Pharmacokinetics of 100/25 mg lopinavir/ritonavir tablets in children when dosed twice daily according to FDA weight bands

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1. INTRODUCTION

- Lopinavir/ritonavir (LPV/r) is recommended by European and US guidelines as part of cART for HIV-infected children.
- Half strength tablets (LPV/r 100/25 mg, Kaletra®/Aluvia®) are approved by the FDA and EMA. LPV/r dosing is based on body weight bands under FDA approval, and body surface area by the EMA. This can lead to differences in number of tablets recommended for some children, and is undesirable from a global access perspective (see Table 1).
- Also, FDA recommended weight band dosing has been derived from pharmacokinetic modeling but not formally studied in the target population.

Table 1: EMA and FDA approved doses for LPV/r (not given with NNRTI, fosamprenavir or nelfinavir)

EMA

Body Surface Area (m^2)	Approx equivalence weight (kg)	Number of tablets twice-daily	Exposure twice-daily (BSA) (mg/m^2)	Exposure twice-daily (weight) (mg/kg)
≥0.5 to <0.9	≥10 to <24	2	400 to 222	20 to 8
≥0.9 to <1.4	≥24 to <44	3	333 to 214	12.5 to 7
≥1.4	≥44	4	<286	<9

FDA

Weight (kg)	Approx equivalence BSA (m^2)	Number of tablets twice-daily	Exposure twice-daily (BSA) (mg/m^2)	Exposure twice-daily (weight) (mg/kg)
≥15 to ≤25	≥0.65 to ≤0.92	2	308 to 217	13 to 8
>25 to ≤35	>0.92 to ≤1.2	3	326 to 250	12 to 9
>35	>1.2	4	<333	<11

2. OBJECTIVES

- To investigate the pharmacokinetics of twice-daily LPV/r half strength formulation tablets dosed on weight band.
- To compare the pharmacokinetics with historical adult (1) and pediatric data (2).

3. METHODS

- This PK study is part of the ongoing PENTA18 trial (KONCERT, ISRCTN02452400), in which children, with fully suppressed HIV viral load (<50 copies/mL) for more than 6 months, are randomized to receive LPV/r twice or once daily, according to FDA weight bands.
- Full PK assessment of LPV/r was conducted before randomization while children were taking the half strength tablets twice daily. Samples were taken at t=0, 2, 4, 6, 8, 12 hours after observed intake, with or without food. It was planned that the first 16 children enrolled in each weight band would participate in the PK study: 15-25kg (lower, 2 tablets); ≥25-35kg (middle, 3 tablets); >35kg (highest weight band, 4 tablets).
- LPV and RTV concentrations were determined by UPLC. The lower limit of quantification for LPV was 0.107 mg/L and for RTV 0.044 mg/L.
- PK parameters were calculated by non-compartmental analysis using WinNonLin version 5.3.

4. RESULTS

- Fifty-one children were included into the PK study, of which 17, 16 and 18 children were enrolled in the 15-25kg, ≥25-35kg and >35kg weight bands, respectively. All children had evaluable PK.
- Twenty-two (43%) children were male and median age (interquartile range) was 10.8 (8.7-14.6) years. Twenty-eight children were from Asian origin, 14 black-African, 6 white, 2 mixed black/white and one had another ethnic origin.
- There were no significant differences in PK parameters between the weight bands (ANOVA, p>0.2).
- CL of LPV in the Asian children was significantly higher than in non-Asian children (independent samples t-test, p=0.01) (Figure 4a). Age was also significantly higher in Asian children (p=0.001) (Figure 3a). There were no significant differences in the other PK parameters between Asian and non-Asian children within each weight band (independent samples t-test, p>0.09) (Figure 3b and 4b).
- One child had a trough level below 1.0 mg/L (ie. 0.559 mg/L). The child was in the middle weight band and received a LPV dose of 11.5 mg/kg.

5. CONCLUSIONS

Lopinavir pharmacokinetic parameters were not significantly different between the FDA weight bands. Mean AUC and trough concentrations were higher than historical pediatric data of LPV/r solution and soft-gel capsules, and similar to adult data reported for tablets. Weight band based dosing recommendations provide adequate exposure when using the half strength tablets.

