OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	21226: lopinavir/ritonavir capsules, S-40, SDN 889 21251: lopinavir/ritonavir solution, S-49, SDN 559 21906: lopinavir/ritonavir tablets, S-42, SDN 745
Submission Date	17 September 2014
Brand Name	Kaletra
Generic Name	Lopinavir/ritonavir
Sponsor	AbbVie, Inc.
Formulation; Strength	Lopinavir/ritonavir capsules (133.3 mg/33.3 mg) Lopinavir/ritonavir tablets (100 mg/25 mg, 200 mg/50 mg) Lopinavir/ritonavir oral solution (80 mg/20 mg per mL)
Approved Dosing Regimen	Adults: 400 mg /100 mg twice daily (BID) or 800 mg/200 mg once daily (QD) in patients with less than three lopinavir resistance-associated substitutions. Pediatrics: Twice daily dose based on body weight or surface area
Approved Indication	Treatment of HIV-1 infection in adults and pediatric patients
Clinical Pharmacology Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
Pharmacometrics Reviewer	Luning Zhuang, Ph.D.
Pharmacometrics Team Leader	Jeffry Florian, Ph.D.
Review Type	PREA Postmarketing requirement (PMR) submission

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1 Executive summary

This review documents the clinical pharmacology and pharmacometrics reviewer comments for a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) submission. The PMR submission contains the PENTA-18 trial report that evaluated once daily dosing of lopinavir/ritonavir in pediatric subjects.

The submission also includes proposed revisions to the lopinavir/ritonavir U.S. prescribing information (USPI) regarding drug-drug interaction information for concomitant use of lopinavir/ritonavir with etravirine, rilpivirine, or simeprevir. The proposed revisions are consistent with the existing information in the etravirine, rilpivirine, or simeprevir U.S. prescribing information. The applicant's changes to the lopinavir/ritonavir U.S. prescribing information and the revisions proposed by the Office of Clinical Pharmacology are outlined below in section 2.
Lopinavir (LPV), co-formulated with ritonavir (RTV), is indicated for the treatment of HIV-1 infection in adult and pediatric patients. The approved dosing regimen of lopinavir/ritonavir for adults is 400/100 mg twice daily or 800/200 mg once daily in patients with less than three lopinavir resistance-associated substitutions. For pediatric patients, depending on the patient characteristics (e.g. age, weight), twice daily dosing using capsules, oral solution or tablets is approved. With lopinavir/ritonavir tablets, a twice daily dosing regimen based on body weight bands (15 kg to ≤ 25 kg; >25 kg to ≤ 35 kg; >35 kg) or body surface area bands (≥0.6 to <0.9; ≥0.9 to < 1.4; ≥ 1.4) is approved for pediatric patients.

The purpose of this supplement included submitting the pharmacokinetic, safety and antiviral activity results from the PENTA-18 (KONCERT) trial evaluating once and twice daily LPV/RTV dosing regimens in pediatric HIV-1-infected subjects. The trial results were submitted in order to fulfill the following postmarketing requirement (PMR) under PREA that was included in the action letter for NDA 21906, supplement 24:

Please submit the 24 week results of PENTA 18 evaluating the pharmacokinetic, safety and activity of twice daily and once daily dosing of Kaletra tablets in a reviewable format. Submit a final report that includes detailed summaries of pharmacokinetic, safety and activity data as well as electronic datasets.

The following are the major clinical pharmacology related findings from the PENTA-18 trial:

- Once daily (QD) dosing of lopinavir/ritonavir tablets resulted in lower exposures than twice daily (BID) dosing for lopinavir/ritonavir in pediatric subjects less than 18 years old. Total daily dosing of the two regimens was equivalent and followed the pediatric recommendations for lopinavir/ritonavir twice daily tablet dosing in the lopinavir/ritonavir U.S. prescribing information. For once daily dosing compared to twice daily dosing, the 90% confidence interval (CI) of the geometric mean ratio (GMR) of lopinavir $AUC_{0\text{-}24h,}$ C_{max} and C_{last} was 0.72 (0.62, 0.83), 1.13 (1.00, 1.26). and 0.18 (0.12, 0.27), respectively
- Including data up to the week 24 assessment, 10 pediatric subjects from the QD arm and 3 pediatric subjects from the BID arm had a HIV-1 RNA viral load confirmed ≥50 copies/mL.

The lower lopinavir $AUC_{0\text{-}24}$ with QD dosing compared to that of BID dosing was unexpected since the same total daily dose was administered. However, the potential contribution of lower LPV exposure to the observed increased rate of virological failure in the QD dosing group cannot be excluded. There are insufficient data to determine the specific factor(s) contributing to these lower AUC values with the QD regimen (e.g., lack of adherence). Given the observed increased rate of virologic failure with the QD regimen and the availability of other treatment options, including the BID option for lopinavir/ritonavir, the Office of Clinical Pharmacology concurs with the review team's assessment that a QD lopinavir/ritonavir dosing regimen in pediatrics should not be included in the lopinavir/ritonavir U.S. prescribing information.

