir degrades under UV-light and rapid breakdown is to be expected based on the molecular structure of lopinavir/ritonavir. Moreover, the MAH provided data on the low incidence of HIV in children under 2 years of age in EU (< 300 / year). This extension of indication constitutes a marginal increased in the environmental exposure and the $PEC_{surfacewater}$ value is below 0.01 µg/L based on the maximum daily dose.

2.4. Clinical aspects

2.4.1. Introduction

As part of the PIP, additional data for dosing recommendations in infants, including newborns younger than 1 month of age, utilizing PK modelling was requested. The MAH committed to providing this update utilizing clinical trial simulations to estimate LPV exposure in paediatric patients with various heights and weights according to established growth chart distributions.

PK simulations were conducted using the population PK model developed by Nikanjam et al in HIV-1-infected infants 14 days to 6 months of age to summarize LPV exposure in a larger number of infants 14 days to younger than 6 months of age, with varying body weight and BSA. The simulations also compare exposures of LPV achieved in infants dosed based on body weight (16 mg/kg LPV BID) and BSA (300 mg/m2 LPV BID). Infant body weight distributions and BSA distributions based on the height and weight profiles from the WHO growth charts were utilized for the simulations. The goal of the simulations is to support dosing recommendations in these younger children < 6 months of age.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical data were collected in 4 completed studies conducted outside the EU: AbbVie Study M98-940, Paediatric AIDS Clinical Trials Group (PACTG) Studies P1030 and P1060 (both open-label paediatric LPV/r studies conducted by the PACTG with support from AbbVie), and CHER.

Table 8. Studies Conducted with LPV/r in the Paediatric Population Younger than 36 Months of Age

Study	Countries	Age groups	Objective	Number treated with LPV/r	LPV/r dosages tested
P1030	US, Brazil, Puerto Rico	14 days to 6 months	To evaluate paediatric dosing requirements, PK, safety, tolerability, and efficacy	31	300/75 mg/m^2 BID
P1060	South Africa, Malawi, Tanzania, Zambia, Uganda, Zimbabwe, and India	2 to 36 months	To compare rates of treatment failure at 24 weeks between NVP based and LPV/r-based ARV regimen	222	16/4, 12/3, or 10/2.5 mg/kg BID
CHER	South Africa	6 to 12 weeks	To evaluate whether early ARV therapy delays progression of disease compared to deferred ARV therapy[b]	411[a]	300/75 or 230/57.5 mg/m^2 BID
M98-940	US, Canada, Bahamas, Panama, Argentina and South Africa	6 months to 2 years[c]	To determine an adult equivalent dose of LPV/r in HIV-infected children based on the PK and tolerability of LPV/r in combination with reverse transcriptase inhibitors and to characterize the safety and antiviral activity of LPV/r in combination with reverse transcriptase inhibitors.	100	230/57.5 mg/m2 or 300/75 mg/m2

a. Of 286 subjects randomized to receive early ARV that included LPV/r, 2 never received ARV. Of 125 subjects randomized to the deferred ARV group, 90 received ARV including LPV/r by Week 48.

b. Results summarized and presented are through Week 48.

c. M98-940 included children aged 3 months – 12 years; patients were stratified by age 6mos – 2 years and > 2 years.

2.4.2. Pharmacokinetics

Intensive PK sampling

The pharmacokinetics of LPV/r were assessed in subjects aged from 14 days to 6 months in study P1030:

Table 9. Pharmacokinetic Subject Demographics at the Time of Pharmacokinetic Sampling (Week 2)

Subject Number	Weight (kg)	Height (cm)	BSA (m^2)	Lopinavir Dose (mg)	Lopinavir Dose (mg/m^2)	Age at Analysis (months)
Age ≥ 14 Days to < 6 Weeks Cohort (N = 9):						
Mean (SD)	4.81 (0.88)	55.74 (4.62)	0.27 (0.04)	71.89 (9.60)	267.19 (31.26)	1.93 (0.48)
Median	4.70	54.50	0.27	64.00	266.67	1.84
Range	3.60-6.10	49.50-65.50	0.21-0.33	64.00-87.00	206.45-304.76	1.38-3.12
Age ≥ 6 Weeks to < 6 Months Cohort (N = 18):						
Mean (SD)	6.03 (1.49)	59.89 (4.56)	0.32 (0.05)	87.56 (16.57)	274.17 (20.04)	4.21 (1.46)
Median	5.50	59.10	0.31	80.00	275.86	3.88
Range	4.40-10.50	53.00-66.00	0.25-0.44	64.00-128.00	235.29-305.88	2.10-6.38

Please refer to the "Clinical Efficacy" section for more details on the study design and enrolled subjects.

The PK results are as follows:

Table 10. Lopinavir Non-compartmental Pharmacokinetic Results at Week 2 in Study P1030

Subject Number	T_{max} (hours)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC_{12} (µg•hr/m)
Age ≥ 14 Days to < 6 Weeks Cohort (N = 9):				
Mean (SD)	3.39 (1.01)	5.17 (1.84)	1.40 (0.48)	43.39 (14.80)
CV%	30	36	34	34
Median	4.00	4.76	1.26	36.60
Range	2.00 – 4.38	2.84 – 7.28	0.92 – 2.31	27.88 – 62.56
Age ≥ 6 Weeks to < 6 Months Cohort (N = 18):				
Mean (SD)	2.87 (1.08)	9.39 (4.91)	1.95 (1.80)	74.50 (37.87)
CV%	37	52	92	51
Median	2.14	8.10	1.39	67.51
Range	1.98 – 4.58	3.02 – 20.40	0.00 – 5.62	23.66 – 164.03

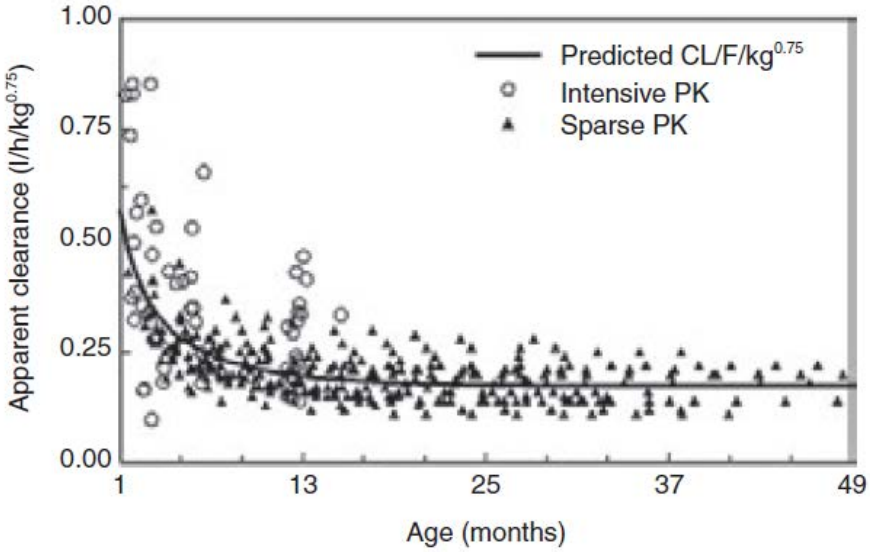
CV = coefficient of variation; NA = not applicable; SD = standard deviation

Population PK modelling

In addition, as part of the PIP, the MAH was requested to provide additional data for dosing recommendations in infants, including newborns younger than 1 month of age, utilizing PK modeling. Therefore, PK simulations were conducted using the population PK model developed by Nikanjam et al[1] in HIV-1-infected infants 14 days to 6 months of age, with varying distributions of body weight and BSA based on WHO growth charts. These analyses used a one-compartment model with first order oral absorption in NONMEM with an exponential error model, and include PK and efficacy data from study P1030. Significant covariates in this model were RTV concentration and age. This model shows a higher apparent clearance and lower bioavailability in younger children:

[1] Nikanjam M, Chadwick EG, Robbins B, et al. Assessment of lopinavir pharmacokinetics with respect to developmental changes in infants and the impact on weight band-based dosing. Clin Pharmacol Ther. 2012;91(2):243-9.

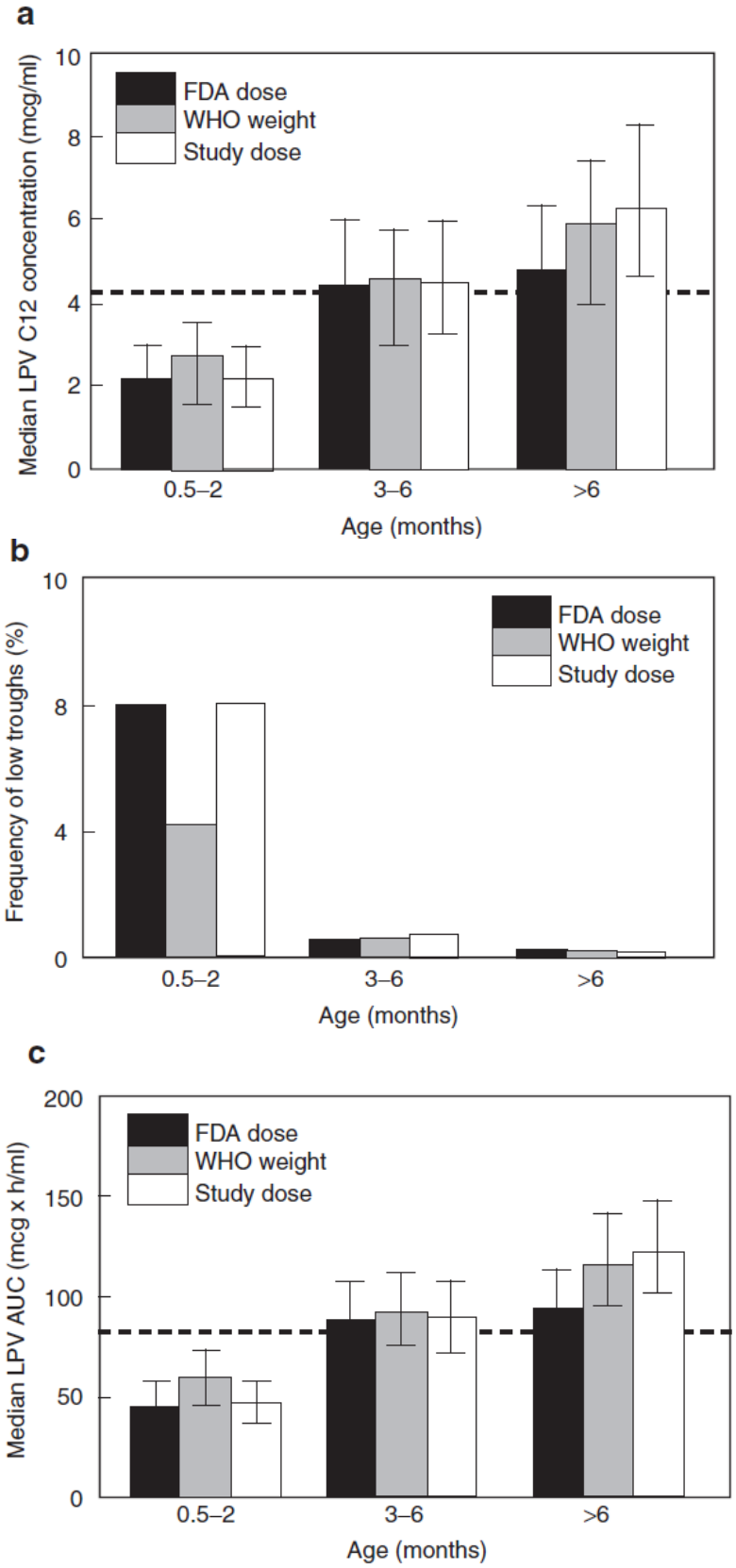
Figure 1. Population PK model results



Estimated lopinavir apparent clearance (CL/F) in relation to age. The post hoc empiric Bayesian estimated value of CL/F was derived from the final pharmacokinetic model for intensive and sparse PK visits. The solid line represents the population-based CL/F profile, which was derived using the allometrically scaled median weight for each age group (WHO 50th percentile weight). Cross-validation of the final model demonstrated a median absolute error of 50% (25–112%, 25th–75th percentile), similar to the residual error of the model. There was positive bias in the model, with a median error of 18% (−29 to 112%, 25th–75th percentile) probably because of nonadherence by some of the subjects before sparse sample collections.

