Poster #843

Second IAS Conference on HIV Pathogenesis and Treatment, Paris, France, 13-16 July 2003

# Steady-State Pharmacokinetics and Short-Term Virologic Response of Two Lopinavir/ritonavir (LPV/r) High-Dose Regimens in Multiple Antiretroviral-Experienced Subjects (Study 049)

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## ABSTRACT

**Purpose:** In patients failing multiple ARV regimens, high-level drug resistance is likely. Increased doses of LPV/r may be needed to achieve higher LPV concentrations and overcome LPV resistance. The purpose was to assess the PK of two high-dose LPV/r regimens.

**Methods:** Multiple PI and NNRTI-experienced HIV+ subjects were randomized to receive one of two twice daily (BID) high-dose LPV/r regimens with food; NRTIs (2-3) were selected by the care provider. PK samples were obtained from 33 subjects; 2 receiving a concurrent NNRTI were excluded from the analysis. LPV/r 667/167 mg was given as 5x133/33 mg LPV/r caps BID (N=18), and LPV/r 400/300 mg was given as 3x133/33 mg LPV/r caps + 2x100 mg ritonavir (RTV) caps BID (N=13). Plasma PK of LPV and RTV was measured over a 12-h dosing interval after 3 wks. PK parameters were log transformed and compared using ANCOVA.

**Results:** LPV/r 667/167 *vs.* 400/300 mg BID produced LPV mean ± SD $C_{max}$ of 16.2 ± 4.5 *vs*. 14.5 ± 5.5 µg/mL (p=0.25), $AUC_{12}$ of 165 ± 54 *vs*. 145 ± 59 µg•h/mL (p=0.3) and $C_{trough}$ of 12.0 ± 4.5 *vs*. 11.6 ± 5.2 µg/mL (p=0.5). RTV $C_{max}$ and AUC were higher (p<0.01) in the 400/300 *vs*. 667/167 mg regimen by 3- and 2.7-fold, respectively. Compared to historical data for LPV/r 400/100 mg BID + NRTIs in HIV+ subjects (N=19), LPV $C_{max}$, AUC and $C_{trough}$ from ANCOVA were 73, 88 and 73% higher for 667/167 mg, and 47, 59 and 56% higher for 400/300 mg, respectively (p<0.01 for all). RTV $C_{max}$ and AUC were 6-fold higher after 400/300 mg and 2-fold higher after 667/167 mg than with LPV/r 400/100 mg (p<0.01). Median viral load (VL) change from baseline to Wk 4 was -1.2 $\log_{10}$ c/mL.

**Conclusions:** Increasing the number of LPV/r caps or adding additional RTV results in relatively similar increases in LPV exposure. Adding RTV 200 mg increases RTV exposure by about 3-fold relative to increasing LPV/r by 267/67 mg. The two high-dose LPV/r regimens produced a short-term median decrease in VL of >1 $\log_{10}$ c/mL in these heavily ARV-experienced subjects.

## BACKGROUND

- Lopinavir (LPV) is an HIV protease inhibitor that is co-formulated with ritonavir (RTV), which functions as a pharmacokinetic enhancer, and is marketed as Kaletra® (LPV/r).
- The approved adult dose of LPV/r is 400/100 mg (3 caps) twice daily (BID) taken with food, and used in combination with other antiretrovirals (ARVs).
- At the BID clinical dose LPV mean pre-dose concentration ($C_{trough}$) exceeds protein binding-adjusted $IC_{50}$ for *wild-type (wt)* HIV by >75-fold.
  - Continued high response rate (70% with HIV RNA <50 copies/mL by intent-to-treat analysis) has been observed for >4 years during ongoing studies in ARV-naïve, HIV-infected subjects.[1]
  - Fewer long-term data are available in more experienced patients.
- High-level drug resistance is likely in patients failing multiple ARV regimens.
- Results from univariate logistic regression analysis identified the importance of LPV $C_{trough}/IC_{50}$ for HIV or inhibitory quotient (IQ) as a predictor of antiviral response through 24 weeks in extensively pretreated HIV-infected patients.[2]
- Increased doses of LPV/r may be needed to achieve higher LPV concentrations and thus IQ, to overcome decreased susceptibility to LPV.

