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Efficacy and Safety of Fosamprenavir/ritonavir (FPV/r) BID or Lopinavir/ritonavir (LPV/r) BID in Antiretroviral Treatment-Naïve Subjects Co-Infected with Hepatitis B (HBV) or C (HCV) and HIV (the KLEAN Study)

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Abstract

Objectives: KLEAN, an, open-label, randomized trial demonstrated the non-inferiority of FPV/r to LPV/r, each in combination with abacavir/lamivudine. We evaluated anti-HIV efficacy and safety in subjects co-infected with hepatitis and HIV from KLEAN.

Methods: Subjects with clinically relevant hepatitis or Grade 4 lab abnormalities at screening were excluded. The primary endpoint was the Week 48 response rate (% with HIV-1 RNA <400 c/mL by TLOVR).

Results: The ITT(E) population included 878 subjects from the US, Europe and Canada: 26 were co-infected with HBV only (FPV/r: 14; LPV/r: 12), 85 with HCV only (47 and 38, respectively), and 5 with both HBV & HCV (3 and 2, respectively). Response rates for the primary endpoint were: FPV/r: 73%; LPV/r: 71%, overall population; 77% (277/358) and 73% (282/386), respectively, HBV/HCV (-) subjects; 79% (11/14) and 58% (7/12), respectively, HBV (+) subjects; 43% (20/47) and 61% (23/38), respectively, HCV (+) subjects; and (0/3) and 50% (1/2), respectively, HBV/HCV (+) subjects.

Grade 2-4 Drug-Related Adverse Events (AEs) and Treatment-Emergent
Grade 3-4 Lab Abnormalities

	HBV & HCV Negative		HBV Positive Only		HCV Positive Only		HBV & HCV Positive	
	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r
	n=359	n=385	n=14	n=12	n=48	n=38	n=3	n=2
Diarrhea	47 (13%)	45 (12%)	3 (21%)	1 (8%)	3 (6%)	2 (5%)	1 (33%)	0
Nausea	23 (6%)	21 (5%)	0	2 (17%)	5 (10%)	0	0	0
Drug Hypersensitivity	21 (6%)	11 (3%)	2 (14%)	1 (8%)	3 (6%)	5 (13%)	0	0
ALT Elevations	4 (1%)	2 (<1%)	3 (21%)	2 (18%)	4 (8%)	5 (14%)	0	0
AST Elevations	5 (1%)	3 (<1%)	3 (21%)	3 (27%)	5 (10%)	5 (14%)	0	0

Conclusions: Variable responses were observed in the few subjects co-infected with HBV or HCV in both treatment groups. Transaminase elevations were more common in co-infected subjects compared to subjects without co-infection. Comparison of AEs is difficult due to the limited number of co-infected subjects; however, no apparent differences in tolerability were noted between HBV/HCV negative and co-infected subjects.

Introduction

- Co-infection with hepatitis viruses and HIV is common due to shared routes of transmission.¹ Studies have demonstrated an increased incidence of hepatotoxic effects associated with antiretroviral drugs in HIV patients co-infected with either hepatitis B virus (HBV) or hepatitis C virus (HCV).²
- Fosamprenavir is a protease inhibitor that has demonstrated safety and efficacy in HIV infected patients. KLEAN, an open-label, randomized trial demonstrated the non-inferiority of fosamprenavir/ritonavir (FPV/r) to lopinavir/ritonavir (LPV/r), each in combination with the abacavir/lamivudine (ABC/3TC) fixed dose combination (FDC).³
- Our objective for this analysis was to explore the anti-HIV efficacy and safety of FPV/r and LPV/r in subjects co-infected with hepatitis and HIV from KLEAN.