Monte-Carlo simulations were performed with several LPV doses: P1030 study dose (300 mg/m² for all subjects), FDA doses and WHO doses. Median LPV trough concentrations (C12) for each of the three age groups (0.5–2 months, 3–6 months, and >6 months) were similar for all dosing methods. The frequency of low concentrations (<1 µg/ml) with both the study doses and the FDA doses was 8.1% in infants <3 months of age but rare (<1%) in older infants. The previously reported median adult trough level of 4.2 µg/ml was approached in older infants (>3 months) but not in younger infants (< 3 months):

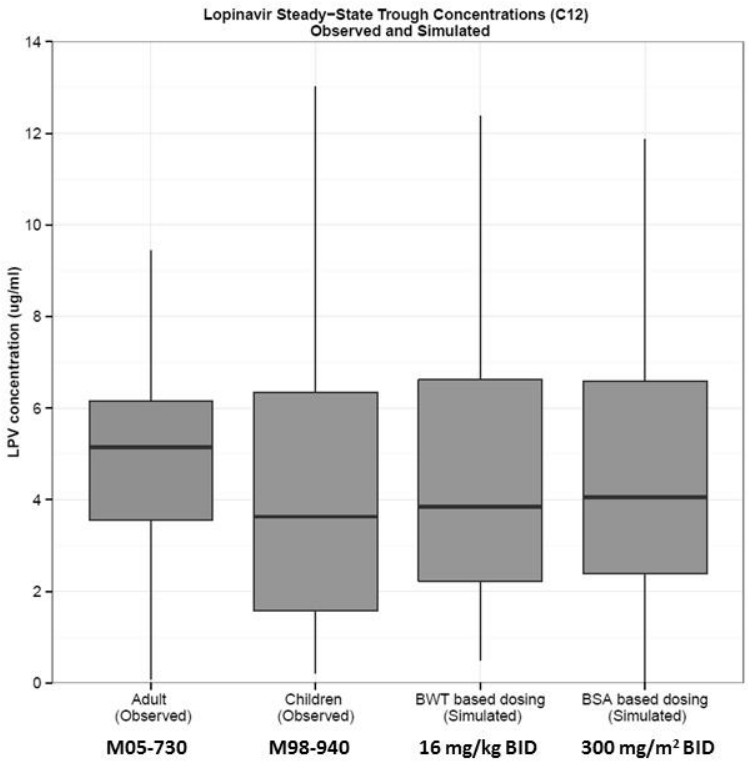
Figure 2. Monte Carlo simulations using the FDA dose (300 mg/m2, <6 months of age; 230 mg/m2, >6 months of age), study dose (300 mg/m2), and WHO weight band–based dosing recommendations



(a) Median LPV trough concentrations (C12). The data represent the median and IQR of LPV trough concentrations. The median trough level in adults is presented as a dashed line (4.2 µg/ml). (b) Predicted frequency of very low LPV troughs (<1 µg/ml). (c) Median drug exposure (AUC). The data represent the median and IQR of the LPV AUC (µg·h/ml). The mean AUC level in adults is presented as a dashed line (82.8 µg·h/ml).

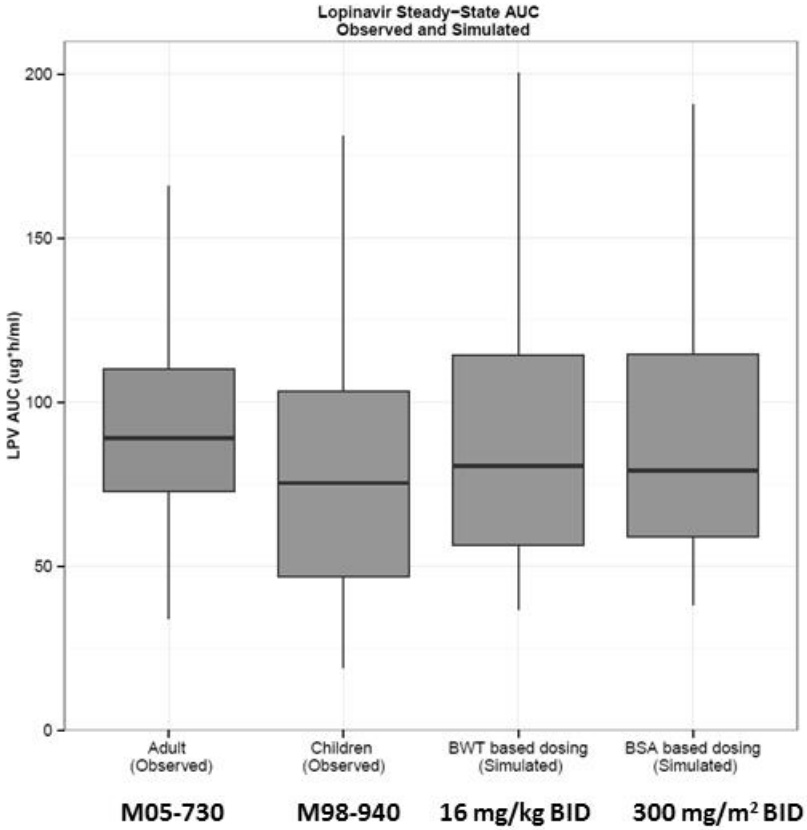
Clinical trial simulations were performed using Trial Simulator software (100 subjects × 100 replicates) for 2 dosing regimens (300/75 mg/m2 BID or 16/4 mg/kg BID) in infants 14 days to younger than 6 months of age. The simulations shown comparable C12 and AUC with adults administered 400/100 mg BID LPV/r (Study M05-730) and children administered 230/57.5 mg/m^2 or 300/75 mg/m^2 LPV/r (Study M98-940):

Figure 3. Cross-Study Comparison of Steady-State C12 Across Populations



Note: LPV PK in adults was summarized using data from Study M05-730 in adults (N = 633) and LPV PK in children was summarized using data from Study M98-940 (300/75 mg/m2 BID N = 50 and 230/57.5 mg/m2 BID N = 50; 6 months to 12 years of age). Simulated LPV exposures in infants were based on body weight dosing (16 mg/kg LPV) and BSA dosing (300 mg/m2).

Figure 4. Cross-Study Comparison of Steady-State AUC12 Across Populations



The median (interquartile range) AUC for adults and children observed in Study M05-730 and Study M98-940 was 89 (72 to 110) µg.h/mL and 75 (47 to 103) µg.h/mL, respectively. The clinical trial simulations based on weight and BSA dosing for infants resulted in median (interquartile range) AUC of 81 (56 to 114) µg.h/mL and 79 (59 to 115) µg.h/mL, respectively, demonstrating comparability across studies and populations of varying age groups. Additionally, the simulations for BID dosing based on weight (16/4 mg/kg LPV/r) or BSA (300/75 mg/m2 LPV/r) showed very comparable exposures in infants 14 days to < 6 months of age.

2.4.3. Discussion and conclusions on clinical pharmacology

In study P1030, the initial dose of LPV/r was 300/75 mg/m^2. The mean lopinavir doses administered to the subjects (267.19 mg/m^2 and 274.17 mg/m^2 BID in the younger and older cohorts, respectively) were less than the protocol-defined dose of 300 mg/m^2, due to growth occurring between study drug initiation and pharmacokinetic samplings at Week 2. Overall, LPV AUC and Cmin was lower than in older children and adults. In addition, the mean LPV exposure in the older cohort (6 weeks – 6 months) was higher than those in the younger cohort (14 days – 6 weeks).

Study	**P1030**		**M98-940**		**SmPC Kaletra**
Dose LPV/r	300/75 mg/m^2 BID (without NNRTI use)				400/100 mg BID
Age	14 days – 6 weeks	6 weeks – 6 months	3 months – 2 years	2 years – 12 years	adults
N	9	18	7	20	-
Mean AUC_{12} (µg.h/ml)	43.39	74.50	81.0	110.4	113.2
Mean Cmin (µg/ml)	1.40	1.95	2.99	5.98	8.1
Mean apparent CL/F (L/h/kg)	0.47	0.23	-	-	-

Lower C_{min} and AUC in the younger subjects were similarly observed for another PI, atazanavir. This may be explained by a lower bioavailability of these PI in younger subjects, resulting in a higher apparent oral clearance. Based on the PKPOP simulation, this lower bioavailability in younger subjects for a similar BSA-based dose is exponential and seems markedly pronounced for subjects <3 months. Additionally, it is known that there is a food effect of on the relative bioavailability of LPV. Dietary change during early life is put forward as a possible explanation, which is along the lines of the food effect. It is also a fact that enzymes responsible for drug metabolism mature during the first year or so. This is not accounted for in the model despite the fact that LPV is metabolized largely by enzymes of the CYP3A family. Therefore, the Applicant should re-discuss the adequacy of the PKPOP model taking into account the different reasons for the lower exposure in these children, notably the food effect and enzyme maturation.

The main PK concern is the potential underexposure of LPV which could result in a suboptimal antiviral activity. For LPV, a C_{trough} > 1 µg/ml was defined in the protocol as the minimal LPV concentration required to maintain an optimal antiviral activity (~15x the human serum-adjusted IC50 of wild-type virus). This PK threshold was previously considered in another clinical paediatric study with LPV (KONCERT study). In P1030 study, 2/27 subjects (7.4%; one subject in each cohort) had a LPV C_{trough} < 1 µg/ml at Week 2, leading to a LPV dose increase to 450/112.5 mg/m^2 BID. One of these subjects returned to the initial LPV/r dose 300/75 mg/m² because of overexposure, suggesting that the low LPV C_{trough} observed at Week 2 was probably related to lack of Kaletra-intake. The PKPOP simulation estimated that 8% of subjects < 3 months of age may had C_{trough} < 1 µg/ml with the LPV/r dose 300/75 mg/m². In addition, both results of the intensive PK sampling in P1030 study and of the PKPOP modelling show that LPV exposure (C_{min} and AUC) is considerably lower in subjects < 3 months of age. Therefore, efficacy results of these subjects should be scrutinized and put in parallel with data from older children.

The lower LPV exposure in subjects aged < 3 months receiving similar weight-based or BSA-based doses of LPV/rtv than in older subjects is due to higher apparent oral clearance in the youngest children. Therefore, higher doses of LPV/rtv may be considered. In study P1030, C_{min} is slightly lower in subjects aged <6 weeks (mean: 1.40 µg/ml, median: 1.26 µg/ml) than in subjects aged ≥6 weeks to <6 months (mean: 1.95 µg/ml, median: 1.39 µg/ml), but the range of C_{min} between these 2 cohorts overlapped. The applicant sticks to the same level of argument as regards the reassuring efficacy data derived from P030 despite lower PK levels than in adults. To obtain higher C_{min} by modifying the dosing interval, an administration three times a day might be required which has not been specifically discussed by the applicant but acknowledged as being potentially confusing given that a twice daily regimen is recommended for older subjects (and a QD regimen may also be used in adults).