1.1 Recommendation

For the portion of the submission relation to the revising of drug-drug interaction information, with the exception of the changes proposed by the Office of Clinical Pharmacology that are outlined in section 2, the applicant's revisions to the lopinavir/ritonavir U.S. prescribing information were acceptable. Because telaprevir has been withdrawn from the U.S. market, the applicant was also requested to remove the telaprevir drug-drug interaction data from the lopinavir/ritonavir U.S. prescribing information.

For the portion of the submission relation to the revision of information for pediatric patients, the submission fulfills the postmarketing requirement for the PENTA-18 trial. The applicant proposes to include a statement that once daily lopinavir/ritonavir dosing is not recommended, which is acceptable. No labeling changes related to including once daily lopinavir pediatric exposure data from the PENTA-18 trial in the lopinavir/ritonavir U.S prescribing information are proposed by the applicant or the review team.

1.2 Pertinent Regulatory Background

In adults, lopinavir/ritonavir can be taken once or twice daily in patients with less than three lopinavir resistance-associated substitutions or twice daily in patients with three or more lopinavir resistance-associated substitutions as specified in the lopinavir/ritonavir USPI. As decreasing the daily frequency with which medication needs to be taken may improve adherence to antiretroviral therapy in HIV-1 infected pediatric patients, once daily versus twice daily dosing

of lopinavir/ritonavir tablets as part of combination antiretroviral therapy (ART) was further explored in HIV-infected pediatric subjects.

1.3 Summary of Important Clinical Pharmacology Findings

PENTA-18 (KONCERT) was a prospective, open label, multicenter, phase II/III trial. Pediatric subjects were randomized (1:1) either to continue their current highly active antiretroviral therapy (HAART) regimen with lopinavir/ritonavir tablets taken twice daily or to switch to lopinavir/ritonavir tablets dosed once daily. Randomization was stratified by body weight band ($\geq$ 15 to $\leq$ 25kg, > 25 to $\leq$ 35kg, > 35kg). The pediatric subjects were to be followed for a minimum of 48 weeks.

Lopinavir exposure data is displayed below. Overall, despite administration of the same LPV/RTV total daily dose, lower lopinavir exposure (AUC) was observed with once daily dosing compared with twice daily dosing.

PK parameters of lopinavir after twice daily (week 0) and once daily (week 4) dosing

	n	BID geometric mean (95% CI)[$]	QD geometric mean (95% CI)[$]	(QD / BID) geometric mean ratio (90% CI)
AUC_{0-24} (h*mg/L)[†]				
Total:	26	223.9 (194.8, 257.4)	160.9 (138.4, 187.0)	0.72 (0.62, 0.83)
Weight: ≥15 to ≤25kg	7	232.1 (153.3, 351.4)	172.6 (121.3, 245.7)	
>25 to ≤35kg	8	256.8 (209.3, 315.2)	159.3 (120.6, 210.5)	
>35kg	11	198.1 (159.8, 245.5)	155.0 (116.8, 205.6)	
C_{max} (mg/L)				
Total:	26	12.5 (11.1, 14.0)	14.0 (12.7, 15.6)	1.13 (1.00, 1.26)
Weight: ≥15 to ≤25kg	7	13.5 (9.8, 18.7)	15.5 (12.4, 19.4)	
>25 to ≤35kg	8	14.1 (11.4, 17.3)	15.0 (12.2, 18.5)	
>35kg	11	10.9 (9.3, 12.6)	12.5 (10.7, 14.7)	
C_{last} (mg/L)				
Total:	26	5.69 (4.58, 7.07)	1.03 (0.61, 1.75)	0.18 (0.12, 0.27)
Weight: ≥15 to ≤25kg	7	4.92 (2.65, 9.16)	0.91 (0.27, 3.07)	
>25 to ≤35kg	8	6.65 (5.22, 8.47)	0.93 (0.38, 2.26)	
>35kg	11	5.57 (3.73, 8.32)	1.20 (0.42, 3.44)	
Clearance (L/(h*kg))[††]				
Total:	26	0.084 (0.074, 0.095)	0.115 (0.099, 0.134)	1.37 (1.19, 1.57)
Weight: ≥15 to ≤25kg	7	0.085 (0.062, 0.117)	0.112 (0.076, 0.165)	
>25 to ≤35kg	8	0.076 (0.062, 0.094)	0.120 (0.091, 0.158)	
>35kg	11	0.089 (0.071, 0.113)	0.114 (0.086, 0.150)	
T_{max} (h)[$]				
Total:	26	3.5 (0.0, 12.0)	4.0 (2.0, 8.0)	
Weight: ≥15 to ≤25kg	7	3.8 (0.0, 4.1)	4.0 (2.0, 8.0)	
>25 to ≤35kg	8	2.8 (1.7, 4.0)	4.0 (2.0, 6.0)	
>35kg	11	3.4 (1.7, 12.0)	4.0 (2.0, 8.0)	

[†] AUC_{0-24} for twice daily dosing = AUC_{0-12}*2

[††] Clearance calculated as Cl/F/kg = dose(mg)/[AUC_{0-24}(h*mg/L)*body weight (kg)]

$ For Tmax median values (minimum, maximum) are reported

Extracted from applicant's PENTA-18 pharmacokinetic report, Table 18.

