

96-Week Efficacy/Safety Data Comparing Two Doses of Ritonavir (r) to Boost Once-Daily Fosamprenavir (FPV), Used in Combination with Abacavir (ABC)/Lamivudine (3TC)

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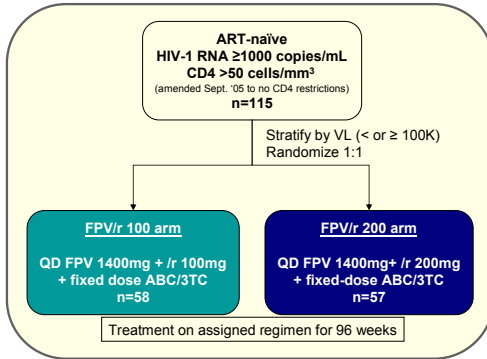
Introduction

- Adherence to antiretroviral therapy (ART) is recognized as an important predictor of treatment success. Thus, initial regimens should be simplified as much as possible by reducing the number of pills, reducing the dosing frequency, and minimizing drug interactions and side effects¹.
- For ART-naïve patients, once-daily (QD), boosted fosamprenavir (FPV) is an attractive treatment option due to its favorable safety profile and convenience of QD dosing. Since the concomitant use of ritonavir (r) may negatively impact the overall safety profile of FPV—particularly with regard to effects on lipid levels—the use of the lowest r dose to achieve a “boosting” effect is desired.
- Long term data on the efficacy and safety of ritonavir-boosted fosamprenavir QD regimens are available for r 200 mg doses, but not for 100 mg doses. This is the first 96-week report to compare the efficacy and safety of these two r dosing options.

Methods

- COL100758 is a randomized, two-arm, open-label, pilot study in ART-naïve patients to evaluate the efficacy, safety, and tolerability of FPV 1400mg QD boosted with r 100mg versus r 200mg, when used in combination with ABC 600mg/3TC 300mg. Figure 1 highlights the study design.

Figure 1. COL100758 Study Design



- Primary efficacy endpoint:
 - Proportion with plasma HIV-1 RNA <400 copies/mL at Week 48
- Secondary safety and efficacy endpoints include:
 - Proportion with plasma HIV-1 RNA <400 copies/mL at Weeks 24, 96
 - Proportion with plasma HIV-1 RNA <50 copies/mL at Weeks 24, 48, 96
 - Absolute values and change from baseline (BL) in CD4+ cell counts at Weeks 24, 48, 96
 - Incidence of Grades 2 to 4 AEs, treatment-limiting AEs, and serious adverse events (SAEs) over 96 weeks
 - Change from BL in fasting lipids (total cholesterol, HDL cholesterol, direct LDL cholesterol, and triglycerides) at Week 96
 - Adherence to each treatment regimen using pill counts of unused study drugs
- The study was not powered and p-values provided are descriptive only. Viral load comparisons between the two arms were made by Cochran-Mantel-Haenszel test. Differences in CD4+ T-cell count were compared by Wilcoxon rank sum test. Adherence p-values were obtained using Fishers Exact.

Results

- A total of 115 subjects enrolled at 12 U.S. centers from March 2005-February 2006. Baseline demographics are shown in Table 1. Eighty-three percent (n=96) completed their Week 48 visit², and 69% (n=79) completed through Week 96 (Table 2).

Table 1. Baseline Characteristics

	FPV/r100 arm N=58	FPV/r200 arm N=57	Total N=115
Male Gender, n (%)	47 (81%)	46 (81%)	93 (81%)
Median Age, years (range)	39 (21-61)	40 (20-59)	39 (20-61)
Race, n (%)			
Black	31 (53%)	30 (53%)	61 (53%)
White	21 (36%)	26 (46%)	47 (41%)
American Indian/Alaskan Native	4 (7%)	1 (2%)	5 (4%)
Mixed	2 (3%)	0	2 (2%)
Median HIV-1 RNA, log ₁₀ copies/mL (range)	4.67 (3.20-5.92)	4.92 (3.35-6.00)	4.84 (3.20-6.00)
HIV RNA Strata, n (%)			
HIV-1 RNA <100,000 copies/mL	38 (66%)	31 (54%)	69 (60%)
HIV-1 RNA ≥100,000 copies/mL	20 (34%)	26 (46%)	46 (40%)
Median CD4+ Cell Count, cells/mm ³ (range)	259 (19-697)	179 (19-991)	211 (19-991)
CDC Class, n (%)			
A (asymptomatic)	45 (78%)	38 (67%)	83 (72%)
B (symptomatic, non-AIDS)	9 (16%)	8 (14%)	17 (15%)
C (AIDS)	4 (7%)	11 (19%)	15 (13%)