This issue is challenging since Kaletra is already part of the US labelling for children from 2 weeks of age, is already part of therapeutic paediatric guidelines, notably by the US, French and WHO guidelines using LPV/rtv-containing regimen to treat infants and small children < 2 years of age. So it has become a standard of care in the management of youngest children. Finally having considered the later together with the lack of particular signal on efficacy/resistance from the limited data derived from study P1030, this extension of the indication could be acceptable provided that further reassurance in terms of efficacy/resistance post marketing.

The model incorporates allometric scaling of drug disposition parameters to body weight. This means that the effect on PK of a difference in body size between subjects, as well as due to individual growth, is built into the model. The disposition parameters are related to body weight but to different extent (clearance to the power of 0.75 and volume of distribution to the power of 1). The predicted effective half-life is a function of both clearance and volume and will also be dependent on body size. Notwithstanding maturation of elimination, half-life will increase with increasing body size. The trough concentration, closely related to half-life, will also show a relative increase even if the dose level is adjusted for body size. For Kaletra, the same dosing interval, twice daily, is proposed for the entire paediatric population. There is a concern that this may lead to low trough concentrations. A warning describing the observed

exposures in young children from 14 days to 3 months of approximately 35% AUC_{12} and 75% lower C_{min} than in adults that may lead to inadequate virologic suppression and emergence of resistance has been introduced in the SmPC.

For subjects > 6 months old, the FDA-dose (LPV/r 230/57.5 mg/m² BID) is more appropriate to provide LPV exposure equivalent to in adults treated by LPV/r 400/100 mg BID.

2.5. Clinical efficacy

Efficacy data of LPV/r in children < 2 years old were provided by the clinical studies M98-940, P1030, P1060 and CHER.

2.5.1. Main studies

Study M98-940: Study Title: *Open-label, randomized, multi-center, multi-country study of ABT-378/ritonavir in combination with reverse transcriptase inhibitors in HIV-infected children.*

This study was previously assessed by the CHMP for the current paediatric indication of Kaletra in children above 2 years old.

Study design

This is an open-label study of LPV/r starting in 1999 in 100 ARV-naïve (44%) and experienced (56%) paediatric subjects. Subjects were randomized to receive either LPV/r 230/57.5 mg/m^2 or LPV/r 300/75 mg/m^2. Naïve patients also received NRTI. Experienced patients received LPV/r, nevirapine + up to two NRTI. Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after 3 weeks of therapy in each patient. Subsequently, all patients were continued on the 300/75 mg/m^2 dose.

Baseline characteristics

Fourteen subjects were 6 months to < 2 years of age and 86 subjects were 2 years to 12 years of age. In addition, 44 were ARV naïve and 56 ARV experienced.

Table 11. Demographic Characteristics by Age Group

Demographic Characteristic	Age Group	
	< 2 Years Old (N=14)	≥ 2 Years Old (N=86)
Sex		
Male	8	35
Female	6	51
Race		
Black	7	50
Caucasian	2	10
Mixed	0	2
Missing[@]	5	24
Height (cm)***		
Mean	76.3	107.7
Range	66.0 - 85.9	80.5 - 147.5
Weight (kg)***		
Mean	10.2	19.5
Range	7.3 - 13.7	9.2 - 55.0
Years Since HIV Diagnosis***		
Mean	1.0	3.5
Range	0.5 - 1.9	0.0 - 10.5
Risk Factors (number of subjects)		
Vertical Transmission	14	82
Transfusion Recipient	0	1
Unknown	0	1
Other	0	2

Table 12. Summary of Baseline Disease Characteristics by Age Group

Age Group	Mean ± Standard Error					
	HIV RNA Level (log_{10} copies/mL)	CD4 Count			CD8 Count	
		Absolute (log_{10} cells/μL)	Absolute (cells/μL)	Relative (%)	Absolute (log_{10} cells/μL)	Absolute (cells/μL)
<2 years old (N=14)	4.75 ± 0.29	3.15 ± 0.09***	1765 ± 262.1***	26.9 ± 3.0	3.33 ± 0.10***	2883 ± 572.3***
≥2 years old (N=86)	4.66 ± 0.08	2.72 ± 0.04	687 ± 46.2	23.8 ± 1.0	3.06 ± 0.02	1285 ± 66.6

*** Indicates statistical significance (two-tailed) at the 0.001 level

Efficacy data

At Week 48, LPV/r 300/75 mg/m² BID achieved a favourable and similar antiviral response in both age groups:

Table 13. Summary of HIV RNA levels abd CD4+ count at Week 48 by age group in study M98-940

	Age < 2 years	Age ≥ 2 years
HIV-RNA <400 cp/mL[a]	79% (11/140	79% (68/86)
Mean increase from baseline in CD4+ (cells/μL)	107	375
Mean increase from baseline in relative CD4+ count	6.9%	8.0 %

a. based on intent to treat, non completer= failure

Study P1030 – Study Title: *A Phase I/II Study of Lopinavir/Ritonavir in HIV-1 Infected Infants < 6 Months of Age*

Study design

This is an open-label, dose-finding study starting in 2002 to assess LPV/r in HIV-infected infants from 14 days to < 6 months of age. Subjects had HIV-1 RNA > 10,000 c/ml and were LPV/r-naïve. They received LPV/r 300/75 mg/m² BID in combination with 2 NRTIs.

Baseline characteristics

A total of 10 and 21 subjects were enrolled into the younger (14 days to <6 weeks old) and older (6 weeks to <6 months old) cohorts, respectively.

Table 14. Summary of Demographic and Baseline Characteristics in Study P1030

	P1030	
	Cohort 1	**Cohort 2**
Characteristic	**≥ 14 Days to < 6 Weeks N = 10**	**≥ 6 Weeks to < 6 Months N = 21**
Age at enrollment	range: 3.6 to 6.0 weeks	range: 6.9 to 25.7 weeks
Gender, n (%)		
Female	3 (30.0)	14 (66.7)
Male	7 (70.0.)	7 (33.3)
Race, ethnicity, n (%)		
White	0	2 (9.5)
Black	7 (70.0)	10 (47.6)
Hispanic	3 (30.0)	9 (42.9)
Colored	-	
Indian	-	
Weight (kg), mean (SD)	3.9 (0.7)	5.6 (1.4)
Height (cm), mean (SD)	52.3 (3.4)	58.4 (4.5)
BSA (m^2), mean (SD)	0.24 (0.03)	0.30 (0.05)
Plasma HIV-1 RNA (log_{10} copies/mL), mean (SD)	5.9 (0.7)	5.6 (0.9)

Characteristic	P1030 Cohort 1 ≥ 14 Days to < 6 Weeks N = 10	P1030 Cohort 2 ≥ 6 Weeks to < 6 Months N = 21
CD4+		
Absolute cell count (cells/mm^3), mean (SD)	2106 (576.3)	2326 (1387.7)
Percentage (%), mean (SD)	41 (13.2)	31 (11.6)
Disease stage		
CDC Classification, n (%)		
Stage N or Stage A[a]	9 (90.0)	13 (61.9)
Stage N	-	
Stage A	-	
Stage B	1 (10.0)	6 (28.6)
Stage C	0	2 (9.5)

Approximately 90% of the NRTIs combinations used with LPV/r were 3TC+AZT or 3TC+d4T

Efficacy data

At Week 48, 60% (6/10) of subjects in the younger cohort (≥ 14 days to < 6 weeks of age) and 76% (16/21) of subjects in the older cohort (≥ 6 weeks to < 6 months of age) achieved reduction of viral load to < 400 copies/mL.

Table 15. HIV-1 RNA Over Time

	Both Cohorts: ≥14 days to < 6 months N = 31			Cohort 1 ≥ 14 days to < 6 weeks N = 10			Cohort 2 ≥ 6 weeks to < 6 months N = 21			
Description	**Week 16**	**Week 24**	**Week 48**	**Week 16**	**Week 24**	**Week 48**	**Week 16**	**Week 24**	**Week 48**	**Week 96**
HIV-1 RNA < 400 copies/mL	15 (48%)	17 (55%)	22 (71%)	7 (70%)	7 (70%)	6 (60%)	8 (38%)	10 (48%)	16 (76%)	15 (71%)
HIV-1 RNA ≥ 400 and < 1000 copies/mL	5	6	2	2	2	1	3	4	1	0
HIV-1 RNA ≥ 1000 copies/mL	9[a]	6[a]	3	1	1	2	8[a]	5[a]	1	2[a]
Off treatment: Never < 400 copies/mL while on treatment[b]	2	2	2	0	0	0	2	2	2	2
Off treatment due to virologic failure[c]	0	0	1	0	0	1	0	0	0	0
Off treatment; last VL< 400[d]	0	0	1	0	0	0	0	0	1	2

a. Includes child with missing HIV-1 RNA measurement where measurement before and/or after missing measurement was ≥ 1000 copies/mL.

b. One child in this category discontinued study treatment at Week 2 due to tolerability issues and 1 child at Week 7 due to severe debilitation.

c. The child in this category had HIV-1 RNA levels of 57,339 copies/mL at Week 32 and 160,334 copies/mL at Week 40 (no measurement was available at Week 36).

d. One child in this category discontinued study treatment at Week 42 due to loss to follow-up (measurements at Weeks 24 and 32 both < 400 copies/mL; no measurement at Week 36 or 40), and 1 child at Week 73 due to site closure (measurements at Weeks 60 and 72 both < 400 copies/mL).

Table 16. Median change from baseline in CD4+cell count

	Cohort 1: ≥ 14 days - < 6 weeks			Cohort 2: ≥ 6 weeks - < 6 months			All		
Time Point	**N**	**Median (95% CI[a])**	**p-value[b]**	**N**	**Median (95% CI[a])**	**p-value[b]**	**N**	**Median (95% CI[a])**	**p-value[b]**
Baseline	7	2426		15	2230		22	2238	
Week 12	6	850 (-629, 2875)	0.094	11	1060 (24, 2360)	0.005	17	1048 (246, 1510)	0.001
Week 24	5	755 (-171, 2944)	0.13	11	739 (-373, 2358)	0.21	16	747 (-171, 1517)	0.039
Week 36	5	394 (-190, 1130)	0.13	10	783 (8, 2166)	0.010	15	555 (28, 1130)	0.003
Week 48	6	520 (167, 1868)	0.031	9	727 (-892, 1854)	0.32	15	683 (167, 1438)	0.036
Week 60	.	.	.	10	648 (-1243, 1907)	0.43	.	.	.
Week 72	.	.	.	9	-492 (-1896, 2119)	0.65	.	.	.
Week 84	.	.	.	9	-267 (-1730, 929)	0.65	.	.	.
Week 96	.	.	.	8	-94 (-1641, 1963)	0.84	.	.	.

There were statistically significant (P < 0.05) increases from baseline in absolute CD4+ count and CD4+ percentage:

These changes need to be interpreted with the caveat that these parameters change with age in uninfected subjects during the first few years of life (e.g., CD4 counts and CD4 percentages show declines).

Study P1060 – Study Title: *Phase II Parallel, Randomized, Clinical Trials Comparing the Responses to Initiation of NNRTI-Based Versus PI-Based Antiretroviral Therapy in HIV-Infected Infants Who Have and Have Not Previously Received Single Dose Nevirapine for Prevention of Mother-to-Child HIV Transmission*

Study design

Study P1060 was a parallel, randomized clinical trial of NVP versus LPV/r-based ART in subjects 2 to 36 months of age infected with HIV-1 who had (Cohort I) and had not (Cohort II) been exposed to NVP for prevention of mother-to-child transmission (PMTCT). LPV/r was administered 16/4, 12/3, 10/2.5 mg/kg or 400/100 mg BID. The study was conducted by the PACTG.

The primary endpoint was treatment failure at week 24, defined as a confirmed plasma HIV-1 RNA level < 1 log10 copies/ml below the study entry value at 12 to 24 weeks after treatment was initiated, a confirmed value > 75,000 copies/ml at 12 to 24 weeks if a subject's study entry HIV-1 RNA was > 750,000 copies/ml, a confirmed plasma HIV-1 RNA level > 400 copies/ml at 24 weeks after randomisation, or permanent discontinuation of study treatment at or prior to 24 weeks of treatment for any reason, including death.