2 Labeling Recommendations

Clinical Pharmacology reviewer note: the changes below reflect the content from the lopinavir/ritonavir prescribing information for tablets and oral solution.

Applicant revisions

Section 7

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Lopinavir or Concomitant Drug**	**Clinical Comments**
Non-nucleoside Reverse Transcriptase Inhibitor: etravirine	↓ etravirine	(b) (4)

Clinical Pharmacology reviewer revisions

Section 7

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Lopinavir or Concomitant Drug**	**Clinical Comments**
Non-nucleoside Reverse Transcriptase Inhibitor: etravirine	↓ etravirine	Because the reduction in the mean systemic exposures of etravirine in the presence of lopinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, no dose adjustment is required.

Applicant revisions

Section 7

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Lopinavir or Concomitant Drug**	**Clinical Comments**
Non-nucleoside Reverse Transcriptase Inhibitor: rilpivirine	↑ rilpivirine	(b) (4)

Clinical Pharmacology reviewer revisions

Section 7

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Lopinavir or Concomitant Drug**	**Clinical Comments**
Non-nucleoside Reverse Transcriptase Inhibitor: rilpivirine	↑ rilpivirine	No dose adjustment is required.

Applicant revisions

Section 7

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comments
HCV-Protease Inhibitor: simeprevir	↑simeprevir	(b) (4)

Clinical Pharmacology reviewer revisions

Section 7

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comments
HCV-Protease Inhibitor: simeprevir	↑simeprevir	It is not recommended to co-administer KALETRA and simeprevir.

Applicant revisions	Clinical Pharmacology reviewer revisions
Section 8 A prospective multicenter, randomized, open-label study evaluated the pharmacokinetic profile, efficacy, and safety of twice-daily versus once-daily dosing of KALETRA 100/25 mg tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included KALETRA, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, the efficacy (b) (4)	*Clinical Pharmacology reviewer note:* (b) (4) Section 8 A prospective multicenter, randomized, open-label study evaluated the efficacy, and safety of twice-daily versus once-daily dosing of KALETRA tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included KALETRA, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 24, the efficacy and safety with twice daily dosing (n=87) in the pediatric population given KALETRA 100/25 mg tablets was consistent with the efficacy and safety findings in previous adult and pediatric studies using KALETRA twice daily.

Applicant revisions	Clinical Pharmacology reviewer revisions
Section 12 None	Section 12

Table 14. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug for Recommended Alterations in Dose or Regimen

Co-Administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	N	Ratio (in combination with Co-administered drug/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Etravirine	NA	400/100 tablet twice daily (tablets)	16	0.89 (0.82-0.96)	0.87 (0.83-0.92)	0.80 (0.73-0.88)

N/A = Not available.

<table>
<tr><th>Applicant revisions</th><th>Clinical Pharmacology reviewer revisions</th></tr>
<tr><td>Section 12

None</td><td>Section 12

Clinical Pharmacology reviewer note: the applicant proposed (b) (4) . The proposal was accepted.
<table>
<tr><th colspan="6">Table 15. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA for Recommended Alterations in Dose or Regimen</th></tr>
<tr><th rowspan="2">Co-Administered Drug</th><th rowspan="2">Dose of Co-administered Drug (mg)</th><th rowspan="2">Dose of KALETRA (mg)</th><th rowspan="2">N</th><th colspan="3">Ratio (in combination with KALETRA/alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00</th></tr>
<tr><th>C_{max}</th><th>AUC</th><th>C_{min}</th></tr>
<tr><td>Etravirine</td><td>NA</td><td>400/100 tablet twice daily (tablets)</td><td>16[10]</td><td>0.70 (0.64-0.78)</td><td>0.65 (0.59-0.71)</td><td>0.55 (0.49-0.62)</td></tr>
</table>
N/A = Not available.
(b) (4)</td></tr>
</table>

Applicant revisions	Clinical Pharmacology reviewer revisions
Section 12 None	Section 12

Table 14. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug for Recommended Alterations in Dose or Regimen

Co-Administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	N	Ratio (in combination with Co-administered drug/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Rilpivirine	150 once daily[14]	400/100 tablet twice daily (capsules)	15	0.96 (0.88-1.05)	0.99 (0.89-1.10)	0.89 (0.73-1.08)

