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Treatment of HIV+ Subjects Co-infected with Hepatitis B or C: Week 60 Safety and Efficacy Comparison of LPV/r vs. Nelfinavir from a Phase III Blinded Randomized Clinical Trial

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BACKGROUND

Lopinavir (LPV) is a novel HIV protease inhibitor (PI) that has shown significant antiviral activity and tolerability in clinical trials to date. LPV is co-formulated with ritonavir, an inhibitor of cytochrome P450 3A. It is uniquely sensitive to pharmacokinetic enhancement by ritonavir, resulting in substantially increased LPV drug exposure, even at low ritonavir doses. The mean LPV C_{trough}/EC_{50} ratio (Inhibitory Quotient or IQ) for wild-type HIV is >75 when dosed at 400/100 mg BID, contributing to durability and potentially providing a pharmacologic barrier to the emergence of viral resistance.[1] The efficacy and safety of LPV/r are currently being studied in both antiretroviral-naïve and PI-experienced subjects. Study M98-863 examines the antiviral activity of LPV/r in a large, randomized, prospective study comparing the activity and safety to that of nelfinavir in antiretroviral-naïve subjects. All subjects remained blinded through Week 60. Results for all study subjects through Week 60 are shown in Table 1, Figure 1a and Figure 1b.[2]

Table 1. M98-863 Subject Disposition at Week 60 for All Subjects

	LPV/r	NFV
Subjects enrolled	326	327
Subjects discontinuing at or before Week 60	19%	24%
Death	2%	1%
Study Drug-Related Adverse Event	4%	4%
Other AE/HIV-Related Event	4%	2%
Virologic Failure*	1%	9%
Lost to Follow-Up	4%	5%
Noncompliance	3%	2%
Required Prohibited Medication	<1%	0%
Personal Reasons/Other	5%	3%

* Indicates significance at the 0.001 level using Fisher's Exact Test.

Figure 1a. M98-863 Proportion <400 Copies/mL (OT)

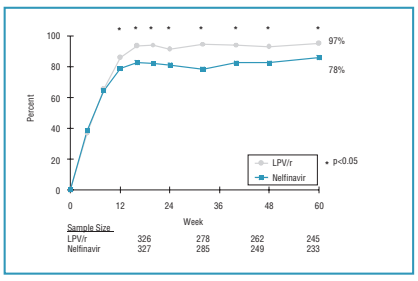
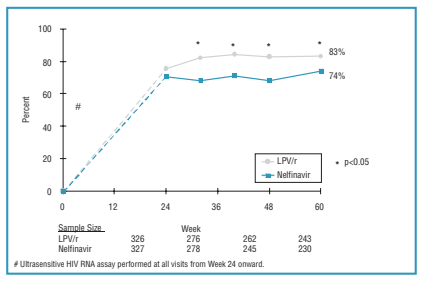


Figure 1b. M98-863 Proportion <50 Copies/mL (OT)



- At Week 60, 74% and 61% of subjects on LPV/r and nelfinavir, respectively, had HIV RNA levels <400 copies/mL using an ITT analysis (p<0.001). 63% and 52% of subjects on LPV/r and nelfinavir, respectively, had HIV RNA levels <50 copies/mL (p=0.002, ITT).

This study examines the safety, tolerability and antiviral activity of LPV/r and nelfinavir in the subset of M98-863 subjects who were hepatitis B/C+ at baseline.

METHODS

Subjects who were hepatitis B/C+ at baseline were allowed to enter the study. Subjects with AST/ALT levels >3 times the upper limit of normal (ULN) at screening were excluded regardless of hepatitis status. Of the 653 subjects enrolled in the study, 125 were hepatitis B surface antigen positive (hepatitis B+) and/or hepatitis C antibody positive (hepatitis C+). In these subjects, study drug was interrupted if the subject developed signs or symptoms of clinical hepatitis associated with LFT elevation >5 x ULN (Grade 3) or if the SGOT/AST or SGPT/ALT values elevated to >10 x ULN (Grade 4). The safety and efficacy of antiretroviral therapy in subjects who were hepatitis B/C+ at baseline was compared with that of subjects who were hepatitis B/C- at baseline.