Methods

- A total of 878 antiretroviral (ART)-naïve subjects were enrolled from the US, Europe, and Canada.
- Hepatitis status was determined by Hepatitis B Surface Antigen or Hepatitis C Antibody testing. Subjects with clinically relevant hepatitis or Grade 4 lab abnormalities at screening were excluded from study participation.
- The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA <400 copies/mL (c/mL) at Week 48 based on the FDA-defined Time to Loss of Virologic Response (TLOVR) algorithm.
- The TLOVR response rates at Week 48 (<400 c/mL) were summarized by baseline hepatitis status (HBV & HCV negative, HBV positive only, HCV positive only, or HBV & HCV positive).
- Treatment-related grade 2 to 4 clinical adverse events and serious adverse events were presented by baseline hepatitis status.
- Treatment-emergent grade 3 to 4 laboratory abnormalities (defined as laboratory abnormalities that developed or increased in intensity post-baseline) and Week 48 changes in ALT and AST were also summarized by baseline hepatitis status.
- No formal statistical comparisons were performed in this sub-group analysis.

Results

Table 1. Baseline (BL) Hepatitis Status; Intent-to-Treat Exposed [ITT(E)] Population

	FPV/r BID N=434 n (%)	LPV/r BID N=444 n (%)	Total N=878 n (%)
HBV & HCV Negative	358 (82%)	386 (87%)	744 (85%)
HBV Positive Only	14 (3%)	12 (3%)	26 (4%)
HCV Positive Only	47 (11%)	38 (9%)	85 (10%)
HBV & HCV Positive	3 (<1%)	2 (<1%)	5 (<1%)

Hepatitis status was missing for 18 subjects. Results for these subjects are not presented.

Table 2. Study Outcomes at Week 48 Based on TLOVR Analysis (HIV-1 RNA <400 c/mL); ITT(E) Population

	HBV & HCV Negative		HBV Positive only		HCV Positive only		HBV & HCV Positive	
	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r
	n=358	n=386	n=14	n=12	n=47	n=38	n=3	n=2
Responder n, (% Subjects)	277 (77%)	282 (73%)	11 (79%)	7 (58%)	20 (43%)	23 (61%)	0	1 (50%)
Virologic Failure	19 (5%)	27 (7%)	1 (7%)	0	4 (9%)	3 (8%)	1 (33%)	0
Study Discontinuations	62 (17%)	77 (20%)	2 (14%)	5 (42%)	23 (49%)	12 (32%)	2 (67%)	1 (50%)
Adverse event	17 (5%)	17 (4%)	0	2 (17%)	5 (11%)	5 (13%)	0	0
Lost to follow-up	13 (4%)	28 (7%)	0	0	6 (13%)	1 (3%)	0	1 (50%)
Subject decision	11 (3%)	5 (1%)	1 (7%)	1 (8%)	4 (9%)	2 (5%)	0	0
Non-compliance	9 (3%)	8 (2%)	0	0	2 (4%)	0	1 (33%)	0
Other	12 (3%)	19 (5%)	1 (7%)	2 (17%)	6 (13%)	4 (11%)	1 (33%)	0

- In general, hepatitis co-infected subjects appeared to have lower response rates (HIV-1 RNA <400 c/mL at Week 48, primary endpoint) compared to those subjects without co-infection, with variability noted between treatment groups (*Table 1*). However, these results should be interpreted with caution as the sample sizes in the hepatitis co-infected sub-groups were small. There were a greater proportion of TLOVR non-responders due to study discontinuations in the hepatitis co-infected population compared to the non co-infected population. The proportion of non-responders due to virologic failure were generally similar across the sub-groups.

Table 3. Selected Adverse Events (AEs); Safety Population

	HBV & HCV Negative		HBV Positive Only		HCV Positive Only		HBV & HCV Positive	
	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r
	n=359	n=385	n=14	n=12	n=48	n=38	n=3	n=2
Any Treatment-Related Grade 2-4 AE	131 (36%)	131 (34%)	8 (57%)	5 (42%)	20 (42%)	11 (29%)	1 (33%)	0
Diarrhea	47 (13%)	45 (12%)	3 (21%)	1 (8%)	3 (6%)	2 (5%)	1 (33%)	0
Nausea	23 (6%)	21 (5%)	0	2 (17%)	5 (10%)	0	0	0
Drug Hypersensitivity	21 (6%)	11 (3%)	2 (14%)	1 (8%)	3 (6%)	5 (13%)	0	0
Any Treatment-Related Serious AE	28 (8%)	19 (5%)	2 (14%)	1 (8%)	5 (10%)	6 (16%)	0	0

- Hepatitis co-infected subjects appeared to report more treatment-related Grade 2-4 AEs (occurring at a incidence of ≥5% in either treatment arm) compared to hepatitis negative subjects in both treatment groups.