14 This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the co-administered drug.

Applicant revisions	Clinical Pharmacology reviewer revisions
Section 12 None	Section 12

Table 15. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA for Recommended Alterations in Dose or Regimen

Co-Administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	N	Ratio (in combination with KALETRA/alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Rilpivirine	150 once daily[11]	400/100 tablet twice daily (capsules)	15	1.29 (1.18-1.40)	1.52 (1.36-1.70)	1.74 (1.46-2.08)

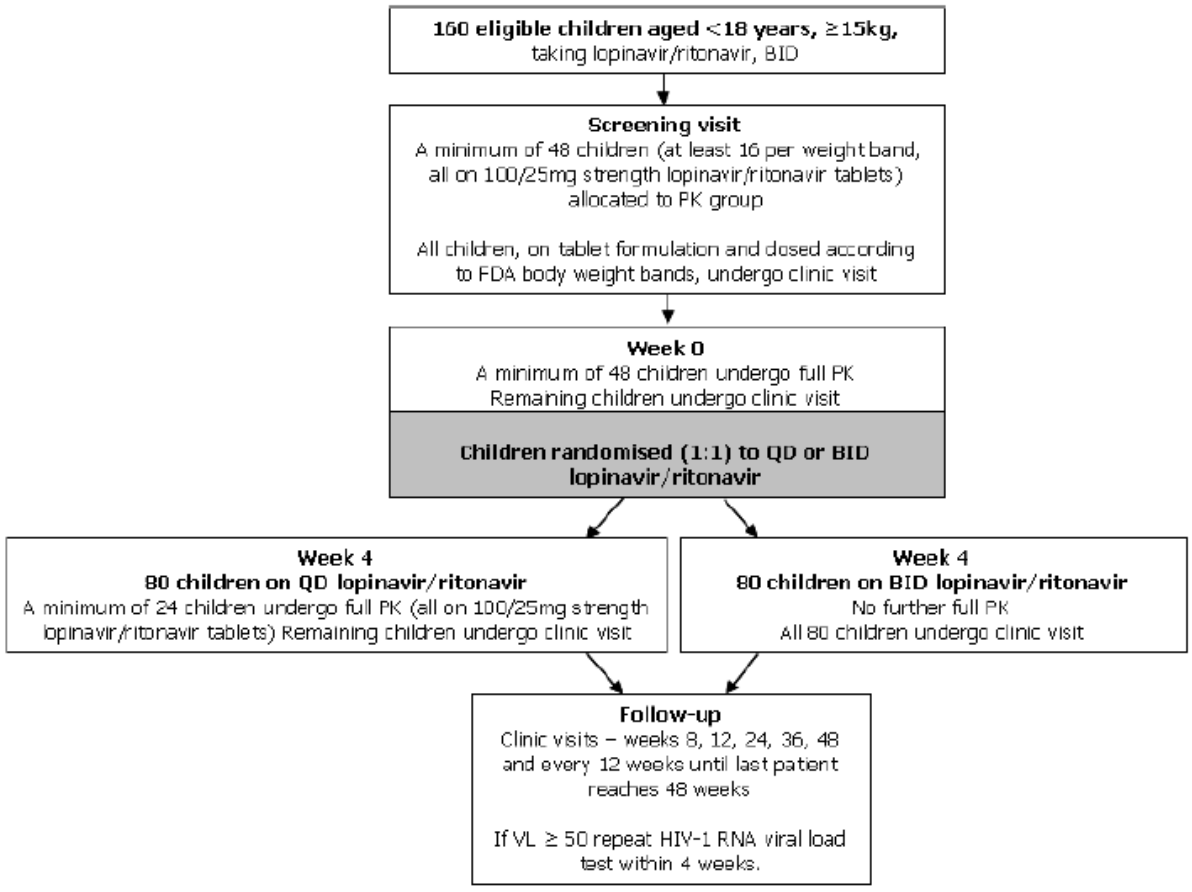
11 This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the co-administered drug.

3 Appendices: **Individual Trial Reviews**

PENTA-18 (KONCERT) was a prospective, open label, multicenter, phase II/III trial. Pediatric subjects were randomized (1:1) either to continue their current highly active antiretroviral therapy (HAART) regimen with lopinavir/ritonavir tablets taken twice-daily or to switch to lopinavir/ritonavir tablets dosed once-daily as shown in Figure 1. Randomization was stratified by body weight band (≥ 15 to ≤ 25kg, > 25 to ≤ 35kg, > 35kg). The pediatric subjects were to be followed for a minimum of 48 weeks.

The same total daily/lopinavr/rtiovavir dosage regimen was evaluated for both the twice daily and the once daily treatment arms.

Figure 1-PENTA-18 (KONCERT) trial design



Extracted from applicant's PENTA -18 trial report, Figure 1.