## OBJECTIVE

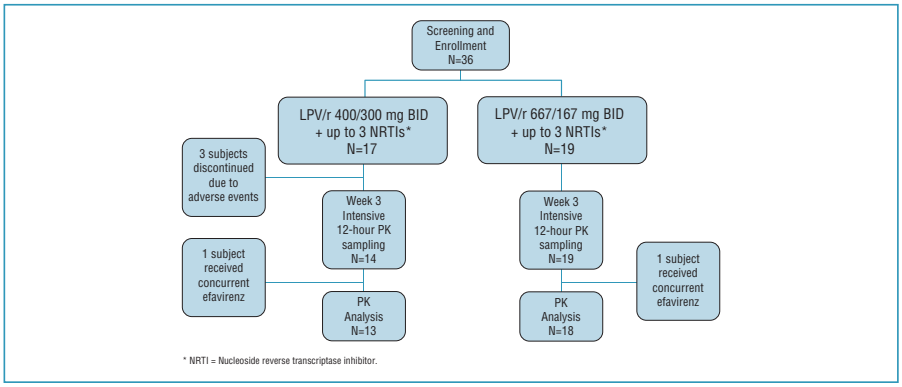
- To assess
  - Pharmacokinetics (PK) of two high-dose LPV/r regimens: 400/300 mg (3 LPV/r caps with 2 caps RTV) BID and 667/167 mg (5 LPV/r caps) BID.
  - Initial virologic response in a highly treatment-experienced population.

## METHODS

### Study Design

- This was a multiple-dose, open-label, multiple-center, non-fasting study in HIV-infected subjects (N=36) who met the following entrance criteria:
  - Multiple protease inhibitor-experienced
  - Non-nucleoside reverse transcriptase inhibitor-experienced
  - No evidence of acute illness
  - HIV RNA level >1000 copies/mL
  - CD4 cell <200 cells/mL
- 3 subjects discontinued from the study prior to Week 3 due to adverse events:
  - Fever
  - Nausea and vomiting
  - Asthenia, vomiting and dizziness
- 2 subjects were excluded from the Week 3 PK analysis for taking concurrent efavirenz.

### Figure 1. Study 049 Schematic



## METHODS *continued*

### Table 1. Study 049 Baseline Disease Characteristics

| | |
|---|---|
| HIV RNA ($log_{10}$ copies/mL) | |
| Mean/Median | 4.70/4.66 |
| 25%–75% IQR* | 4.27–5.40 |
| CD4 count (cells/mm$^3$) | |
| Mean/Median | 163/96 |
| 25%–75% IQR* | 32–205 |
| Min | 2 |
| LPV Phenotype (fold-change from *wt*-HIV) | |
| Mean/Median | 19.6/3.6 |
| 25%–75% IQR* | 0.8–17 |
| (Min–Max) | 0.5–273 |

* IQR = Interquartile range.

- Results from a previous Study 056 in which ARV-naïve, HIV-infected subjects (N=19) received LPV/r 400/100 mg BID with NRTIs, stavudine (d4T) and lamivudine (3TC) BID for 3 weeks served as historical comparison for PK.[3]