Treatments

Lopinavir/ritonavir was administered twice daily at 16/4 mg/kg for subjects 2 months to < 6 months, 12/3 mg/kg for subjects ≥ 6 months and < 15 kg, 10/2.5 mg/kg for subjects ≥ 6 months and ≥ 15 kg to < 40 kg, or 400/100 mg for subjects ≥ 40 kg. The nevirapine-based regimen was 160-200 mg/m2 once daily for 14 days, then 160-200 mg/m2 every 12 hours. Both treatment arms included zidovudine 180 mg/m2 every 12 hours and lamivudine 4 mg/kg every 12 hours.

Baseline characteristics

A total of 451 subjects (164 in Cohort I [82 nevirapine and 82 lopinavir/ritonavir] and 287 in Cohort II [147 nevirapine and 140 lopinavir/ritonavir]) received study treatment.

At entry, median age was 0.7 years, median CD4 T-cell count was 1147 cells/mm3, median CD4% T-cell was 19%, and median HIV-1 RNA was > 750,000 copies/ml.

Efficacy data

Table 17. Outcomes at Week 24: Study P1060

Outcomes at Week 24: Study P1060				
	Cohort I		**Cohort II**	
	lopinavir/ritonavir **(N=82)**	nevirapine **(N=82)**	lopinavir/ritonavir **(N=140)**	nevirapine **(N=147)**
Virologic failure	21.7%	39.6%	19.3%	40.8%

p=0.015 (Cohort I); p< 0.001 (Cohort II)

Study Children with HIV Early Antiretroviral Therapy (CHER) – Study Title: *A Phase III, Randomized, Open-label Trial to Evaluate Strategies for Providing Antiretroviral Therapy to Infants Shortly after Primary Infection in a Resource Poor Setting*

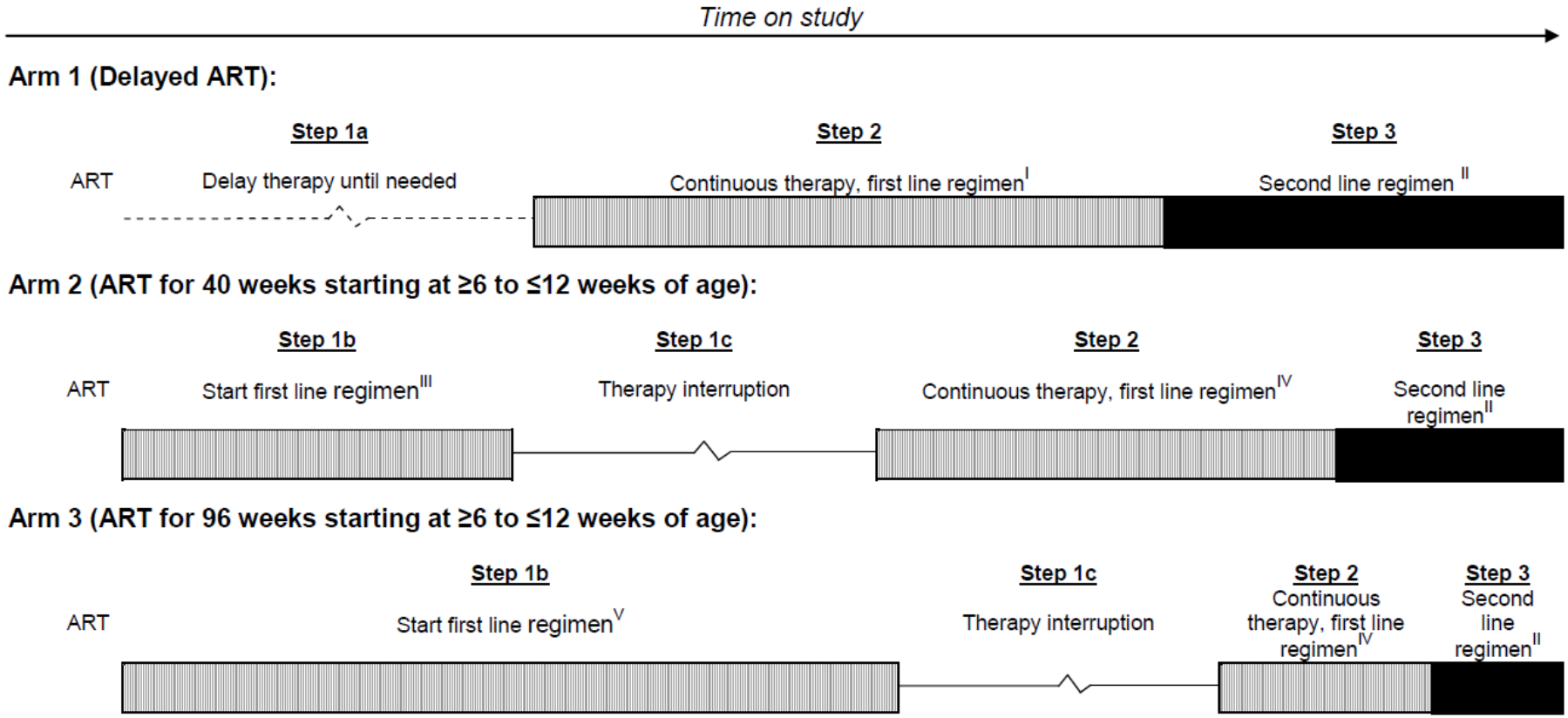
Study design

This is a randomized, open-label Phase 3 study starting in 2004 comparing 3 treatment strategies (ART deferred [ART-def], early ART for 40 weeks [ART-40W], or early ART for 96 weeks [ART-96W]) in children with prenatally acquired HIV-1 infection diagnosed between 6 and 12 weeks of age. The trial had two parts: Part A and Part B.

- Infants in Part A were randomized in a 1:1:1 ratio to deferred ART (Arm 1), ART for 40 weeks (Arm 2) or ART for 96 weeks (Arm 3)

- Infants in Part B were randomized to Arms 2 (ART-40W) and 3 (ART-96W), as randomization into Arm 1 (ART-Def) would be unethical.

Figure 5. Schematic Representation of Study Treatment Strategies



I Start first line regimen if CD4% falls below 20% or participant develops a severe CDC Stage B or Stage C disease.

II Any child who has failed the first line regimen will be considered for switching to a second line therapy; these children will continue to be followed until completion of the study visits for secondary objectives.

III Start first line regimen in Arm 2 (ART-40W) between 6 and 12 weeks of age, continuing until approximately the first birthday (40 weeks).

IV Start continuous therapy, first line regimen if CD4% falls below 20% or participant develops a severe CDC Stage B or Stage C disease.

V Start first line regimen in Arm 3 (ART-96W) at ≥ 6 weeks continuing until approximately second birthday (96 weeks).

Subjects had HIV-1 RNA > 10,000 copies/mL, CD4+ ≥ 25% and were ARV-naïve. The first line regimen used for this study was AZT+3TC+LPV/r. Doses of LPV/r were:

- <6 months of age: 300/75 mg/m^2 BID
- ≥6 months of age and <7 kg: 230/57.5 mg/m^2 BID
- ≥6 months of age and ≥7 kg:

7 to 10 kg: 1.25 mL twice daily

>10 to <15 kg: 1.75 mL twice daily

15 to 20 kg: 2.25 mL twice daily

>20 to 25 kg: 2.75 mL twice daily

>25 to 30 kg: 3.5 mL twice daily

>30 to 35 kg: 4.0 mL twice daily

>35 to 40 kg: 4.75 mL twice daily

Baseline characteristics

A total of 411 subjects were enrolled in Part A and randomized in a 1:1:1 ratio to the ART-def, ART-40W, or ART-96W arm. Forty subjects with a Baseline CD4+ percentage of < 25% were enrolled in Part B and randomized to the ART-40W and ART-96W arms. The results of Part A are presented. The results of Part B were similar to the results of Part A.

Table 18. Summary of Demographic and Baseline Characteristics in the CHER Study

	CHER		
Characteristic	**ART-def N = 125**	**ART-40W N = 143**	**ART-96W N = 143**
Age at enrollment	IQR: 6 to 9 weeks	IQR: 7 to 9 weeks	IQR: 7 to 9 weeks
Gender, n (%)			
Female	74 (59)	84 (59)	79 (55)
Male	51 (41)	59 (41)	64 (45)
Race, ethnicity, n (%)			
White	-	-	-
Black	122 (98)	136 (95)	138 (97)
Hispanic	-	-	-
Colored	3 (2)	7 (5)	5 (3)
Indian	-	-	-
Weight (kg), mean (SD)	4.5 (0.8)	4.5 (0.7)	4.4 (0.8)
Height (cm), mean (SD)	54.5 (4.0)	54.0 (2.6)	54.1 (2.7)
BSA (m^2), mean (SD)	-	-	-
Plasma HIV-1 RNA (log_{10} copies/mL), mean (SD)	5.7 (0.4)	5.6 (0.3)	5.7 (0.4)

Characteristic	ART-def N = 125	ART-40W N = 143	ART-96W N = 143
CD4+			
Absolute cell count (cells/mm^3), mean (SD)	2303.3 (1061.6)	2309.8 (2068.5)	2356.9 (1182.0)
Percentage (%), mean (SD)	36.1 (9.0)	35.4 (8.1)	35.4 (8.6)
Disease stage			
CDC Classification, n (%)			
Stage N or Stage A[a]		-	
Stage N	106 (85)	111 (78)	120 (84)
Stage A	13 (10)	26 (18)	14 (10)
Stage B	6 (5)	6 (4)	9 (6)
Stage C	0	0	0

Efficacy data

The primary efficacy endpoint was time to death or failure of first-line ART, defined as follows:

- Failure to reach a CD4+% of 20% or more by Week 24;

- A decrease in CD4+% to less than 20% after the first 24 weeks on ARV therapy (immunologic failure);

- Severe CDC Stage B or Stage C events (clinical failure);

- Toxicity requiring one or more drug substitutions within the same class or a switch to a new class or requiring permanent discontinuation of treatment;

- HIV-1 RNA value ≥ 10,000 copies/mL recorded on 2 consecutive separate occasions after 24 weeks of treatment (initial therapy or restart).

Table 19. Primary Outcomes by Study Arm at Week 48 (n=411)

Variable	ART-Def	ART-40W	ART-96W	Total
Number of participants enrolled	125	143	143	411
Number of children that reached a primary endpoint (%)	32 (25.6)	13 (9.1)	13 (9.1)	58
Death	21 (16.8)	9 (6.3)	7 (4.9)	37
Immunological failure (%)	4 (3.2)	2 (1.4)	4 (2.8)	10
Failure of CD4% to reach a level of ≥ 20% by week 24	4 (3.2)	2 (1.4)	3 (2.1)	9
CD4% fell below 20% on 2 two occasions within 4 weeks after 24 weeks of treatment	0 (0.0)	0 (0.0)	1 (0.7)	1
Clinical failure (%)	4 (3.2)	2 (1.4)	2 (1.4)	8
Severe CDC Stage B disease	3 (2.4)	1 (0.7)	1 (0.7)	5
CDC Stage C disease	1 (0.8)	1 (0.7)	1 (0.7)	3
Virological failure	3 (2.4)	0 (0.0)	0 (0.0)	3
Failure due to ART limiting toxicity (%)	0 (0)	0 (0)	0 (0)	0

Relative to the ART-def arm, the hazard ratio for death by Week 48 was 0.355 (95% CI: 0.162 to 0.774; P = 0.0093) in the ART-40W arm and 0.275 (95% CI: 0.117 to 0.646; P = 0.0031) in the ART-96W arm. There was no difference in the hazard of death between the ART-40W and ART-96W arms.

