Predicted Lopinavir and Ritonavir Pharmacokinetics of High Dose Lopinavir/Ritonavir as the Tablet Formulation

Poster 87

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Background

Lopinavir/ritonavir (LPV/r) 400/100 mg twice daily (BID) is indicated for the treatment of HIV infection with other antiretroviral agents.

A new LPV/r 200/50 mg tablet was recently developed which reduces pill count and offers less restrictive storage requirements compared to the LPV/r 133.3/33.3 mg capsule (SGC); it may also be taken without regard to meals.[1]

The pharmacokinetics of high dose LPV/r following administration of the SGC formulation at 667/167 mg BID (5 LPV/r capsules) and 400/300 mg BID (3 LPV/r capsules + 2 ritonavir capsules) have been previously characterized, demonstrating antiviral activity in heavily protease inhibitor experienced HIV-infected subjects (Study 049).[2]

The pharmacokinetics of high doses of the LPV/r tablet have not yet been characterized.

Objective

The purpose of this analysis is to predict the pharmacokinetics of high doses of the tablet formulation of LPV/r.

Methods

Model Building

- A pharmacokinetic model was constructed using Trial Simulator™ (V.2.1.2 Pharsight Corporation, Mountain View, CA) to simulate LPV and ritonavir (RTV) concentrations following various regimens of the tablet or SGC formulations.
- The base model was constructed utilizing data from three Phase 1 studies in healthy volunteers receiving the SGC formulation.[3]
  - LPV and RTV were each described using a one-compartment model with zero-order absorption and dose-dependent bioavailability.
  - Ritonavir oral clearance was modeled as a product of baseline oral clearance ($CL0_{RTV}$) and enzyme induction. Induction, I(t) was calculated as

$$= -k_{el} \bullet I(t) + k_{el} \bullet (1 + A_{RTV} \bullet C_{RTV}(t) + A_{LPV} \bullet C_{LPV}(t))$$

    where k_{el}, A and C(t) represent the elimination rate constant of enzymes, linear coefficient relating drug exposure to extent of induction and drug concentrations in plasma at time t, respectively.
  - LPV oral clearance increased with enzyme induction, I(t) as listed above, and was decreased by the ritonavir concentration. LPV oral clearance was calculated as

$$CL_{LPV}(t) = CL0_{LPV} \bullet I(t)/(1 + C_{RTV}(t)/K_i)$$

- The model for high doses of LPV/r SGC was validated by comparing the predicted LPV pharmacokinetic parameters following SGC dosing of 667/167 mg BID and 400/100 mg BID to the observed data in HIV- infected subjects in Study 049 and historical 400/100 mg BID data.[4] Further validation was performed by visual inspection of the distribution of predicted pharmacokinetic parameters in 100 replicates.
- This model was then modified with the absorption characteristics of the tablet.
  - Tablets had shorter absorption lag time for RTV; the duration of input for the zero-order absorption of LPV and RTV was also decreased approximately 20% for the tablet compared to the SGC.
- 100 subjects were simulated for each dosing group including the tablet dosing regimens of 400/100 mg BID, 600/150 mg BID and 800/200 mg BID.
- The predicted pharmacokinetics from these regimens were compared to each other and to those previously reported for the SGC 667/167 mg BID regimen in HIV-infected subjects (Study 049).