Table 1-LPV/RTV dosage regimens administered in the PENTA-18 trial

A) Twice daily dosage regimens

≥15 to ≤	
>25 to ≤	
>35	

B) Once daily dosage regimens

≥15 to ≤25	
>25 to ≤35	
>35	

3.1 Pharmacokinetic subtrial

As part of the PENTA-18 (KONCERT) trial, a pharmacokinetic subtrial was performed to compare the exposure of once daily versus twice daily dosing of lopinavir/ritonavir tablets in the same pediatric subjects in each of the specified body weight bands. The subtrial enrolled 53 HIV-1 infected subjects that were less than 18 years old weighing ≥ 15 kg, and were virologically suppressed (HIV-1 RNA <50 copies/mL) for at least the prior 24 weeks. Subjects also had to be able to swallow tablets. Of the 53 subjects, 27 subjects were randomized to the QD arm (Table 2) that received lopinavir/ritonavir BID up to week 0 and then switched to lopinavir/ritonavir QD dosing at week 0. Subjects were also converted to the LPV/RTV 100 mg/25 mg tablet dosage strength if necessary. The pharmacokinetics of lopinavir and ritonavir were determined with BID dosing at week 0 and QD dosing at week 4. PK samples were obtained at pre-dose and, 2h, 4h, 6h, 8h and 12h (BID dosing) or 24h (with QD dosing) after the observed intake.

Table 2-PENTA 18 subtrial subject demographics

	Weight band							
	≥15 - ≤25kg		>25 - ≤35kg		>35kg		Total	
Children randomised: n	8*		8		11		27*	
Sex: n (%)								
male:	4	(50)	5	(63)	3	(27)	12	(44)
female:	4*	(50)	3	(38)	8	(73)	15*	(56)
Age (years)								
mean (SD)	7.4	(1.6)	11.6	(3.4)	14.5	(1.2)	11.5	(3.6)
median (IQR)	7.1	(6.8, 8.8)	10.6	(9.5, 15.0)	14.3	(13.5, 15.4)	12.7	(8.7, 14.7)
[range]		[4.4, 9.6]		[6.3, 16.0]		[12.7, 16.8]		[4.4, 16.8]
Weight (kg)								
mean (SD)	20.9	(3.3)	30.7	(2.2)	46.1	(10.2)	34.0	(12.7)
median (IQR)	20.9	(19.1, 23.6)	30.7	(29.8, 32.1)	42.0	(38.5, 49.5)	31.7	(24.1, 41.0)
[range]		[15.0, 24.5]		[26.4, 33.8]		[36.0, 72.5]		[15.0, 72.5]
BMI (kg/m^2)								
mean (SD)	14.7	(1.4)	16.4	(2.0)	19.1	(3.2)	17.0	(3.1)
median (IQR)	15.1	(14.5, 15.5)	15.7	(14.8, 18.0)	17.7	(17.4, 20.6)	16.4	(15.1, 18.6)
[range]		[11.5, 15.8]		[14.5, 19.4]		[16.0, 27.6]		[11.5, 27.6]
Route of infection: n (%)								
vertical	8*	(100)	8	(100)	11	(100)	27*	(100)
Ethnic origin: n (%)								
white	1*	(13)	1	(13)	1	(9)	3*	(11)
black: African or other	2	(25)	3	(38)	2	(18)	7	(26)
mixed black/white	1	(13)	1	(13)	0	(0)	2	(7)
Asian	4	(50)	3	(38)	7	(64)	14	(52)
other	0	(0)	0	(0)	1	(9)	1	(4)

*One patient excluded from analysis as no week 4 PK data available

Extracted from applicant's PENTA-18 pharmacokinetic report, Table 11.

Of the 27 subjects randomized to the QD dosing arm, BID and QD LPV/RTV pharmacokinetic data was available for 26 subjects. The pharmacokinetic parameters from all the pediatric subjects with PK samples available (n=26), stratified by weight bands, from the pharmacokinetic subtrial are summarized below in Table 3 (lopinavir) and Table 4 (ritonavir). The bioanalytical information for the pharmacokinetic subtrial was not reviewed because the pediatric lopinavir exposure data from the subtrial will not be included in the lopinavir/ritonavir U.S. prescribing information.

Table 3-PK parameters of lopinavir after twice daily (week 0) and once daily (week 4) dosing