The mean changes from baseline in the viral load were as follows:

Table 20. Viral load (log_{10} copies/ml) Change from baseline (n=411)

Variable	ART-Def		ART-40W		ART-96W		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	P-Value
Week 24 - Baseline	53	-1.0 (1.5)	103	-2.8 (1.3)	108	-2.9 (1.3)	<.0001
Week 40 - Baseline	32	-2.2 (1.7)	95	-3.1 (1.2)	101	-3.0 (1.4)	0.0106
Week 48 - Baseline	30	-2.5 (1.4)	59	-0.4 (1.0)	88	-2.6 (1.1)	<.0001
Repeated Measures Analysis							<.0001

The mean changes from baseline in the CD4 count and percentages were as follows:

Table 21. CD4% Change from baseline (n=411)

Variable	ART-Def		ART-40W		ART-96W		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	P-Value
Week 12 - Baseline	108	-7.2 (9.8)	135	5.4 (9.2)	138	4.7 (8.1)	<.0001
Week 24 - Baseline	105	-5.9 (11.5)	131	6.2 (9.2)	133	5.0 (9.2)	<.0001
Week 36 - Baseline	78	-4.9 (12.3)	130	4.2 (10.4)	133	4.2 (10.1)	<.0001
Week 40 - Baseline	64	-5.4 (12.5)	126	3.3 (9.4)	129	2.8 (11.2)	<.0001
Week 48 - Baseline	88	-3.0 (11.0)	125	-7.0 (9.3)	130	2.0 (10.7)	<.0001
Repeated Measures Analysis							<.0001

Table 22. CD4 Count (cells/mm3) During Follow-up (n=411)

Variable	ART-Def		ART-40W		ART-96W		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	P-Value
Baseline	125	2303.3 (1061.6)	143	2309.8 (2068.5)	143	2356.9 (1182.0)	0.9501
Week 12	108	1690.9 (1006.2)	135	2308.7 (1092.9)	138	2388.1 (914.3)	<.0001
Week 24	105	1651.6 (853.6)	131	2309.0 (930.5)	133	2347.5 (1006.1)	<.0001
Week 36	78	1771.7 (969.7)	130	2223.3 (976.7)	133	2317.5 (969.6)	0.0003
Week 40	64	1666.0 (733.3)	126	2043.5 (810.6)	129	2117.7 (865.7)	0.0012
Week 48	88	1731.8 (653.4)	125	1577.0 (744.6)	130	2056.7 (839.4)	<.0001
Repeated Measures Analysis							0.0002

Analysis performed across trials

Data from the paediatric Studies M98-940, P1030, P1060, and Children with HIV Early Antiretroviral Therapy (CHER) and Studies M05-730 and M10-336 (in antiretroviral therapy [ART]-naïve adults) were provided in a tabulated manner.

Subjects from the paediatric studies were categorized by age into the following strata:

- 0 to < 3 months (or 0 to 91 days)
- 3 to < 6 months (or 92 to 182 days)
- months to < 2 years (or 183 to 729 days)
- ≥ 2 years (or ≥ 730 days)

Table 23. Number and Percentage of LPV/r Subjects with HIV-1 RNA ≥ 400 Copies/mL at Treatment Weeks 24 and 48 by Age Strata

Study/ Treatment Week[a]	Paediatric Studies[b] Age Strata n/N (%)				Treatment-Naïve Adult Studies[c] n/N (%)
	0 to < 3 mos	3 to < 6 mos	6 mos to < 2 yrs	≥ 2 yrs	
P1030					
Week 24	5/18 (27.8)	4/11 (36.4)	N/A	N/A	-
Week 48	4/16 (25.0)	1/11 (9.1)	N/A	N/A	-
P1060					
Week 24	N/A	0/2	29/140 (20.7)	5/51 (9.8)	-
Week 48	N/A	0/2	19/113 (16.8)	6/45 (13.3)	-
CHER[d]					
Week 24	92/267 (34.5)	N/A	N/A	N/A	-
Week 48	50/132 (37.9)	N/A	N/A	N/A	-
M98-940					
Week 24	N/A	N/A	4/14 (28.6)	22/85 (25.9)	-
Week 48	N/A	N/A	3/14 (21.4)	16/84 (19.0)	-
Paediatric Total					
Week 24	97/285 (34.0)	4/13 (30.8)	33/154 (21.4)	27/136 (19.9)	-
Week 48	54/148 (36.5)	1/13 (7.7)	22/127 (17.3)	22/129 (17.1)	-
M05-730					
Week 24	-	-	-	-	31/613 (5.1)
Week 48	-	-	-	-	17/580 (2.9)
M10-336					
Week 24	-	-	-	-	2/99 (2.0)
Week 48	-	-	-	-	2/97 (2.1)
Adult Total					
Week 24	-	-	-	-	33/712 (4.6)
Week 48	-	-	-	-	19/677 (2.8)

mos = months; N/A = not applicable; yrs = years

a. Subjects in the Week 24 analysis received ≥ 154 days of treatment, and subjects in the Week 48 analysis received ≥ 322 days of treatment. For P1060, duration of treatment was determined by availability of HIV-1 RNA data.

b. Studies include Studies P1030, P1060, M98-940, and CHER.

c. Studies include Studies M05-730 and M10-336 (LPV/r + FTC/TDF treatment group only).

d. Includes only the ART-40W and ART-96W treatment groups at 24 weeks and the ART-96W treatment group at 48 weeks.

Note: The ITT NC=F algorithim was used where missing values were treated as ≥ 400 copies/mL unless bracketed by values < 400 copies/mL for all studies except Study P1060; an observed data analysis was used for Study P1060 where subjects with missing data were excluded.

Data on virological failure were provided. It should be noted that the criteria for virological failure differed across 3 studies.

For Study M98-940, the number and percentage of subjects with both baseline and post-baseline genotyping data available of those subjects who had an HIV-1 RNA value ≥ 400 copies/mL at either Week 24 or Week 48 are presented.

For Study M05-730, beginning at Week 24, if the subject's plasma HIV-1 RNA level was > 50 copies/mL and at the previous visit the plasma HIV-1 RNA was < 50 copies/mL, confirmatory plasma HIV-1 RNA (including a sample for HIV-1 drug resistance genotyping) was repeated within 4 weeks. If the confirmatory plasma HIV-1 RNA was ≥ 400 copies/mL, the sample collected for HIV-1 drug resistance genotyping at the time of the confirmatory plasma HIV-1 RNA level was to be analyzed.

For Study M10-336, beginning at Week 8, if the subject's plasma HIV-1 RNA level was ≥ 40 copies/mL and at the previous visit the plasma HIV-1 RNA was < 40 copies/mL, confirmatory plasma HIV-1 RNA (including a sample for HIV-1 drug resistance genotyping) was repeated within 4 weeks. If the confirmatory plasma HIV-1 RNA was > 400 copies/mL, the sample collected for HIV-1 drug resistance genotyping at the time of the confirmatory plasma HIV-1 RNA level was to be analyzed.

Table 24. Number and Percentage of Subjects with Genotyping Data of Those with Virologic Failure in Study M98-940 and Studies in Treatment-Naïve Adults

Study	n/N (%)
M98-940[a]	22/28 (78.6)
M05-730[b]	16/51 (31.4)
M10-336[c]	2/11 (18.2)
Adult Total	**18/62 (29.0)**

mos = months; N/A = not applicable; yrs = years

a. Virologic failure was defined as HIV-1 RNA value ≥ 400 copies/mL at Week 24 or Week 48.

b. LPV/r + FTC/TDF treatment group only. Virologic failure was defined as 2 consecutive HIV-1 RNA values ≥ 50 copies/mL (through Week 96) for subjects who had 2 prior consecutive HIV-1 RNA values < 50 copies/mL.

c. Virologic failure was defined as 2 consecutive HIV-1 RNA values ≥ 40 copies/mL (through Week 96) for subjects who had 2 prior consecutive HIV-1 RNA values < 40 copies/mL.

2.5.2. Discussion and conclusions on clinical efficacy

Currently, LPV/r is indicated in EU in subjects ≥ 2 years of age, this is different from the US situation where this boosted PI is registered in children from 2 weeks of age. The MAH is now claiming an extension of indication to align the paediatric age limit in EU and US. In the context of this paediatric extension application, all of the 4 clinical studies submitted provide efficacy data of LPV/r in subjects below 2 years of age, but with different lower limits of age: the younger subjects were mainly studied in studies **P1030 (14 days – 6 months old) and CHER (6 weeks – 12 weeks old),** and children above 6 months were studied in studies P1060 (2 months – 36 months old) and M98-940 (6 months – 2 years old).

Based on these pooled data, it is observed that the rate of subjects with virologic failure (i.e. HIV-1 RNA ≥ 400 c/ml) seems higher in the lower age strata: At week 48, this rate was respectively 36.5%, 17% and 3% in ART-naïve subjects aged <3 months, between 6 months to 2 years and in adults (subjects aged from 3 months to 6 months were not considered as their number – n=13 – was too low to be relevant). Nevertheless, rates of virologic suppression of 70-80% have been reported in HIV-infected infants initiating therapy at <12 months (NIH Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, 2016), which is consistent with the results of these paediatric studies. Furthermore, a suboptimal LPV exposure might be associated to emergence of PI-RAM, which was not the case in these studies. In conclusion, no efficacy concern was highlighted in these studies. However, while these pooled

data give an overview in children <3 months of age it is important to keep in mind that the 4 clinical studies in support of this extension of indication (P1030, P1060, CHER, M98-940) have different lower limits of age and that the younger subjects (source of concern for potential suboptimal exposure) were mainly studied in studies P1030 (14 days – 6 months old) and CHER (6 weeks – 12 weeks old), while older children above 6 months were studied in studies P1060 (2 months – 36 months old) and M98-940 (6 months – 2 years old). Overall, LPV/r 300/75 mg/m² is used for children < 6 months old. In study P1060, the FDA weight-based doses were used, resulting in similar LPV exposures than with the BSA-based doses. In study CHER, the LPV doses correspond to those in the AbbVie's monograph of Kaletra.

Due to the diversity of these studies, all ages from 14 days to 2 years old are more or less represented. The main relevant efficacy endpoints available within these studies are the rate of subjects with HIV-1 RNA level < 400 c/ml and the mean changes from baseline in the CD4 count at Week 48. In general, the efficacy data issued from these studies did not highlight specific concern for children < 2 years of age.

Study	**M98-940 N=14**	**P1030 N=31**	**P1060 N=119[a]**	**CHER N=143[b]**
Age at baseline	6 months – 2 years	14 days – 6 months	2 months – 36 months	6 weeks – 12 weeks
LPV/r posology	300/75 mg/m² BID	300/75 mg/m² BID	FDA weight-based doses	<6 months: 300/75 mg/m² BID ≥6 months and <7 kg: 230/57.5 mg/m² BID ≥6 months and ≥7 kg: weight-based (from 1.25 ml BID to 4.75 ml BID)
% of subjects with HIV-1 RNA < 400 c/ml at Week 48	79%	71%	85%	N/A
Mean change from baseline to Week 48 in CD4 count (cells/mm³)	+107	+683	+541	-300

a : subjects treated by LPV/r at Week 48 in Cohort II (including subjects > 2 years old)
b : subjects always treated at Week 48 (= group ART-96W)

More specifically in each study, it may be highlighted:

- An equivalent antiviral efficacy and immunologic response between different age groups treated by LPV/r-based regimen (< or ≥ 2 years old in study M98-940; < or ≥ 6 weeks old in study P1030; < or ≥ 12 months old in study P1060).
- A better antiviral response with LPV/r-based regimen than NVP-based regimen in subjects study P1060 in subjects between 2 months and 36 months of age (study P1060).
- A decrease of the mean CD4 count through Week 48 in subjects under LPV/r-based regimen in CHER study. Nevertheless, subjects without ART experienced a significant higher decrease of their CD4 count (-572 cells/mm³). As stated by the MAH, it should be taken into account that a decrease in CD4 counts during the first few years of life is observed in uninfected subjects.