### Table 2. Subject Demographics

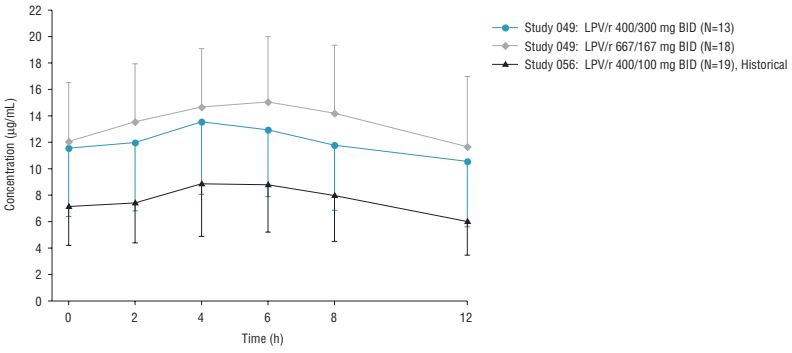
| | LPV/r 400/300 mg BID (N=13) | LPV/r 667/167 mg BID (N=18) | Historical 056 LPV/r 400/100 mg BID (N=19) |
|---|---|---|---|
| Gender | | | |
| Male | 10 | 15 | 13 |
| Female | 3 | 3 | 9 |
| Age (years) | 40.0 (28–51) | 42.7 (25–57) | 34.8 (22–54) |
| Weight (kg) | 74.1 (57.0–130.2) | 75.9 (55.8–171.1) | 75.2 (46.3–131.1) |
| Height (cm) | 172.8 (162.0–195.6) | 172.1 (150.0–188.0) | 171.5 (152.4–192.0) |
| Race | | | |
| Caucasian | 11 | 11 | 10 |
| Black | 0 | 7 | 9 |
| Hispanic | 2 | 0 | 0 |

### Analysis

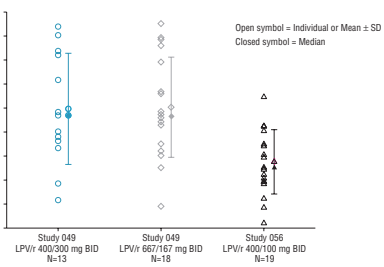
- Blood samples were collected for measurement of LPV and RTV concentrations pre-dose and at 2, 4, 6, 8 and 12 hours after dosing at Week 3.
- LPV and RTV concentrations were measured by LC/MS/MS.
  - LPV limit of quantitation (LOQ) = 5.0 ng/mL
  - RTV LOQ = 1.0 ng/mL
- Noncompartmental methods were used to calculate PK parameters.
- Samples were collected at Baseline and Week 4 for assessment of:
  - HIV RNA levels *via* the Roche Amplicor assay
  - CD4 cell counts *via* flow cytometry
- LPV IQ was calculated as $C_{trough}$/*wt* $IC_{50}$ based on protein binding-adjusted $IC_{50}$ of 0.07 µg/mL.[4]
- Actual IQ was calculated as $C_{trough}$/(phenotypic fold-change*0.07 µg/mL).[2]
- PK parameters from Study 056 served as a historical comparison.
- Log-transformed PK parameters were compared using ANCOVA with effects for regimen and weight; point estimates and 90% confidence intervals for ratio of central values were also determined for each comparison:
  - LPV/r 400/300 mg BID *vs.* 667/167 mg BID
  - LPV/r 400/300 mg BID *vs.* 400/100 mg BID (Historical)
  - LPV/r 667/167 mg BID *vs.* 400/100 mg BID (Historical)

## PHARMACOKINETIC RESULTS

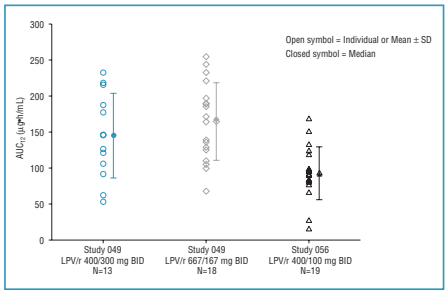
### Figure 2. Steady-State Lopinavir Mean (SD) Concentration-Time Profile