	n	BID geometric mean (95% CI)[$]	QD geometric mean (95% CI)[$]	(QD / BID) geometric mean ratio (90% CI)
AUC_{0-24} (h*mg/L)[†]				
Total:	26	223.9 (194.8, 257.4)	160.9 (138.4, 187.0)	0.72 (0.62, 0.83)
Weight: ≥15 to ≤25kg	7	232.1 (153.3, 351.4)	172.6 (121.3, 245.7)	
>25 to ≤35kg	8	256.8 (209.3, 315.2)	159.3 (120.6, 210.5)	
>35kg	11	198.1 (159.8, 245.5)	155.0 (116.8, 205.6)	
C_{max} (mg/L)				
Total:	26	12.5 (11.1, 14.0)	14.0 (12.7, 15.6)	1.13 (1.00, 1.26)
Weight: ≥15 to ≤25kg	7	13.5 (9.8, 18.7)	15.5 (12.4, 19.4)	
>25 to ≤35kg	8	14.1 (11.4, 17.3)	15.0 (12.2, 18.5)	
>35kg	11	10.9 (9.3, 12.6)	12.5 (10.7, 14.7)	
C_{last} (mg/L)				
Total:	26	5.69 (4.58, 7.07)	1.03 (0.61, 1.75)	0.18 (0.12, 0.27)
Weight: ≥15 to ≤25kg	7	4.92 (2.65, 9.16)	0.91 (0.27, 3.07)	
>25 to ≤35kg	8	6.65 (5.22, 8.47)	0.93 (0.38, 2.26)	
>35kg	11	5.57 (3.73, 8.32)	1.20 (0.42, 3.44)	
Clearance (L/(h*kg))[††]				
Total:	26	0.084 (0.074, 0.095)	0.115 (0.099, 0.134)	1.37 (1.19, 1.57)
Weight: ≥15 to ≤25kg	7	0.085 (0.062, 0.117)	0.112 (0.076, 0.165)	
>25 to ≤35kg	8	0.076 (0.062, 0.094)	0.120 (0.091, 0.158)	
>35kg	11	0.089 (0.071, 0.113)	0.114 (0.086, 0.150)	
T_{max} (h)[$]				
Total:	26	3.5 (0.0, 12.0)	4.0 (2.0, 8.0)	
Weight: ≥15 to ≤25kg	7	3.8 (0.0, 4.1)	4.0 (2.0, 8.0)	
>25 to ≤35kg	8	2.8 (1.7, 4.0)	4.0 (2.0, 6.0)	
>35kg	11	3.4 (1.7, 12.0)	4.0 (2.0, 8.0)	

[†] AUC_{0-24} for twice daily dosing = AUC_{0-12}*2

[††] Clearance calculated as CI/F/kg = dose(mg)/[AUC_{0-24}(h*mg/L)*body weight (kg)]

$ For Tmax median values (minimum, maximum) are reported

Extracted from applicant's PENTA-18 pharmacokinetic report, Table 18.

Table 4-PK parameters of ritonavir after twice daily (week 0) and once daily (week 4) dosing

	n	BID geometric mean (95% CI)[$]	QD geometric mean (95% CI)[$]	(QD / BID) geometric mean ratio (90% CI)
AUC_{0-24} (h*mg/L)[†]				
Total:	26	12.63 (10.77, 14.80)	11.34 (9.58, 13.42)	0.90 (0.79, 1.02)
Weight: ≥15 to ≤25kg	7	11.44 (8.21, 15.94)	11.55 (8.09, 16.47)	
>25 to ≤35kg	8	15.71 (12.02, 20.53)	12.26 (8.40, 17.90)	
>35kg	11	11.48 (8.61, 15.30)	10.60 (7.88, 14.24)	
C_{max} (mg/L)				
Total:	26	0.97 (0.82, 1.13)	1.35 (1.14, 1.59)	1.39 (1.20, 1.62)
Weight: ≥15 to ≤25kg	7	0.92 (0.68, 1.26)	1.38 (1.08, 1.77)	
>25 to ≤35kg	8	1.21 (0.84, 1.76)	1.58 (1.01, 2.48)	
>35kg	11	0.84 (0.67, 1.07)	1.18 (0.91, 1.51)	
C_{last} (mg/L)				
Total:	26	0.21 (0.16, 0.27)	0.055 (0.040, 0.076)	0.27 (0.21, 0.35)
Weight: ≥15 to ≤25kg	7	0.16 (0.11, 0.25)	0.050 (0.023, 0.109)	
>25 to ≤35kg	8	0.23 (0.17, 0.31)	0.051 (0.026, 0.102)	
>35kg	11	0.22 (0.12, 0.39)	0.062 (0.037, 0.105)	
Clearance (L/(h*kg))[††]				
Total:	26	0.37 (0.32, 0.44)	0.41 (0.34, 0.49)	1.09 (0.97, 1.24)
Weight: ≥15 to ≤25kg	7	0.43 (0.33, 0.57)	0.42 (0.29, 0.61)	
>25 to ≤35kg	8	0.31 (0.23, 0.42)	0.39 (0.26, 0.58)	
>35kg	11	0.39 (0.28, 0.52)	0.42 (0.31, 0.57)	
T_{max}[$]				
Total:	26	2.7 (0.0, 12.0)	4.0 (2.0, 8.0)	
Weight: ≥15 to ≤25kg	7	3.8 (0.0, 6.0)	4.3 (2.0, 8.0)	
>25 to ≤35kg	8	2.1 (1.7, 5.5)	4.0 (2.0, 5.8)	
>35kg	11	3.4 (0.0, 12.0)	4.0 (2.0, 8.0)	

[†] AUC_{0-24} for twice daily dosing = AUC_{0-12}*2
[††] Clearance calculated as CL/F/kg = dose(mg)/[AUC_{0-24}(h*mg/L)*body weight (kg)]
$ For Tmax median values (minimum, maximum) are reported

Extracted from applicant's PENTA-18 pharmacokinetic report, Table 19.