Given that a lower LPV exposure was observed in subjects < 3 months of age based on the observed data from study P1030 and the simulated data from the PKPOP model, a focus should be made on these younger subjects. Thus, study P1030 compared very young children (< 6 weeks of age) with older (> 6 weeks to 6 months of age), and study CHER enrolled subjects below 3 months of age. The data from other studies did not allow substantiating efficacy in such very young subjects: a higher age-cut off was used in study P1060 (< or ≥ 1 year old) and study M98-940 enrolled subjects above 6 months of age. Efficacy data from P1030 and CHER studies are reassuring on the antiviral efficacy of LPV/r 300/75 mg/m² BID in children below 3 months of age, with significant rates of virologically suppressed subjects

and low rates of clinical, virologic and/or immunologic failures. In both studies, LPV/r was mainly associated with AZT+3TC, a reference treatment for paediatric patients.

In conclusion, LPV/r in combination with 2 NRTIs and at doses equivalent to 300/75 mg/m² for children < 6 months and 230/57.5 mg/m^2 BID for older children (i.e. the FDA BSA- or weight-based doses) seems effective in children from 14 days to 2 years old. Further reassurance on the risk of inadequate virologic suppression in children <3 month of age (due to suboptimal PK exposure of Kaletra in this subgroup) is nevertheless expected.

In addition, it is noted that the proposed posology of LPV/r in patients from 14 days to 6 months of age is only BSA-based (300/75 mg/m²) whereas in US the posology in these subjects is both BSA-based (300/75 mg/m²) and weight-based (16/4 mg/kg). The MAH was requested to add weight-based dosing recommendations for paediatric patients aged 14 days to 6 months to section 4.2 Posology and method of administration of the Kaletra oral solution SmPC. The information reflected in the EU SmPC and US product information is aligned.

2.6. Clinical safety

Introduction

The safety of Kaletra oral solution in paediatric patients older than 2 years of age and infected with HIV was initially established and supported in the authorization application by Study M98-940. For this extension of indication, safety data for children from 14 days to 2 years old were issued from the clinical studies M98-940, P1030, P1060 and CHER, and from the post-marketing safety data review of LPV/r for this paediatric population.

Patient exposure

Study	Number of subjects exposed to LPV/r	Duration of exposure to LPV/r
M98-940	N = 100: 6 months to < 2 years old: 14 ≥ 2 to 12 years old: 86	60 to 807 days Median: 757 days and 682 days for the younger and older cohort, respectively 98% and 67% of subjects exposed ≥ 48 weeks and 96 weeks, respectively
P1030	N = 31: 14 days to < 6 weeks old: 10 6 weeks to < 6 months old: 21	2 to 252 weeks Median: 103 weeks and 124 weeks for younger and older cohort, respectively
P1060	N = 222: 2 to < 12 months old: 99 ≥ 12 to 36 months old: 123	0 to 192 weeks Median: 37 and 60 weeks for cohort I and cohort II (both in younger and older subjects), respectively
CHER	N = 286	40 weeks or 48 weeks depending on the group (n=123 subjects in both groups)

Adverse events

Study M98-940:

The most commonly reported (> 30% of subjects) adverse events (AEs) were related to infections (or symptoms of infections), related to the digestive system (including vomiting and diarrhea), rash, or accidental injury. The majority of AEs were reported as mild and considered probably not related to study

drug. Eight subjects reported AEs of at least moderate severity and of possible, probable, or unknown relationship to study drug. Of those AEs, rash was the only event reported by ≥ 2% of subjects.

In total, 2 subjects prematurely discontinued the study due to an adverse event or HIV-related event. One subject prematurely discontinued the study on Day 93 due to an HIV-related event (Burkitt's lymphoma) and died as a result 16 days later. A second subject prematurely terminated prior to the Week 48 visit due to pancreatitis, which was considered possibly related to study drug. Serious adverse events (SAEs) were reported for 27/100 subjects during the study, of which one event (pancreatitis, mentioned in the previous sentence) was considered possibly-related to study drug by the investigator.

No clinically relevant differences were seen with respect to age or treatment experience.

Table 25. Adverse Events of at Least Moderate Severity and of Probable, Possible, or Unknown Relationship to ABT-378/Ritonavir by Age Group

Body System/ COSTART Term	Age Group	
	<2 Years Old (N=14)	≥2 Years Old (N=86)
Total Subjects		
Any adverse event	2 (14.3%)	6 (7.0%)
Body as a Whole		
Allergic reaction	0 (0.0%)	1 (1.2%)
Fever	0 (0.0%)	1 (1.2%)
Viral infection	0 (0.0%)	1 (1.2%)
Digestive System		
Constipation	1 (7.1%)	0 (0.0%)
Hepatomegaly	0 (0.0%)	1 (1.2%)
Pancreatitis	0 (0.0%)	1 (1.2%)
Vomiting	0 (0.0%)	1 (1.2%)
Metabolic and Nutritional System		
SGPT increased	1 (7.1%)	0 (0.0%)
Skin and Appendages		
Dry skin	0 (0.0%)	1 (1.2%)
Rash	0 (0.0%)	3 (3.5%)
Special Senses		
Taste perversion@	0 (0.0%)	1 (1.2%)

Note: Mild adverse events and events not considered related were excluded

@taste perversion is equivalent to taste aversion

No consistent statistically significant differences between age groups were observed for haematology variables. The proportion of subjects with very high and very low clinical chemistry values is as follows:

Clinical Chemistry Variable	Age Group	
	<2 Years Old (N=14)	≥2 Years Old (N=86)
Uric Acid > 12.4 mg/dL	0 (0%)	1 (1%)
Sodium > 149 MEQ/L	1 (7%)	2 (2%)
Potassium > 6.4 MEQ/L	0 (0%)	1 (1%)
Total bilirubin > 2.9 XULN	0 (0%)	4 (4.7%)
SGOT/AST ≥ 10X ULN	0 (0%)	2 (2%)
SGPT/ALT ≥ 10X ULN	0 (0%)	3 (4%)
Total cholesterol >300 mg/dL	1 (7%)	3 (4%)
Triglycerides >750 mg/dL	0 (0%)	1 (1%)
Amylase >2.5 X ULN	0 (0%)	6 (7%)

Clinical Chemistry Variable	Age Group	
	<2 Years Old (N=14)	≥2 Years Old (N=86)
Sodium < 130 MEQ/L	0 (0%)	3 (4%)
Potassium < 2.5 MEQ/L	0 (0%)	1 (1%)
Calcium < 7 MEQ/L	0 (0%)	2 (2%)

Study P1030:

Seven subjects (23%), 3 from the younger cohort and 4 from the older cohort, had AEs that were considered possibly related to study treatment while no adverse event (AE) was considered definitely related to study treatment. The maximal grade for the AEs was Grade 3 for these 7 subjects. All possibly treatment-related Grade 3 AEs for the younger cohort were low absolute neutrophil count occurring at either Week 8 or Week 12. These AEs resolved after adjusting or temporarily withholding concurrent NRTI therapy. For the older cohort, the possibly related Grade 3 AEs were hyperkalemia, hypernatremia, hyponatremia, and elevated alanine aminotransferase (ALT). These events were transient and did not require premature discontinuation from the study or treatment adjustment.

Across both cohorts combined, 11 subjects (35%) had Grade 3 or higher signs or symptoms, including 3 (30%) in the younger cohort and 8 (38%) in the older cohort. Two of the 11 subjects affected had Grade 4 events. The most frequent Grade 3 or 4 signs/symptoms were fever and blister/ulcer/lesions. The most frequent laboratory toxicities were low absolute neutrophil count and potassium abnormalities.

Table 26. Most Frequent Grade 3 or Higher Signs/Symptoms Reported in at Least 2 Subjects from Date of First Dose through Date of Last Dose in Study P1030

	N = 31		
	Toxicity Grade		n (%)
Signs/Symptoms	**3**	**4**	
Fever	5	0	5 (16.1)
Blister/ulcer/lesions	3	0	3 (9.7)
Ache/pain/discomfort	2	0	2 (6.5)
Diarrhea/loose stools	2	0	2 (6.5)
Other	1	1	2 (6.5)

Four subjects prematurely discontinued from the study because of AEs: one subject from the younger cohort (failure to thrive), and 3 subjects from the older cohort (Grade 1 vomiting and soft stools, CMV infection with severe respiratory involvement leading to death and Grade 3 anemia). None of them were considered related to study treatment.

Twelve SAEs that were considered probably or possibly related to study treatment or ones whose relationships were unable to be judged by the study team occurred in 8 subjects. The SAEs included decreased absolute neutrophil count, neutropenia, decreased hemoglobin, anemia, hyperkalemia, abnormal stools, vomiting, hyponatremia, increased ALT, and abnormal amylase. Many of these SAEs were considered possibly related to concomitant ARV medications or improved with ongoing or resumed therapy.

Overall, the AEs seen in this paediatric study of very young subjects were similar to those seen in previous paediatric and adult studies of LPV/r. The study did not identify any drug-specific safety concerns related to gastrointestinal, hepatic, or metabolic effects that have not previously been identified in paediatric subjects who have received LPV/r.

Study P1060:

A secondary objective of Study P1060 was to compare the safety profile of a NVP-based HAART regimen with a LPV/r-based regimen in HIV-infected children between 2 months and 36 months of age who had (Cohort I) or had not (Cohort II) been exposed to single-dose NVP for PMTCT of HIV.

Among the LPV/r-treated subjects in Cohort I (82 subjects), the most frequently reported Grade 3 or 4 AEs was diarrhoea/loose stools (Grade 3 in 2 subjects). The most frequent laboratory toxicity was low absolute neutrophil counts. One subject was taken off study treatment because of protocol-defined elevated liver function tests toxicity (Grade 4 ALT and jaundice) that was not life-threatening and was treatment-related. Three subjects (4%) died while on study. The causes of death were burns, pneumonia, and cardiac and pulmonary arrest. The burns and pneumonia were considered not related to study treatment, and the relationship of the cardiac/pulmonary arrest to study drug remains unassigned.

Among the LPV/r-treated subjects in Cohort II (140 subjects), the most frequently reported Grade 3 or 4 AEs were fever and diarrhoea/loose stools. The most frequent laboratory toxicities were low absolute neutrophil counts and low haemoglobin.

Table 27. Most Frequent Grade 3 or Higher Signs/Symptoms Reported in at Least 2 Subjects Among LPV/r-Treated Subjects on Treatment in Cohort II in Study P1060

	LPV/r N = 140		
	Toxicity Grade		n
Signs/Symptoms	**3**	**4**	
Fever	16	2	18
Diarrhea/loose stools	5	0	5
Vomiting	3	0	3
Cough	2	0	2
Respiratory system dysfunction	1	1	2

Five subjects were taken off study treatment for treatment-related events (3 neutropenia, 1 anemia and 1 thrombocytopenia). Three subjects (2%) died while on study. The causes of death were congestive cardiac failure, gastroenteritis and measles. All 3 deaths were considered not related to study treatment.

Overall, LPV/r was tolerated well by subjects, with no overall difference in ≥ Grade 3 AEs or frequency of AEs between cohorts. There were no concerning safety trends observed and no new safety signal was identified specific to subjects in the study population. The safety findings from this paediatric study were consistent with the safety profile of LPV/r when used in the adult and paediatric population, as detailed in the current LPV/r product information.