### Figure 3. Individual, Mean ± SD and Median Lopinavir $C_{min}$ Values




### Figure 4. Individual, Mean ± SD and Median Lopinavir AUC Values



## Table 3. Lopinavir Mean ± SD Pharmacokinetic Parameters

| | LPV/r 400/300 mg BID (N=13) | LPV/r 667/167 mg BID (N=18) | Historical LPV/r 400/100 mg BID (N=19) |
|---|---|---|---|
| $T_{max}$ (h) | 4.6 ± 3.2 | 5.0 ± 3.1 | 4.4 ± 2.4 |
| $C_{max}$ (µg/mL) | 14.5 ± 5.5* | 16.2 ± 4.5* | 9.8 ± 3.7 |
| $AUC_{12}$ (µg•h/mL) | 144.9 ± 58.8* | 164.5 ± 53.9* | 92.6 ± 36.7 |
| $C_{min}$ (µg/mL) | 9.9 ± 4.6* | 10.1 ± 4.2* | 5.5 ± 2.7 |
| $C_{trough}$ (µg/mL) | 11.6 ± 5.2* | 12.0 ± 4.5* | 7.1 ± 2.9 |
| IQ (*wt*-HIV $IC_{50}$)^$ | 173 (47.1–263)* | 164 (72–313)* | 98.1 (44.0–196) |
| Phenotype^**& | 3.9 (0.6–77.0) | 5.0 (0.6–273) | – |
| IQ (*actual*-HIV $IC_{50}$)^#& | 70.7 (2.8–438) | 27.0 (0.7–241) | – |
| CL/F (L/h)& | 3.4 ± 1.8 | 4.6 ± 1.8 | 6.0 ± 5.8 |
| $t_{1/2}$ (h)&% | 12.5 ± 8.3 | 11.1 ± 7.8 | 9.1 ± 3.7 |

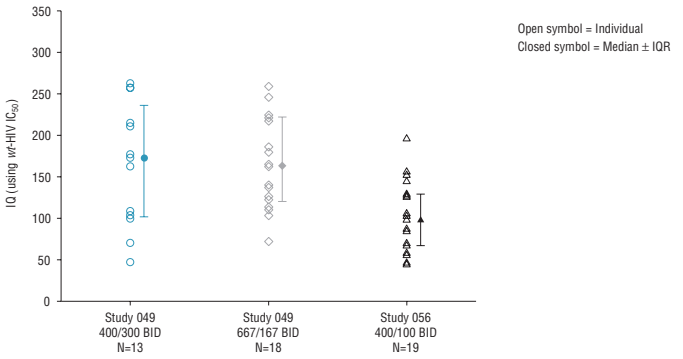
^ Presented as median (range).
# Based on patients' actual fold-change in LPV $IC_{50}$ with resistant virus; 400/300 BID (N=12) and 667/167 BID (N=16).
$ Based on protein binding-adjusted *wt*-HIV $IC_{50}$=0.07 µg/mL.
** Fold-change in LPV $IC_{50}$ with resistant virus; 400/300 BID (N=12) and 667/167 BID (N=16).
^ Statistically significantly different from LPV/r 667/167 mg BID (ANCOVA, p<0.05).
* Statistically significantly different from historical LPV/r 400/100 mg BID (ANCOVA, p<0.05).
& Parameter not tested statistically.
% Peak-to-trough half-life presented as harmonic mean ± pseudostandard deviation.

## Table 4. Lopinavir Point Estimates and 90% Confidence Intervals

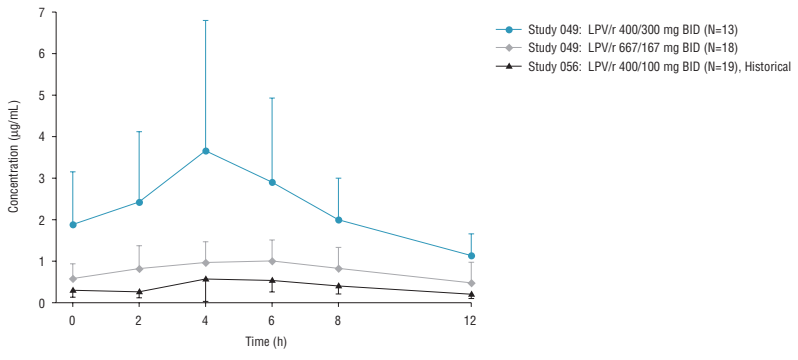
| Test *vs.* Reference | Parameter | Point Estimate# | 90% Confidence Interval |
|---|---|---|---|
| 400/300 BID *vs.* 667/167 BID | $C_{max}$ (µg/mL) | 0.848 | 0.670–1.073 |
| | $AUC_{12}$ (µg•h/mL) | 0.846 | 0.633–1.130 |
| | $C_{trough}$ (µg/mL) | 0.905 | 0.690–1.188 |
| 400/300 BID *vs.* 400/100 BID* | $C_{max}$ (µg/mL) | 1.467 | 1.162–1.850 |
| | $AUC_{12}$ (µg•h/mL) | 1.593 | 1.196–2.122 |
| | $C_{trough}$ (µg/mL) | 1.562 | 1.194–2.043 |
| 667/167 BID *vs.* 400/100 BID* | $C_{max}$ (µg/mL) | 1.729 | 1.398–2.138 |
| | $AUC_{12}$ (µg•h/mL) | 1.884 | 1.450–2.449 |
| | $C_{trough}$ (µg/mL) | 1.725 | 1.350–2.205 |