Results

Model Validation—SGC

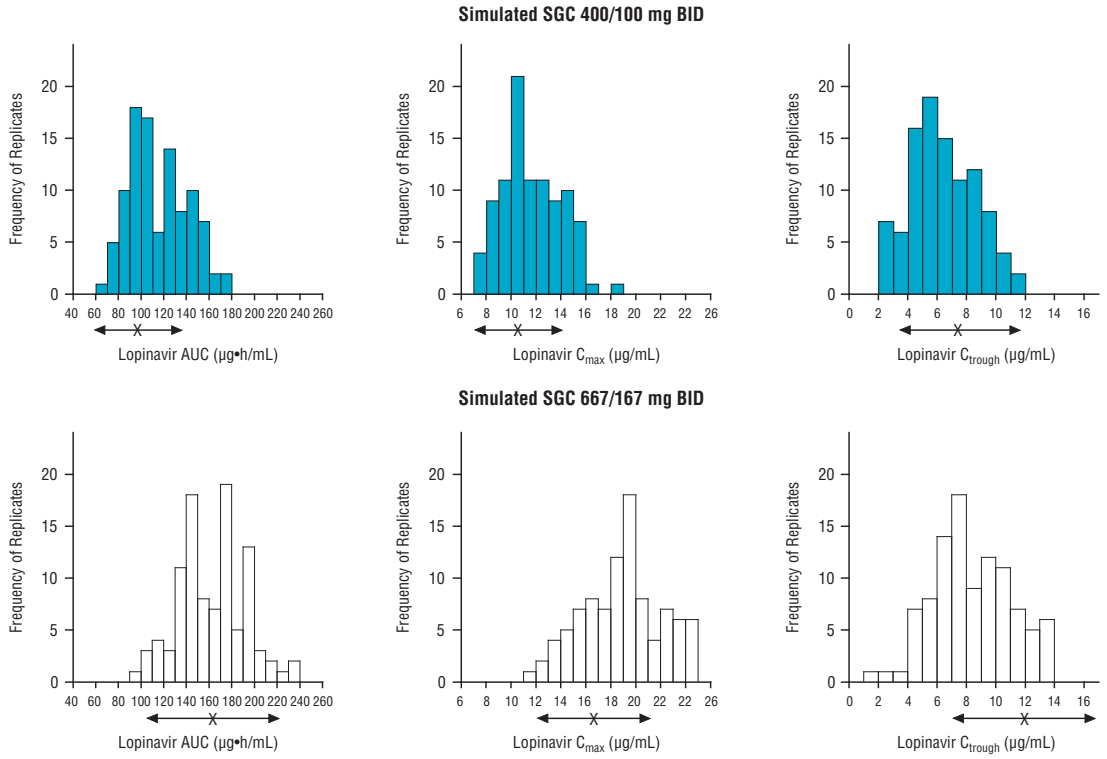
- The model predicts lopinavir AUCs within 1 and 4% of those observed for subjects receiving SGC LPV/r 667/167 mg and 400/100 mg, respectively. The model underpredicts C_{trough} by 18 and 25% and overpredicts C_{max} by 16 and 18%, respectively (Table 1).

Table 1. SGC Model Validation for Lopinavir

Pharmacokinetic Parameters (Units)	SGC 400/100 mg BID Observed (N=19)	SGC 400/100 mg BID Simulated	SGC 667/167 mg BID Observed (N=18)	SGC 667/167 mg BID Simulated
C_{max} (µg/mL)	9.8 ± 3.7	11.4 ± 2.5	16.2 ± 4.5	19.1 ± 3.2
AUC_{12} (µg•h/mL)	92.6 ± 36.7	96.5 ± 23.8	164.4 ± 53.8	162.5 ± 33.8
C_{trough} (µg/mL)	7.1 ± 2.9	5.8 ± 2.09	12.0 ± 4.5	8.9 ± 3.4

- Further validation of the SGC model for AUC and C_{max} is demonstrated through 100 replicates (Figure 1).

Figure 1. SGC Replicates by Dose



Frequency of replicates shown as boxes. Average observed parameter shown as X with +/- one SD as arrow.