Study CHER:

Out of the 411 subjects included in the safety analysis, 142 subjects (34.5%) reported a total of 279 Grade 3 or 4 AEs: 56 subjects (44.8%) in the ART-deferred arm, 38 subjects (26.6%) in the ART-40W arm, and 48 subjects (33.6%) in the ART-96W arm. The most frequently reported Grade 3 or 4 AEs (among those reported in at least 5% of subjects in any arm) were gastroenteritis and pneumonia.

Table 28. Grade 3 or 4 AEs Reported in at Least 5% of Subjects in Any Arm in CHER Study

	Treatment Arm		
Preferred term	**ART-Def N = 125**	**ART-40W N = 143**	**ART-96W N = 143**
Gastroenteritis[a]	25 (20.0)	15 (10.5)	15 (10.5)
Pneumonia	24 (19.2)	8 (5.6)	10 (7.0)
Neutropenia	3 (2.4)	8 (5.6)	13 (9.1)
Gastroenteritis[b]	7 (5.6)	3 (2.1)	1 (0.7)

a. Listed under system organ class (SOC) of Infections and Infestations.

b. Listed under SOC of Gastrointestinal Disorders.

Across all 3 arms, 31 subjects (7.5%) reported 44 events that were considered LPV/r ART-related with similar frequencies seen across the arms. The most frequent ART-related events across the arms were neutropenia (15 events in 13 subjects) as well as 6 events each of anaemia (5 subjects) and gastroenteritis (6 subjects). The rates of laboratory events (particularly those considered ART-related) were similar and low in all 3 arms. There were no study treatment discontinuations because of laboratory toxicity.

The most frequently occurring SAEs (at least 50 events) were gastroenteritis infection and pneumonia. Hospitalizations were reported in a higher number of subjects in the ART-deferred arm (52 subjects) than in the ART-40W arm (31 subjects) and the ART-96W arm (36 subjects). A total of 37 deaths occurred during the first 48 weeks of study participation in the 411 subjects included in the safety analysis. The mortality rate was higher in the ART-def arm (21 subjects; 16.8%) relative to the ART-40W (9 subjects; 6.3%) and ART-96W (7 subjects; 4.9%) arms. The majority of the deaths occurred within the SOCs of General Disorders and Administration Site Conditions and Infections and Infestations.

Overall, the data show a limited number of drug-related AEs. The CHER study results provide supporting evidence of the durability of LPV/r-based first-line ART for children and demonstrate a safety profile of LPV/r in children from 6 weeks of age that is consistent with the known safety profile in adults and older children as detailed in the LPV/r product information.

Post marketing experience

The AbbVie global post-marketing safety database was searched for all reports that satisfy the following case definition: reports coincident with LPV/r oral solution received from **01 January 1900 through 12 March 2015 in children and infants younger than 2 years of age.**

Of the 65 unique reports describing adverse events associated with Kaletra oral solution in the paediatric population younger than 2 years of age, 11 reports were confounded, 26 reports had an alternative ethology for the adverse event(s), and 19 (excluding 1 likely duplicate) had no apparent alternative ethology for the adverse event(s).

In total, 9 reports had a fatal outcome. Of these, 8 reports had an alternate ethology for the event(s) and 1 fatal outcome was the result of a medication error.

In total, there are 11 serious reports of toxicity associated with Kaletra oral solution (including LPV/r, propylene glycol, and/or ethanol) in (preterm) neonates. All serious reports of toxicity were received prior to the implementation of 2011 labelling revisions in the EU regarding the risk associated with dosing in (premature) neonates. The 5 reports of medication error were received prior to the implementation of these labelling revisions.

In 2011, revisions to the Kaletra Summary of Product Characteristics (SmPC) were made in section 4.4 and section 4.9 to reflect the important identified risk of medication error and toxicity in neonates, especially in premature neonates. In addition, the risk of toxicity in preterm neonates was included in the Kaletra risk management plan, and routine risk minimization, including product labelling, was considered adequate to manage this risk.

Excluding reports of toxicity associated with Kaletra oral solution, the remaining reports include reports of medication error, taste intolerance, treatment failure as a result of resistance development, and labelled drug-drug interactions with fluticasone and nevirapine and adverse reactions that are already labelled for LPV/r. These adverse reactions include upper and lower respiratory tract infections, diarrhoea, vomiting, gastroenteritis, abdominal distension, anaemia, hepatitis, lactic acidosis, IRIS, dermatitis, and seizure. Analyses of the reports in this focused review indicate that the adverse reactions described are all consistent with the known safety profile of Kaletra in older children and in adults, as described in the Kaletra product labelling.

2.6.1. Discussion on clinical safety

Overall, the results of the 4 paediatric studies did not highlight new safety concerns specific to the paediatric subjects below 2 years of age. Given that LPV/r was associated to a backbone regimen mainly composed of AZT+3TC, neutropenia and anaemia were frequently reported. Potential impact of LPV/r on growth in these subjects is difficult to appreciate due to other cofounders (malnutrition, low care system) but is not particularly expected based on animal juvenile data. The safety profile of LPV/r in children <2 years of age is consistent with the known safety profile in adults and older children as detailed in the LPV/r product information.

Nevertheless, a focus should be made on the known-toxicity of the excipients of Kaletra oral solution. Indeed, Kaletra oral solution contains approximately 42.4% (v/v) alcohol (or 356.3 mg alcohol per mL) and 152.7 mg of propylene glycol per mL. Serious cases of alcohol or propylene glycol toxicity associated with Kaletra oral solution in (preterm) neonates were reported in post marketing experience.

The serious AEs associated to these excipients are: hyperosmolality, renal toxicity, central nervous system (CNS) depression (including stupor, coma, and apnoea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and haemolysis. Deaths were reported in case of overdose. It is noted that

pharmacokinetic parameters of propylene glycol in neonates differ significantly from adult values leading to its accumulation following repeated administration (longer elimination half-life, limited renal and metabolic clearances) or when administered in combination with another substrate of alcohol dehydrogenase (limiting step of metabolism) such as ethanol (e.g. toxicity of some anti-viral treatments in neonates).

To mitigate this risk, a warning was added in 2011 in the SmPC to alert the prescribers. No further reports of alcohol or propylene glycol toxicity in neonates associated with Kaletra oral solution have been reported since these SmPC revisions.

As part of this paediatric extension, new oral dosing syringes of 2 ml, in addition to the current syringes of 5 ml, are now proposed in order to reduce the risk of overdose in younger subjects. This measure was recommended by the PDCO. In clinical practice, this new 2 ml syringe would be more appropriate for subjects < 6 months of age and for subjects > 6 months of age with low BSA (<0.7 m²) and weight (<13 kg). Therefore the new packaging consisting in two 60 ml bottles of Kaletra with two 2 ml syringes should be prescribed only for these patients, and the current packaging with five 60 ml bottles of Kaletra and two 5 ml syringes must continue to be prescribed for other patients requiring volumes of Kaletra > 2 ml. A special attention should be exercised by the pharmacists on the adequate packaging to be dispensed in accordance to the volume of Kaletra to be administered, and notably to inform the care administrators when a switch of packaging is required. The MAH should discuss the risk minimization measures envisaged to mitigate the risk of confusion relative to the adequate packaging to be delivered.

The estimated amount of alcohol in subjects <2 years of age was calculated by the MAH:

Table 29. Amount of Alcohol Ingested by Children 14 Days to 2 Years of Age Relative to Potential Dose of LPV/r Oral Solution (BSA-Based Dosing)

Age	Average Weight (kg)	Average BSA[a] (m^2)	LPV/r Dose[b] (mg)	Volume of Oral Solution[c] (mL)	Amount of Alcohol (mg)	Maximum Blood Alcohol Concentration[d] (mg/dL)
14 days	3.6	0.23	69.0	0.9	321	11.89
2 months	5.0	0.28	84.0	1.1	392	10.45
6 months	7.3	0.37	111.0	1.4	499	9.11
2 years	11.5	0.53	121.9	1.5	534	6.19

a. BSA was calculated based on the Haycock equation: BSA = (weight in kg) 0.5378 × (height in cm) 0.3964 × 0.024265. Average height and weight were determined using the 50th percentile weights from Female WHO Growth Charts. Source: WHO.

b. LPV/r dose was calculated as 300/75 mg/m2 in children ≤ 6 months of age and 230/57.5 mg/m2 in children older than 6 months of age.

c. Concentration of LPV/r oral solution is 80 mg/mL, with an alcohol concentration of 0.3563 g/mL.

d. Blood alcohol concentration (BAC) (mg/dL) = (amount of alcohol (in mg)/[(distribution coefficient, 0.75 L/kg) × (weight in kg)]) × 0.1 L/dL. Note: Volume of distribution coefficient obtained from Cordoni.

It appears that the estimated maximum blood alcohol concentrations will be approximately 10-12 mg/dl for the younger subjects, which is accordance to the WHO guidelines (<20-25 mg/dl) and EMA guidelines (<12.5 mg/dl).

The estimated amount of propylene glycol with Kaletra 300/75 mg/m² in subjects < 6 months of age or 230/57.5 mg/m2 in children > 6 months of age was estimated by the MAH to be generally below 10 mg/dL. In children 6 months of age and older, a LPV/r dose increase to 300 mg/m2 (equivalent to LPV 13 mg/kg for patients < 15 kg and 11 mg/kg for patients ≥ 15 kg) may be considered when co-administered with CYP-inducing ARVs. Therefore, an approximate 10% to 30% increase in propylene glycol intake (similar percentage increase observed for alcohol) may result. Overall, according to the MAH, this is

nearly 100-fold below the concentration reported in cases of propylene glycol toxicity in infants, in which propylene glycol maximum concentrations of 930 to 1,060 mg/dL were reported.

However, a draft background review for the excipient propylene glycol is under review by the EMA. According the published draft, it is noted that a PDE of 1 mg/kg with very conservative safety limits based upon non clinical data, was derived for children below five years of age. Despite the fact that at the present time the published clinical data demonstrate that higher propylene glycol load may be safely administered to patients particularly to children above 4 years of age and adults, a more cautious approach is still recommended for patients below 5 years of age because of the paucity of clinical data in this population.

Concerning children below 1 month of age: "*In (pre)term neonates De Cock et al. have demonstrated that total body clearance is very low compare to the adult clearance, but also that the contribution of renal clearance to the total body clearance is very low. The results of this study may indicate that due to maturational changes, some drug/drug metabolic interactions are more relevant for this specific population. This may explain the toxicities observed in neonates given Kaletra® which contains 356.3 mg ethanol/mL and 152.7 mg propylene glycol/mL. Considering also the data produced by Shehab and Whittaker showing the multiple sources of propylene glycol and ethanol in neonatalogy units,* ***it is proposed to restrict the safety limit to 1 mg/kg*** *in preterm neonates below 44 weeks of post menstrual age,* ***or below one month post-natal age for term neonates."***

When referring to the draft background review for the excipient propylene glycol under review by the EMA, the propylene glycol content in children >1 month of Kaletra is higher than the limit of 50 mg/kg set by the EMA for this subgroup. Overall, **the total daily intake of propylene glycol will be above the safety limit considered by EMA of 1 mg/kg/day (for neonates up to 28 days) and 50 mg/kg/day (for children aged 1 month up to 4 years)** and should therefore be closely monitored, especially given ABC and 3TC oral solutions (both containing propylene glycol) may be co-administered with Kaletra.

It is also important to note that based on the EMA guideline under review ethanol content >75 mg/kg would preclude the use of medicinal product in children < 6 years of age. Kaletra administration in children > 3.5 kg would imply a borderline acceptable approximately 70 mg/kg ethanol content.