* Historical comparison.
# Antilogarithm of the least squares means for logarithms.

## Figure 5. Individual and Median (IQR) Lopinavir IQ Values Relative to *wt*-HIV $IC_{50}$

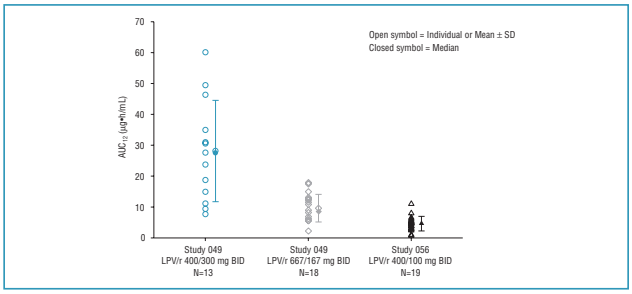



## Figure 6. Steady-State Ritonavir Mean (SD) Concentration-Time Profile

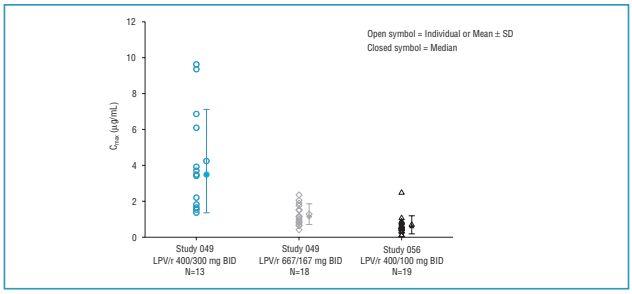


## PHARMACOKINETIC RESULTS *continued*

### Figure 7. Individual, Mean ± SD and Median Ritonavir AUC Values




### Figure 8. Individual, Mean ± SD and Median Ritonavir $C_{max}$ Values




### Table 5. Ritonavir Mean ± SD Pharmacokinetic Parameters

| | LPV/r 400/300 mg BID (N=13) | LPV/r 667/167 mg BID (N=18) | Historical LPV/r 400/100 mg BID (N=19) |
|---|---|---|---|
| $T_{max}$ (h) | 4.6 ± 3.0 | 5.3 ± 2.8 | 4.3 ± 2.2 |
| $C_{max}$ (µg/mL) | 4.23 ± 2.87*+ | 1.28 ± 0.58* | 0.68 ± 0.50 |
| $AUC_{12}$ (µg•h/mL) | 28.1 ± 16.4*+ | 9.6 ± 4.5* | 4.6 ± 2.4 |
| $C_{min}$ (µg/mL) | 0.97 ± 0.50*+ | 0.34 ± 0.17* | 0.17 ± 0.08 |
| $C_{trough}$ (µg/mL) | 1.88 ± 1.27*+ | 0.58 ± 0.36* | 0.30 ± 0.16 |
| CL/F (L/h)[&] | 15.6 ± 10.8 | 22.6 ± 14.8 | 33.3 ± 33.6 |
| $t_{1/2}$ (h)[&%] | 4.14 ± 15.1 | 3.66 ± 1.40 | 3.61 ± 1.15 |

+ Statistically significantly different from LPV/r 667/167 mg BID (ANCOVA, p<0.05).
* Statistically significantly different from historical LPV/r 400/100 mg BID (ANCOVA, p<0.05).
& Parameter not tested statistically.
% Peak-to-trough half-life presented as harmonic mean ± pseudostandard deviation.