The PK subtrial showed that once daily dosing resulted in lower lopinavir AUC_{0-24h} compared to twice daily dosing despite administration of the same total daily dose with lower C_{last} and higher C_{max} values also observed.

The pharmacokinetics of once daily lopinavir/ritonavir has been evaluated in both treatment-naïve and experienced adults. For lopinavir, minimal differences were observed for the AUC_{0-24h} with higher C_{max} and lower C_{trough} values with the QD group compared to the BID group (Table 5).

Table 5 Median (Min-Max) lopinavir exposure in HIV infected adult treatment-experienced subjects and treatment-naïve subjects

Lopinavir PK Parameters[a] Median (Min – Max)	M06-802 Antiretroviral-Experienced Subjects		M05-730: Week 2 Antiretroviral-Naïve Subjects	
	QD (N = 252)	BID (N = 254)	QD (N = 16)	BID (N = 18)
AUC_{24} (µg•h/mL)	195.9 (121.4 – 486.8)	191.26 (91.48 – 506.18)	200.08 (99.5 – 483.7)	206.89 (87.6 – 621.2)
C_{max} (µg/mL)	12.49 (9.94 – 24.5)	9.67 (5.66 – 22.8)	15.12 (8.02 – 24.83)	10.99 (6.4 – 28.8)
C_{trough} (µg/mL)	3.79 (1.06 – 16.03)	6.33 (2.13 – 19.47)	4.18 (0.93 – 22.63)	7.09 (0.92 – 26.99)

PK = pharmacokinetic; Min = minimum; Max = maximum
* outliers as determined by Tukey's method were excluded from this table

Extracted from LPV/RTV clinical pharmacology review (Table 1), NDA21906, SDN 133.

Trials evaluating once versus twice daily dosing of LPV/RTV in pediatric subjects are also available from the literature. Chokephaibulkit et al compared the pharmacokinetics of lopinavir/ritonavir twice daily versus once daily in virologically suppressed, HIV infected children (ages 9-18 years). The subjects received LPV/RTV tablets with oral solution dosing: 230/57.5 mg/m^2 or 300/75 mg/m^2 with non-nucleoside reverse transcriptase inhibitors. The dosing was consistent with the recommendations in the LPV/RTV U.S. prescribing information. The trial demonstrated that similar to the results from HIV infected adults, when evaluating the data from all 12 subjects (including subjects receiving efavirenz), lopinavir/ritonavir tablets administered once daily resulted in comparable lopinavir exposure (AUC) to twice daily dosing, with higher observed C_{max} and lower C_{trough} values (Table 6)[1].

Table 6A-Lopinavir PK parameters following once daily and twice daily administration of lopinavir/ritonavir in pediatric subjects[1]

	LPV/r twice daily, median (range)			LPV/r once daily, median (range)		
PK parameter	all (*n*=12)	regimens without EFV (*n*=6)	regimens with EFV (*n*=6)	all (*n*=12)	regimens without EFV (*n*=6)	regimens with EFV (*n*=6)
LPV dose (mg/m^2/dose)	277 (255–338)	271 (255–283)	303 (273–338)	562 (514–645)	544 (514–570)	612 (538–645)
AUC_{0-24} (µg · h/mL)	170[a] (124–201)	172[a] (125–201)	168[a] (124–190)	167 (95.1–228)	200 (95–228)	154 (145–182)
C_{max} (µg/mL)	9.5 (7.4–12.9)	8.8 (7.4–9.8)	10.3 (9.5–12.9)	12.6[b] (8.5–15.6)	12.1[b] (8.5–15.0)	13.5[b] (11.4–15.6)
T_{max} (h)	3.0 (1.0–6.0)	3.0 (1.8–6.0)	3.0 (1.0–4.0)	6.0[b] (2.0–12.0)	7.0[b] (2.0–12.0)	4.0[b] (2.0–8.0)
C_{trough} (µg/mL)	3.1 (1.2–6.5)	4.2 (2.0–6.5)	3.1 (1.2–3.4)	0.38[b] (0.08–7.3)	3.9 (0.2–7.3)	0.17[b] (0.08–0.43)
C_{trough} >1.0 µg/mL	11/12	6/6	6/6	5/12	5/6	0/6
CL/F (L/h)	4.2 (3.2–6.4)	4.2 (3.2–6.4)	4.1 (3.2–6.4)	4.1 (3.3–6.3)	4.0 (3.3–6.3)	4.3 (4.0–5.1)