RESULTS

Table 2. Demographic Characteristics by Baseline Hepatitis Status

	LPV/r Hepatitis B/C+ (N=57)	LPV/r Hepatitis B/C- (N=269)	NFV Hepatitis B/C+ (N=68)	NFV Hepatitis B/C- (N=259)
Gender				
Male	82%	79%	78%	81%
Female	18%	21%	22%	18%
Age (years)	41	38	37	37
Mean (range)	(23-84)	(19-70)	(22-68)	(20-60)
Race				
Caucasian	54%	57%	56%	59%
Black	30%	24%	28%	26%
Hispanic	11%	16%	12%	11%
Other	5%	3%	4%	4%
Hepatitis Status				
Hepatitis B+	35%	N/A	31%	N/A
Hepatitis C+	63%	N/A	69%	N/A
Hepatitis B+ and C+	2%	N/A	0%	N/A

Table 3. Baseline CD_4 Cell Count and Viral Load by Baseline Hepatitis Status

	LPV/r Hepatitis B/C+ (N=57)	LPV/r Hepatitis B/C- (N=269)	NFV Hepatitis B/C+ (N=68)	NFV Hepatitis B/C- (N=258)
Baseline HIV RNA (log_{10} copies/mL)				
Mean	4.8	4.9	5.0	4.9
Range	3.0 - 6.3	2.6 - 6.8	3.0 - 6.8	2.8 - 6.8
CD_4 Count (cells/μL)				
Mean	283	255	244	261
Range	3 - 868	2 - 944	13 - 818	3 - 949

One NFV subject who was Hepatitis B/C- at baseline did not have a baseline CD_4 cell count measurement.

Table 4. M98-863 Subject Disposition for Hepatitis B/C+ Subjects at Week 60

	LPV/r	NFV
Subjects enrolled	57	68
Subjects discontinuing at or before Week 60	20 (35%)	14 (21%)
Death	1 (2%)	2 (3%)
Study Drug-Related Adverse Event	2 (4%)	2 (3%)
Other AE/HIV-Related Event	2 (4%)	3 (4%)
Virologic Failure	1 (2%)	1 (1%)
Lost to Follow-Up	6 (11%)	6 (9%)
Noncompliance	2 (4%)	1 (1%)
Required Prohibited Medication	1 (2%)	0 (0%)
Personal Reasons/Other*	7 (12%)	1 (1%)

* Indicates significance at the 0.05 level using Fisher's Exact Test.

- No hepatitis B/C+ subjects discontinued due to elevated liver enzymes or clinical hepatitis.

Figure 2a. M98-863 Proportion of LPV/r Subjects <400 Copies/mL by Baseline Hepatitis Status (OT)

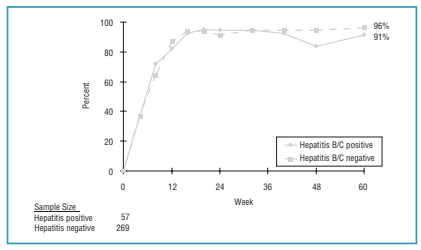


Figure 2b. M98-863 Proportion of Nelfinavir Subjects with VL <400 Copies/mL by Baseline Hepatitis Status (OT)

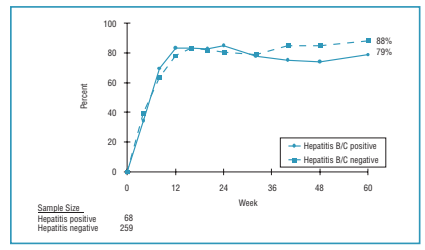


Figure 3a. M98-863 Proportion of LPV/r Subjects <50 Copies/mL by Baseline Hepatitis Status (OT)

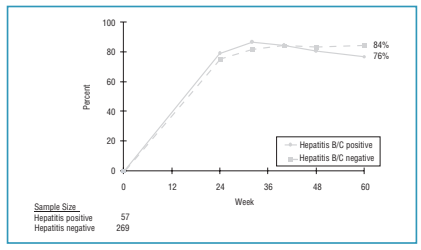


Figure 3b. M98-863 Proportion of Nelfinavir Subjects with VL <50 Copies/mL by Baseline Hepatitis Status (OT)

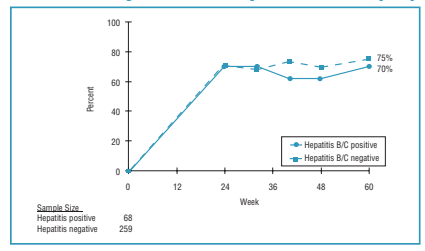


Figure 4a. M98-863 LPV/r Mean CD_4 Cell Count Change from Baseline by Baseline Hepatitis Status

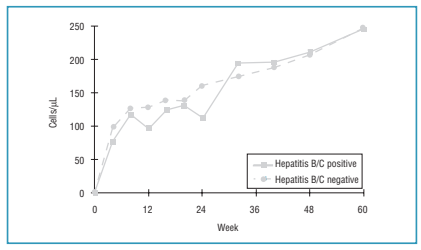
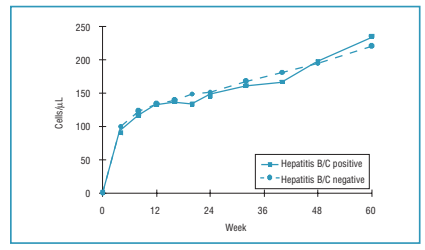


Figure 4b. M98-863 Nelfinavir Mean CD_4 Cell Count Change from Baseline by Baseline Hepatitis Status



- Within each treatment group, response for subjects who were hepatitis B/C+ at baseline were similar to those subjects who were hepatitis B/C- at baseline.
- Within each treatment group, the mean change in CD_4 cell counts for subjects who were hepatitis B/C+ at baseline were similar to those subjects hepatitis B/C- at baseline.