Table 4. Lab Abnormalities at Week 48; Safety Population

	HBV & HCV Negative		HBV Positive Only		HCV Positive Only		HBV & HCV Positive	
	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r	FPV/r	LPV/r
	n=359	n=385	n=14	n=12	n=48	n=38	n=3	n=2
BL ALT (U/L), median (IQR)	22 (15, 33)	22 (16, 33)	53 (22, 116)	27 (15, 43)	40 (24, 49)	37 (23, 64)	33 (17, 214)	48 (16, 79)
Median Δ from BL (IQR) in ALT	-8 (-17, -2)	-8 (-19, -1)	-9.5 (-64, 2.5)	-1 (-4, 5)	-0.5 (-14, 6)	-7 (-25, 5)	-6 (-6, -6)	4 (4, 4)
BL AST (U/L), median (IQR)	25 (20, 31)	25 (21, 33)	52 (28, 83)	33 (26, 40)	35 (29, 55)	39 (27, 62)	36 (24, 246)	50 (28, 72)
Median Δ from BL (IQR) in AST	-7 (-12, -3)	-7 (-15, -3)	-12 (-43, -3)	-7.50 (-11.5, -1.5)	-3.5 (-12, 14)	-8 (-22, 5)	-4 (-4, -4)	-20 (-20, -20)
ALT Elevations*	4 (1%)	2 (<1%)	3 (21%)	2 (18%)	4 (8%)	5 (14%)	0	0
AST Elevations*	5 (1%)	3 (<1%)	3 (21%)	3 (27%)	5 (10%)	5 (14%)	0	0
Alkaline Phosphatase*	1 (<1%)	0	0	0	0	0	0	0
Total Bilirubin*	3 (<1%)	2 (<1%)	0	0	1 (2%)	0	0	0

*Treatment-emergent Grade 3-4 Lab Abnormalities

- In general, co-infected subjects had higher median ALT and AST values at baseline compared to HBV/HCV negative subjects. HBV positive subjects in the FPV/r arm also appeared to have higher baseline transaminase values than HBV positive subjects in the LPV/r group. Less than 1% of non co-infected subjects experienced treatment-emergent transaminase elevations at Week 48 compared to >20% of co-infected subjects.

Discussion

- Results of this analysis should be interpreted with caution as the sample sizes in the various sub-groups were small (n=2 to n=47).
- At 48 weeks, subjects co-infected with HBV or HCV and HIV appeared to have lower HIV-1 virologic response rates compared to the non-co-infected population. These apparent differences are in part the result of a greater number of study discontinuations (adverse events, lost to follow-up, etc.) in the co-infected group which suggests the complexities of treating this patient population.
- Hepatitis co-infected subjects experienced more Grade 2-4 treatment-related AEs. Although the clinical and pathophysiologic significance of transaminase elevations are not the same in subjects co-infected with HBV versus HCV, hepatitis co-infected subjects overall experienced more transaminase elevations compared to non co-infected subjects. No apparent changes were observed in alkaline phosphatase and total bilirubin values for subjects in this study.

Conclusion

- **In this analysis, subjects co-infected with HBV or HCV in both treatment groups had a greater number of study discontinuations (adverse events, lost to follow-up, etc.) compared to subjects without hepatitis co-infection.**
- **Transaminase elevations were more common in hepatitis co-infected subjects compared to subjects without hepatitis co-infection.**
- **Comparison of AEs is difficult due to the limited number of co-infected subjects; however, hepatitis co-infected subjects appeared to have a higher incidence of Grade 2-4 treatment-related AEs compared to subjects without hepatitis co-infection.**

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