[a] Calculated as 2 × AUC_{0-12}

[b] p<0.05, comparison between twice- and once daily dosing for the specified regimen

Table 6B-Lopinavir statistical analysis following once daily and twice daily administration of lopinavir/ritonavir in pediatric subjects[1]

C_{trough} >1.0 μg/mL	—
CL/F (L/h)	1.00 (0.84–1.1

Another trial in pediatrics was conducted by van der Flier et al. The LPV/RTV dosing using body surface area were similar to the recommendations in the LPV/RTV U.S. prescribing information with the exception of pediatric subjects with body surface areas ranging from 1.33 to 1.5 m^2 that could receive either 600 mg/150 mg or 800 mg/200 mg once daily. In this trial, with once daily dosing, the observed AUC_{0-24} value was higher and comparable to the once daily and twice daily dosing AUC_{0-24h} values, respectively, from the PENTA-18 trial (Table 7).

Table 7-Lopinavir once daily pharmacokinetic parameters using the tablet formulation[2]

Characteristic	New tablet formulation (*n*=15)
Median age, years (range)	8.7 (4.4–15.0)
Median weight, kg (range)	33.8 (19.1–56.8)
Median BSA, m^2 (range)	1.12 (0.79–1.56)
Median dose, mg/m^2 (range)	498 (424–548)
Mean $AUC_{0-24\,h}$, mg/l•h (±SD)	217.9 (44.9)*
Mean C_{max}, mg/l (±SD)	14.8 (2.4)*
Median T_{max}, h (range)	5.8 (1.8–12.2)
Mean C_{trough}, mg/l (±SD)	3.1 (2.6)
Mean $T_{½}$, h (±SD)	5.8 (4.5)
Subtherapeutic C_{trough} (<1.0 mg/l), *n* (%)	3 (20)

Once-daily lopinavir/ritonavir target dose of 460/115 mg/m^2. *Statistically significant difference (P<0.05).

All these results demonstrated that the overall lopianvir exposure (AUC) in the once daily dosing group from the PENTA-18 trial are not consistent to those from historical results. The specific reasons for the discrepancies are unknown. The pharmacokinetic information for lopinavir provided by the applicant from the PENTA-18 trial does not support pediatric once daily dosing of lopinavir/ritonavir.

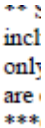
3.2 Safety observations from the PENTA-18 and pharmacokinetic subtrial

For the 26 pediatric subjects included in the pharmacokinetic subtrial, no deaths and one moderate adverse event (sore throat) and one severe adverse event (diarrhea) were reported.

For the main trial, no deaths were reported. Information regarding grade 3 or grade 4 adverse events or laboratory abnormalities from the PENTA-18 trial report is provided in Table 8.

Overall, no specific safety issues were identified based on the information from the PENTA-18 trial for either treatment arm.

Table 8-Grade 3 or grade 4 adverse events or laboratory abnormalities from the PENTA-18 trial



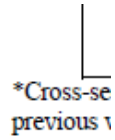
Extracted from applicant's PENTA-18 trial report, Table 60.

3.3 Antiviral activity information

For the main trial, information regarding pediatric subjects with HIV-1 RNA ≥50 copies/mL up to week 24 are provided in Table 9 and Table 10. Overall, there were more subjects with HIV-1 RNA ≥ 50 copies/mL in the QD dosing arm compared with the BID dosing arm.

Once daily lopinavir/ritonavir dosing has been approved in HIV infected adults, with less than three lopinavir resistance-associated substitutions. However, in the PENTA-18 trial, more pediatric subjects failed to achieve virological suppression (HIV-1 RNA < 50 copies/mL) through 24 weeks in the QD dosing group.

Table 9-Pediatric subjects with HIV-1 RNA≥50 copies/mL (QD vs BID dosing)-Intention to treat (ITT) population



Extracted from applicant's PENTA-18 trial report, Table 26.

Table 10-Comparison of reported causes for confirmed HIV-1 RNA ≥ 50 copies/mL-Intention to treat (ITT) population

	QD	BID
Number of patients with HIV-1 RNA ≥50 copies/ml at any of weeks 4, 8, 12, 24	10	3
Reason for HIV-1 RNA ≥50 copies/ml		
Adherence	9*	3
Resistance**	1	

*One patient had an adverse event which lead to their adherence becoming poor.
**Minor PI resistance detected in resistance FASTA file

Extracted from applicant's PENTA-18 trial report, Table 27.

4 References

1. Chokephaibulkit K, Nuntarukchaikul M, Phongsamart W, et al. Once- versus twice-daily lopinavir/ritonavir tablets in virologically suppressed, HIV-infected, treatment-experienced children: comparative pharmacokinetics and virological outcome after switching to once-daily lopinavir/ritonavir. *J Antimicrob Chemother* 2012; **67**: 2927-31.
2. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther* 2008; **13**: 1087-90.

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