### Table 6. Ritonavir Point Estimates and 90% Confidence Intervals

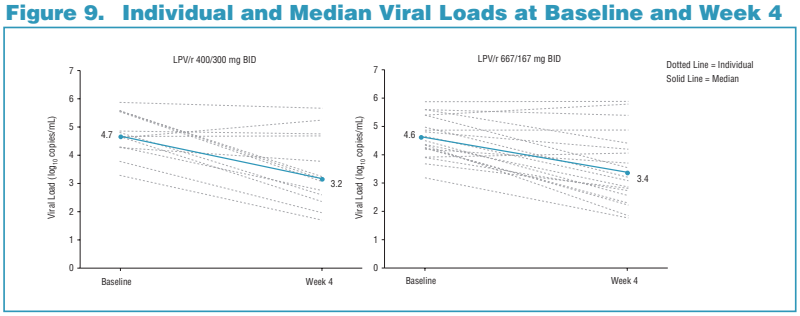
| Test *vs.* Reference | Parameter | Point Estimate# | 90% Confidence Interval |
|---|---|---|---|
| 400/300 BID *vs.* 667/167 BID | $C_{max}$ (µg/mL) | 2.954 | 2.002–4.359 |
| | $AUC_{12}$ (µg•h/mL) | 2.741 | 1.883–3.991 |
| 400/300 BID *vs.* 400/100 BID* | $C_{max}$ (µg/mL) | 6.229 | 4.239–9.152 |
| | $AUC_{12}$ (µg•h/mL) | 5.996 | 4.136–8.692 |
| 667/167 BID *vs.* 400/100 BID* | $C_{max}$ (µg/mL) | 2.109 | 1.484–2.997 |
| | $AUC_{12}$ (µg•h/mL) | 2.187 | 1.558–3.071 |

* Historical comparison.
# Antilogarithm of the least squares means for logarithms.

## FOUR-WEEK VIROLOGIC RESPONSE

- The overall mean and median (IQR) viral load change from baseline to Week 4 was -1.2 and -1.5 (-0.2, -2.0) $log_{10}$ copies/mL, respectively.
- Viral changes from baseline to Week 4 were similar between LPV/r dosing regimens.

### Figure 9. Individual and Median Viral Loads at Baseline and Week 4




## DISCUSSION AND CONCLUSIONS

- Increasing the number of LPV/r capsules to 5 or adding 2 additional RTV capsules to the standard dose of LPV/r given BID results in relatively similar LPV exposure.
- LPV/r 667/167 mg (5 caps) BID regimen results in a 73% increase in $C_{trough}$, 88% increase in AUC and 73% increase in $C_{max}$ relative to the approved dose of LPV/r 400/100 mg BID; LPV/r 400/300 mg BID results in increases in $C_{trough}$, AUC and $C_{max}$ by 56, 59 and 47%, respectively.
- Adding RTV 200 mg BID increases RTV exposure by about 3-fold relative to increasing LPV/r by 267/67 mg (2 caps) BID.
- The two LPV/r dosing strategies to increase LPV concentrations resulted in an initial median decrease in viral load of ≥1.2 $log_{10}$ copies/mL in these heavily ARV-experienced subjects.
- Pharmacokinetic/pharmacodynamic relationships and tolerability will be further explored after all Study 049 subjects reach 1 year of treatment.

## REFERENCES


1. Murphy R., *et al.*, Poster #H-165, 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, September 2002, San Diego, CA.
2. Hsu A., *et al.*, Antimicrobial Agents and Chemotherapy, Jan 2003, Vol. 47, No. 1, p 350-359.
3. Bertz R., *et al.*, Paper #126, 9th Conference on Retroviruses and Opportunistic Infections, February 2002, Seattle, WA.
4. Molla A., *et al.*, *Virology* 1998; 250:255-262.


## ACKNOWLEDGMENTS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