Model Validation—Tablet

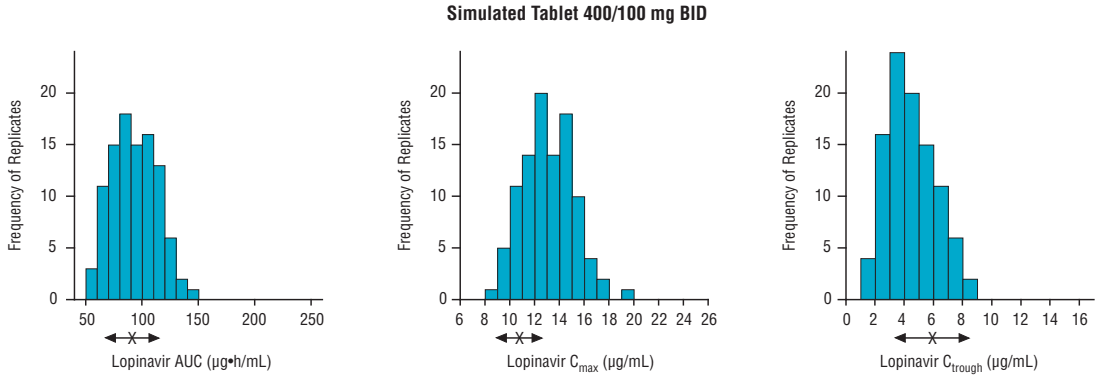
- The model predicts lopinavir AUC and C_{max} within 2 to 3% of those observed for subjects receiving tablet LPV/r 400/100 mg BID, respectively. The model underpredicts C_{trough} by approximately 20% (Table 2).

Table 2. Tablet Model Validation for Lopinavir

Pharmacokinetic Parameters (Units)	Tablet 400/100 mg BID Observed (N=23)	Tablet 400/100 mg BID Simulated
C_{max} (µg/mL)	10.6 ± 1.7	10.9 ± 2.06
AUC_{12} (µg•h/mL)	90.6 ± 18.7	92.4 ± 20.7
C_{trough} (µg/mL)	5.7 ± 1.8	4.5 ± 1.7

- Further validation of the Tablet model for AUC and C_{max} is demonstrated through 100 replicates (Figure 2).

Figure 2. Tablet Replicates



Frequency of replicates shown as boxes. Average observed parameter shown as X with +/- one SD as arrow.

Prediction of Tablet High Doses—Lopinavir

- LPV/r tablet regimens of 600/150 mg BID and 800/200 mg BID are predicted to produce lopinavir AUCs approximately 55% and 2-fold higher, respectively, than a modeled 400/100 mg BID regimen. Lopinavir C_{trough} is predicted to increase approximately 40 and 60%, respectively, for a tablet 600/150 mg BID and 800/200 mg BID regimen compared to a modeled 400/100 mg BID regimen (Table 3 and Figure 3).

Table 3. Predicted Lopinavir Pharmacokinetic Parameters: Tablet

Pharmacokinetic Parameters (Units)	Tablet 400/100 mg BID Simulated	Tablet 600/150 mg BID Simulated	Tablet 800/200 mg BID Simulated
C_{max} (µg/mL)	10.9 ± 2.1	17.7 ± 3.0	23.7 ± 4.2
AUC_{12} (µg•h/mL)	92.4 ± 20.7	145.3 ± 29.4	189.8 ± 36.6
C_{trough} (µg/mL)	4.5 ± 1.7	6.3 ± 2.6	7.2 ± 3.3

Prediction of Tablet High Doses—Ritonavir

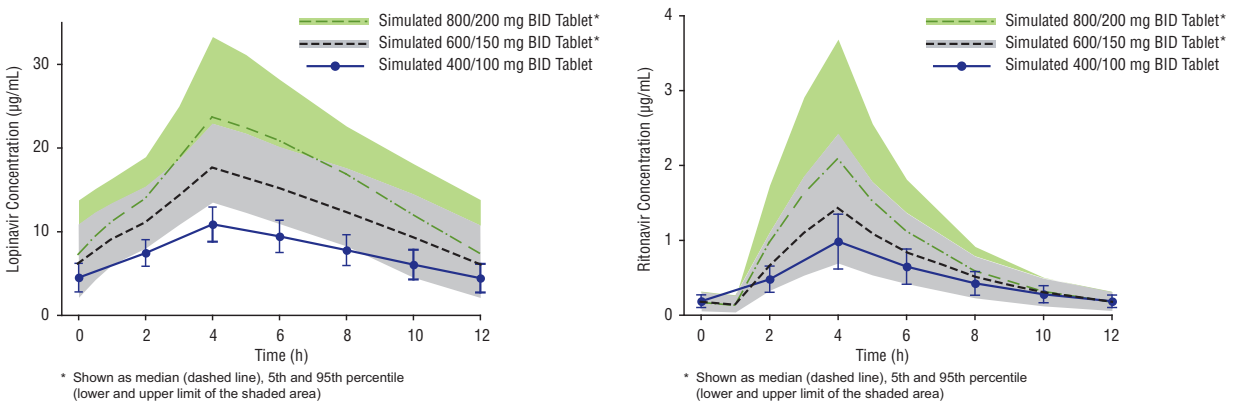
- LPV/r tablet regimens of 600/150 mg BID and 800/200 mg BID are predicted to produce ritonavir AUCs approximately 30% and 70% higher, respectively, than a modeled 400/100 mg BID tablet regimen. (Table 4, Figure 3).