SAFETY/TOLERABILITY

Table 5. Most Common Adverse Events Within Treatment Groups by Baseline Hepatitis Status

	LPV/r Hepatitis B/C+ (N=57)	LPV/r Hepatitis B/C- (N=269)	NFV Hepatitis B/C+ (N=68)	NFV Hepatitis B/C- (N=259)
Diarrhea	18%	16%	12%	20%
Nausea	7%	7%	4%	5%
Asthenia	4%	4%	4%	4%
Abdominal Pain	5%	4%	4%	3%
Vomiting	4%	3%	6%	2%
Headache	2%	3%	1%	2%

Moderate/Severe events of probable, possible, or unknown relationship to protease inhibitor are included.

- The presence of baseline positive hepatitis serologies did not significantly affect the incidence of adverse events within treatment groups.

Table 6. Incidence of Grade 3/4 Lab Abnormalities Through Week 60 by Treatment Group and Baseline Hepatitis B/C Status

	LPV/r Hepatitis B/C+	LPV/r Hepatitis B/C-	NFV Hepatitis B/C+	NFV Hepatitis B/C-
Glucose (>250 mg/dL)	2%	2%	3%	1%
SGOT/AST (>5 x ULN)	4%	3%	13%	2%***
SGPT/ALT (>5 x ULN)	12%	3%*	17%	<1%***
Total Cholesterol (>300 mg/dL)	10%	11%	8%	6%
Triglycerides (>750 mg/dL)	10%	11%	0%	3%
Amylase (>2 x ULN)	4%	3%	3%	2%

*, *** Indicate significance at the 0.05 and 0.001 statistical levels when comparing hepatitis status within treatment groups using Fisher's exact test. Among all subjects, the only significant differences between treatment groups are for Cholesterol and Triglycerides.

50 LPV/r and 64 nelfinavir hepatitis B/C+ subjects had post baseline laboratory determinations.

- No subjects who were hepatitis B/C+ at baseline discontinued study drug due to adverse events of abnormal liver function tests.
- Among subjects who were hepatitis B/C+ at baseline:
  - Interruptions due to elevations of liver function tests occurred in 4 nelfinavir and 2 LPV/r subjects who were hepatitis B/C+ at baseline.
  - Grade 4 SGOT/SGPT elevations were observed in 3 of the 64 nelfinavir subjects and 1 of the 50 LPV/r subjects who had both baseline and post baseline values.

Table 7. Relative Risk (RR) of Grade 3/4 LFT Elevation Through Week 60

Treatment Group	Hepatitis Status			RR (95% CI)
LPV/r	Hepatitis B+	vs.	Hepatitis B/C-	4.7 (1.7, 12.7)
	Hepatitis C+	vs.	Hepatitis B/C-	1.8 (0.5, 5.7)
	Hepatitis B/C+	vs.	Hepatitis B/C-	3.3 (1.4, 8.2)
Nelfinavir	Hepatitis B+	vs.	Hepatitis B/C-	2.8 (0.9, 9.0)
	Hepatitis C+	vs.	Hepatitis B/C-	7.8 (3.3, 18.7)
	Hepatitis B/C+	vs.	Hepatitis B/C-	10.2 (3.8, 27.5)

- Hepatitis B/C+ subjects had a significantly greater risk of Grade 3/4 SGOT/SGPT elevation when compared to hepatitis B/C- subjects in each treatment group.

CONCLUSIONS

- Within each treatment group antiviral activity and immunologic response rate were similar in hepatitis B/C+ subjects compared to hepatitis B/C- subjects.
- Presence of HBsAg or HCV antibody at baseline significantly increased risk of Grade 3/4 SGOT/SGPT elevations.
- Grade 4 SGOT/SGPT elevations were uncommon occurrences in hepatitis B/C+ subjects. One of the LPV/r and 3 of the nelfinavir subjects were noted to have Grade 4 elevations.

REFERENCES

1. Bertz R, Lam W, Brun S, et al. Multiple-dose pharmacokinetics (PK) of ABT-378/ritonavir (LPV/r) in HIV+ subjects. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, USA, 1999 (abstract 0327).

2. P. Ruane, J. Mendoca, A. Timerman, P. Cernohous, E. Bauer, B. Bernstein and E. Sun, Kaletra™ vs. Nelfinavir in Antiretroviral-Naïve Subjects: Week 60 Comparison in a Phase III, Blinded, Randomized Clinical Trial. 1st IAS Conference on HIV Pathogenesis and Treatment, Buenos Aires, July 2001.