Table 2: PK parameters of lopinavir and ritonavir after twice-daily dosing

Geometric mean (95% CI)	n	lopinavir	ritonavir
$AUC_{0\text{-}12}$ (h*mg/L)	51	107.1 (97.7,117.5)	6.00 (5.35,6.74)
≥15 to ≤25kg	17	104.1 (84.9,127.5)	5.67 (4.71,6.84)
>25 to ≤35kg	16	116.9 (100.6,135.8)	6.75 (5.27,8.64)
>35kg	18	101.9 (87.8,118.3)	5.71 (4.66,7.00)
p-value		0.442	0.400
CL (L/(h*kg))	51	0.089 (0.080,0.099)	0.398 (0.346,0.457)
≥15 to ≤25kg	17	0.092 (0.078,0.109)	0.422 (0.358,0.497)
>25 to ≤35kg	16	0.085 (0.071,0.100)	0.366 (0.281,0.477)
>35kg	18	0.091 (0.077,0.107)	0.405 (0.325,0.506)
p-value		0.754	0.900
C_{last} (mg/L)	51	4.87 (3.97,5.97)	0.18 (0.15,0.22)
≥15 to ≤25kg	17	4.21 (3.07,5.78)	0.16 (0.12,0.20)
>25 to ≤35kg	16	5.10 (3.53,7.36)	0.18 (0.14,0.24)
>35kg	18	5.35 (4.03,7.11)	0.20 (0.13,0.30)
p-value		0.498	0.521
C_{max} (mg/L)	51	12.0 (11.0,13.2)	0.90 (0.78,1.03)
≥15 to ≤25kg	17	12.2 (10.4,14.5)	0.87 (0.71,1.06)
>25 to ≤35kg	16	13.0 (11.4,14.8)	1.02 (0.76,1.35)
>35kg	18	11.1 (9.9,12.4)	0.83 (0.70,0.98)
p-value		0.220	0.363

Clearance (Cl/F/kg) = dose(mg)/($AUC_{0\text{-}12}$(h*mg/L)*body weight (kg))

Table 3: Reference data lopinavir (Summary of product characteristics)[1]

Mean +/- SD	Adult (400/100mg BID)	Pediatrics (230/57.5 mg/m^2 BID) (oral solution)
$AUC_{0\text{-}12}$ (mg*h/L)	113.2 +/- 60.5	72.6 +/- 31.1
C_{max} (mg/L)	12.3 +/- 5.4	8.2 +/- 2.9
C_{trough} (mg/L)	8.1 +/- 5.7	3.4 +/- 2.1

[1] http://www.emea.europa.eu/ema/

Figure 1: Mean LPV concentrations by weight band

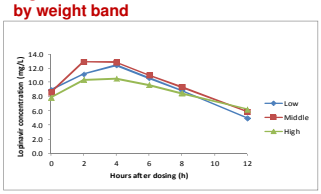


Figure 2: Mean RTV concentrations by weight band

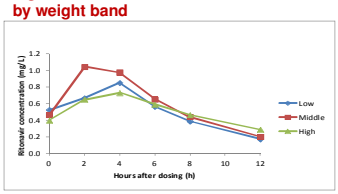


Figure 3a: mean LPV CL against age for total group, and grouped by ethnic origin

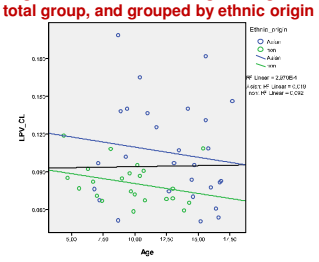


Figure 3b: mean LPV AUC against age for total group, and grouped by ethnic origin

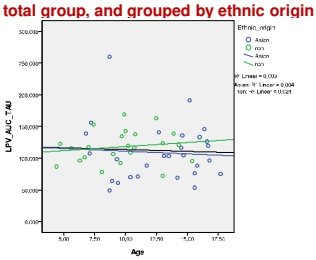


Figure 4a: mean LPV CL grouped by ethnic origin

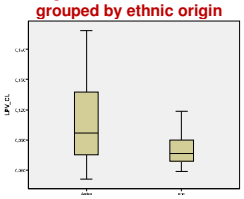
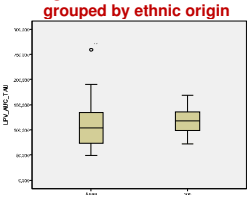


Figure 4b: mean LPV AUC grouped by ethnic origin



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