Table 4. Predicted Ritonavir Pharmacokinetic Parameters: Tablet

Pharmacokinetic Parameters (Units)	Tablet 400/100 mg BID Simulated	Tablet 600/150 mg BID Simulated	Tablet 800/200 mg BID Simulated
C_{max} (µg/mL)	0.98 ± 0.37	1.44 ± 0.50	2.09 ± 0.72
AUC_{12} (µg•h/mL)	5.8 ± 2.1	7.6 ± 2.6	10.0 ± 3.2

- With the LPV/r tablet dosed as 600/150 mg BID and 800/200 mg BID, predicted RTV concentrations are approximately 6 to 8% of those achieved with the approved therapeutic dose of RTV (600 mg BID).

Figure 3. Predicted Lopinavir and Ritonavir Concentrations: Tablet



Comparison of High Dose Tablet and SGC

- The LPV/r 600/150 mg BID regimen is predicted to provide similar exposure to that observed with 667/167 mg BID as the SGC, Table 5.

Table 5. Comparison of SGC and Tablet High Dose Regimens

Pharmacokinetic Parameters (Units)	SGC 667/167 mg BID Observed (N=18)	Tablet 600/150 mg BID Simulated
	Lopinavir	
C_{max} (µg/mL)	16.2 ± 4.5	17.7 ± 3.0
AUC_{12} (µg•h/mL)	164.4 ± 53.8	145.3 ± 29.4
	Ritonavir	
C_{max} (µg/mL)	1.28 ± 0.58	1.44 ± 0.50
AUC_{12} (µg•h/mL)	9.6 ± 4.5	7.6 ± 2.6

Conclusions

Pharmacokinetic modeling suggests that increasing the LPV/r tablet dose may significantly increase exposure to lopinavir and ritonavir, improving the lopinavir inhibitory quotient (IQ, C_{trough}/IC_{50}).

- IQ has been shown to be correlated with antiviral activity in protease inhibitor experienced patients.

Increasing lopinavir IQ may be of particular importance in treatment of viral isolates with reduced susceptibility to lopinavir.

- Significant antiviral activity of LPV/r 667/167 mg BID dosed as the SGC in highly protease inhibitor experienced HIV-positive subjects was demonstrated in Study 049.[2]
- A LPV/r dose of 600/150 mg BID as the tablet is expected to produce overall similar concentrations to the 667/167 mg BID SGC dose.

Further studies are needed to assess the safety, tolerability and efficacy of high doses of LPV/r tablets in patients with HIV demonstrating reduced susceptibility to lopinavir.

References

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2. Podzamczer D. et al. *Higher Doses of Lopinavir/ritonavir (LPV/r) in Highly Treatment-Experienced, HIV-Infected Patients: 48-Week Safety/Efficacy Evaluation.* 15th IAC, Bangkok, Thailand, poster TuPeB4555, 2004.
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4. Flexner C. et al. *Steady-State Pharmacokinetic and Short-Term Virologic Response of Two Lopinavir/Ritonavir (LPV/r) High-Dose Regimens in Multiple Antiretroviral-Experienced Subjects (Study 049).* 2nd IAS, Paris, France, Poster 843, 2003.

Note: LPV/r tablet approval pending in EU.