It is important to underline that the PDCO has recommended setting a Pharmacovigilance cohort based on the high ethanol and propylene glycol exposure. The MAH committed to perform targeted follow-up of spontaneously reported cases specific to the patient group (2 weeks to 2 years of age) administered Kaletra oral solution via the use of a structured questionnaire in order to ensure improved collection of information specifically related to ethanol and propylene glycol levels, and to the duration of Kaletra oral solution use. In addition, the MAH will submit a safety review (LEG procedure with a 1 year interval) focused on adverse events in children 14 days to 2 years of age that may suggest toxicity with ethanol or propylene glycol. The review should include a discussion of the benefit/risk balance in this population, in light of emerging data.

2.6.2. Conclusions on clinical safety

The safety of Kaletra is well characterised. However, chronic exposure to propylene glycol and ethanol in youngest children should be monitored. The MAH will submit a yearly safety review (LEG procedure) focused on adverse events in children 14 days to 2 years of age that may suggest toxicity with ethanol or propylene glycol. The review should include a discussion of the benefit/risk balance in this population, in light of emerging data. The CHMP considers the MAH should submit the first yearly safety review (LEG procedure) within 2 months following EC decision.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.2 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8.2 with the following content:

Safety concerns

Addition or modification of the safety concerns are highlighted in bold below:

Important identified risks	• Toxicity in preterm neonates of Kaletra (Lopinavir/ritonavir [LPV/r]) oral solution. • Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves disease). • Lipid elevations.
Important potential risks	• Drug interaction with HCV PIs telaprevir and boceprevir. • QT prolongation with supratherapeutic doses. • PR prolongation at therapeutic dosing. • **Risks of overdose resulting from medication errors with LPV/r oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg**
Missing information	• Use of Lopinavir/ritonavir in elderly patients. • **Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age**

Pharmacovigilance plan

The planned Pharmacovigilance for these 2 highlighted safety concerns is presented below. No additional PV activity was requested.

Areas Requiring Confirmation or Further	**Proposed Routine and Additional PV Activities**	**Objectives**

Investigation		
Safety Concern (potential risk): Risk of overdose resulting from medication errors with LPV/r oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg		
Medication errors resulting in overdose and potential ethanol and/or propylene glycol toxicity	• Routine PV activities o Targeted follow-up questionnaire o Quarterly trend analysis of product quality complaints	To understand the root cause of medication errors, so that corrective and preventative actions may be taken. • To evaluate the response rate and encourage the reporter to use these questionnaires
Safety Concern (missing information): Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age		
The effect of long-term exposure, even to low levels of ethanol and propylene glycol, in medicines on the health and development of children has not been evaluated.	• Routine PV activities	• To detect any long-term safety concerns associated with chronic use from infancy.

Risk minimisation measures

Addition or modifications of the RMMS are highlighted in bold in the table below:

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Toxicity in preterm neonates of LPV/r oral solution	SmPC: Currently, section 4.2 and section 4.9 of the SmPC alert prescribers regarding the possibility of toxicity due to excipients; similar text is in the CCDS.	None proposed
Immune reconstitution inflammatory syndrome (IRIS) manifesting as autoimmune disorders (such as Graves disease)	SmPC: Section 4.4 of the SmPC provides further information on risk of autoimmune disorders in the setting of immune reactivation; similar text is in the CCDS.	None proposed
Lipid elevations	SmPC: Currently, section 4.4 and section 4.5 of the SmPC warn about lipid elevations and provide recommendations for cholesterol and triglycerides monitoring; similar text is in the CCDS.	None proposed
Drug interaction with HCV PIs telaprevir and boceprevir	SmPC: Section 4.5 of the SmPC provides information on the co-administration of LPV/r with telaprevir and boceprevir; similar text is in the CCDS. Routine PV activities: Ongoing review of relevant scientific literature.	None proposed
QT prolongation with supratherapeutic doses	SmPC: Section 4.4 of the SmPC provides further information on QT prolongation; similar text is in the CCDS.	None proposed
PR prolongation at therapeutic dosing	SmPC: Section 4.4 of the SmPC provides further information on PR prolongation; similar text is in the CCDS.	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Risk of overdose resulting from medication errors with LPV/r oral solution in patients 14 days to 9 weeks of age and weighing less than 3.8 kg	**SmPC:** **Section 4.2 of the SmPC provides guidance on posology and administration.** **Section 4.4 warns about toxicity in relation to the amount of alcohol and propylene glycol contained in LPV/r oral solution.** **PIL:** **Detailed guidance of administration provided.** **Prescription only medicine**	**None proposed**
Use of Lopinavir/ritonavir in elderly patients	None.	None proposed
Safety of chronic exposure to propylene glycol and ethanol in patients 14 days to 2 years of age	**SmPC:** **Section 4.2 of the SmPC provides guidance on posology and administration.** **Section 4.4 of the SmPC provides warning regarding excipients ethanol and propylene glycol.**	**None proposed**

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.3, 4.3, 4.8, 5.1, 5.2, of the SmPC have been updated. Labelling and the Package Leaflet have been updated accordingly.

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.9. Significance of paediatric studies

The CHMP is of the opinion that studies PACTG 1030, PACTG 1060 and CHER, which are contained in the agreed Paediatric Investigation Plan EMEA-001005-PIPO1-10-M01, which is completed, and have been completed after 26 January 2007, are considered as significant.

Of note, study M98-940 is not part of the PIP. This study was submitted to the EMA in June 2000 in support of the Marketing Authorisation application for Kaletra. The study is being provided again for ease of reference.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Kaletra is characterised by a high potency and genetic barrier to resistance. A large clinical experience has been gained since its original MA in 2001.

3.1.1. Available therapies and unmet medical need

It is already part of therapeutic guidelines (US and EU-PENTA guidelines) for the first-line ARV regimens in the treatment of HIV-infected infants and children < 2 years of age.

3.1.2. Main clinical studies

In the context of this paediatric extension application, clinical data of LPV/r in children < 2 years old were provided by the clinical studies M98-940, P1030, P1060 and CHER.

All of the 4 clinical studies submitted provide clinical data of LPV/r in subjects below 2 years of age, but with different lower limits of age: the younger subjects were mainly enrolled in studies P1030 (14 days – 6 months old) and CHER (6 weeks – 12 weeks old).

3.2. Favourable effects

The virologic responses did not raise concerns.

Study	M98-940 N=14	P1030 N=31	P1060 N=119[a]	CHER N=143[b]
Age at baseline	6 months – 2 years	14 days – 6 months	2 months – 36 months	6 weeks – 12 weeks
% of subjects with HIV-1 RNA < 400 c/ml at Week 48	79%	71%	85%	N/A

a : subjects treated by LPV/r at Week 48 in Cohort II (including subjects > 2 years old)
b : subjects always treated at Week 48 (= group ART-96W)

3.3. Uncertainties and limitations about favourable effects

Based on PK data derived from the clinical studies covering the targeted pediatric population, younger children might have underexposure to LPV.

Study	P1030		M98-940		SmPC Kaletra
Dose LPV/r	300/75 mg/m^2 BID (without NNRTI use)				400/100 mg BID
Age	14 days – 6 weeks	6 weeks – 6 months	3 months – 2 years	2 years – 12 years	adults
N	9	18	7	20	-
Mean AUC_{12} (µg.h/ml)	43.39	74.50	81.0	110.4	113.2
Mean Cmin (µg/ml)	1.40	1.95	2.99	5.98	8.1
Mean apparent CL/F (L/h/kg)	0.47	0.23	-	-	-

While no particular alert was raised from the clinical studies and US postmarketing experience, the MAH should make a proposal to derive further reassurance on the risk of suboptimal PK exposure of Kaletra in children <3 month of age (particular focus on inadequate virologic suppression in this subgroup).

3.4. Unfavourable effects

Based on the clinical experience derived from the clinical studies performed to cover the targeted paediatric population and the US post-marketing experience there is no apparent concern of a differential safety profile in children from 14 years of age from the well substantiated safety profile in adults, adolescents and children from 2 years of age.

The sensitive issue in relation to the use of Kaletra in very young children relies on the high content of ethanol and propylene glycol (PG) in the existing oral solution. This has been extensively discussed by the PDCO, which finally has considered that this oral solution could be regarded as compatible with the use in neonates from 14 days of age, taking into account the followings:

- Kaletra is intended to be used for the treatment of HIV-1 infected children so that the benefits related to the use of Kaletra are expected to outweigh the potential risks related to the presence of ethanol and PG,

- Kaletra is already authorized in children > 2 years (as well as Norvir) in Europe,

- Kaletra is authorized in children above 14 days in the US therefore, clinical experience has been gained.

To minimize the risk of overdosage, a 2 ml volume syringe is available.

3.5. Uncertainties and limitations about unfavourable effects

It is important to underline that the PDCO has recommended setting a Pharmacovigilance cohort based on the high ethanol and propylene glycol exposure in the target patient population. The MAH committed to perform targeted follow-up of spontaneously reported cases specific to the patient group (2 weeks to 2 years of age) administered Kaletra oral solution via the use of a structured questionnaire in order to ensure improved collection of information specifically related to ethanol and propylene glycol levels, and to the duration of Kaletra oral solution use. In addition, the MAH will submit a safety review (LEG procedure with a 1 year interval) focused on adverse events in children 14 days to 2 years of age that may suggest toxicity with ethanol or propylene glycol. The review should include a discussion of the benefit/risk balance in this population, in light of emerging data.

3.6. Benefit-risk assessment and discussion

Kaletra is recommend in the EU and US therapeutic guidelines for the first line regimens in young children due to its high potency and high genetic barrier to resistance, the availability of an oral solution. Kaletra has a well characterized safety profile based on large clinical experience gained since its MA in 2001.

The benefit/risk balance of Kaletra oral solution in children from 14 days of age can be considered positive. However, adequate warnings on the high content of ethanol and propylene glycol and particular scrutiny of pharmacovigilance data (safety and efficacy) in the younger subgroup of paediatric patients <3 months of age have been put in place.

The clinical development programme in support of this extension of indication and the 2 ml syringe to minimize the risk of overdosage in younger children is overall in line with the PDCO discussion on the PIP.

3.7. Conclusions

The overall B/R of Kaletra is positive.

The CHMP considers the MAH should submit the first yearly safety review (LEG procedure) focused on adverse events in children 14 days to 2 years of age that may suggest toxicity with ethanol or propylene glycol within 2 months following EC decision.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	Annex A, I, IIIA and IIIB
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	Annex A, I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include children aged 14 days and older in the treatment of HIV-1; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. The studies provided in support of the paediatric indication are part of the agreed PIP (decision P/0144/2012). In addition, the Marketing authorisation holder (MAH) further updated section 4.4 to add a warning regarding the use of Kaletra oral solution with feeding tubes. The updated RMP v.8.2 is provided accordingly.

IB-B.II.e.5.a.2-To add a new pack size of 120 ml in (2X 60ml bottles) for Kaletra 80mg/ml/20 mg/ml oral solution (EU/1/01/172/009).

IA-B.IV.1.a.1-To add a new 2 ml oral dose syringe for the 120ml presentation.

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-001005-PIPO1-10-M01 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and in the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan EMEA-001005-PIPO1-10-M01 have been completed after the entry into force of that Regulation.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include children aged 14 days and older in the treatment of HIV-1; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. The studies provided in support of the paediatric indication are part of the agreed PIP (decision P/0144/2012). In addition, the Marketing authorisation holder (MAH) further updated section 4.4 to add a warning regarding the use of Kaletra oral solution with feeding tubes. The updated RMP v.8.2 is provided accordingly.

IB-B.II.e.5.a.2-To add a new pack size of 120 ml in (2X 60ml bottles) for Kaletra 80mg/ml/20 mg/ml oral solution (EU/1/01/172/009).

IA-B.IV.1.a.1-To add a new 2 ml oral dose syringe for the 120ml presentation.

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Summary

Please refer to the scientific discussion Kaletra-H-C-368-II-0161G