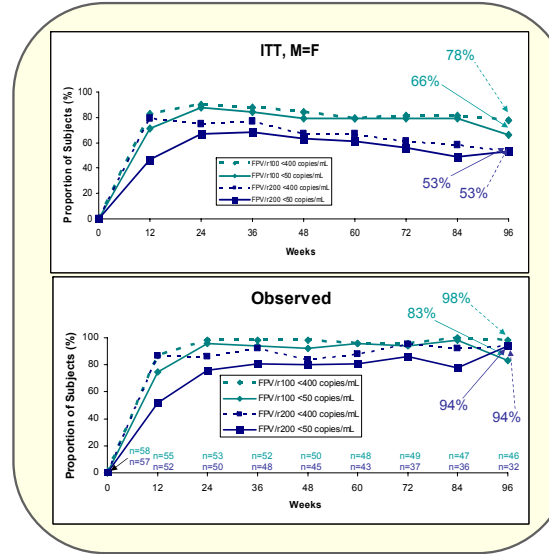
Table 2. Subject Disposition at End of Week 96

	FPV/r100 arm	FPV/r200 arm	Total
Completed through Week 96	46 (79%)	46 (81%)	79 (69%)
Prematurely Withdrawn	12 (21%)	24 (42%)	36 (31%)
Primary Reason for Withdrawal			
Adverse Event	1 (2%)	3 (5%)	4 (3%)
Lost to Follow-up	5 (9%)	8 (14%)	13 (11%)
Protocol Violation	1 (2%)	0	1 (<1%)
Subject decided to withdraw from study	1 (2%)	3 (5%)	4 (3%)
Protocol-defined virologic failure	2 (3%)	3 (5%)	5 (4%)
Non-compliance	1 (2%)	5 (9%)	6 (5%)
Other	1 (2%)*	2 (4%)**	3 (3%)

*Other reason: Week 84 due to pregnancy
 **Other reasons: Week 2 due to death, Week 36 due to pre-existing resistance with detectable viral load

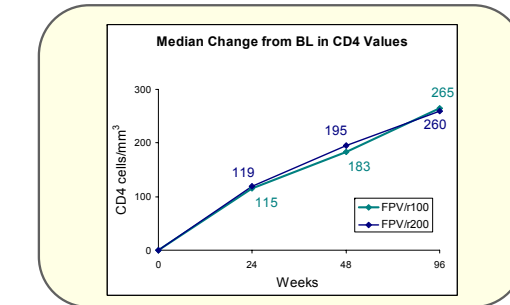
- Overall, the FPV/r100 treatment provided the best virologic efficacy (Figure 2).
 - At Week 48, by Intent to Treat, Missing=Failure (ITT, M=F) analysis, 84% (n=49) of subjects in the FPV/r100 arm had a viral load (VL) <400 copies/mL compared with 67% (n=38) in the FPV/r200 arm (p=0.026). Similarly, by Observed analysis, 98% (n=49) of FPV/r100 subjects versus 84% (n=38) of FPV/r200 subjects achieved a VL <400 copies/mL (p=0.018). There was no significant difference between the arms in the proportion of subjects with a VL <50 copies/mL by ITT, M=F or by Observed analyses.
 - At Week 96, 78% (n=45) of FPV/r100 versus 53% (n=30) of FPV/r200 subjects had a VL <400 copies/mL by ITT, M=F analysis (p=0.006). The differences were not significant between arms in the proportions with <400 copies/mL by the Observed analysis, or by either analysis for the <50 copies/mL stratum.

Figure 2. Subject Virologic Response



- CD4 gains in both arms were nearly identical and continued increasing over 96 weeks (Figure 3).

Figure 3. Subject CD4 Responses



- After censoring patient data for consumption of lipid-lowering agents, all median fasting lipid values increased over 96 weeks (Figure 4). The median total cholesterol/HDL ratio improved in both the FPV/r100 arm (from 4.6 to 4.0) and FPV/r200 arm (from 4.6 to 4.1).
- The incidence of any treatment-related grade 2 to 4 adverse event (AE) was not significantly different between the two groups (Table 3). Most AE's occurred during the first 48 weeks of the trial. After Week 48, only one treatment-related grade 2 to 4 AE was reported (fatigue in the FPV/r100 arm).

Figure 4. Median Fasting Lipids

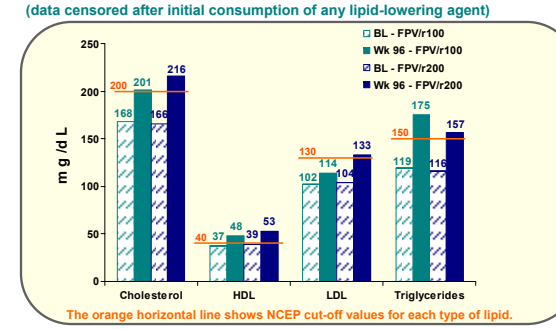


Table 3. Summary of Grade 2 to 4 Treatment-Related Adverse Events by Overall Frequency (>5%)

	FPV/r100 arm	FPV/r200 arm
Any	24 (41%)	25 (44%)
Diarrhea	8 (14%)	10 (18%)
Drug hypersensitivity*	6 (10%)	1 (2%)
Headache	5 (9%)	2 (4%)
Fatigue	4 (7%)	1 (2%)
Nausea	2 (3%)	3 (5%)
Abdominal pain	4 (7%)	0
Rash	3 (5%)	1 (2%)

*To abacavir, prospective HLA-B*5701 allele testing was not done

Table 4. Adherence Through Week 96 by Pill Count

	FPV/r100 arm	FPV/r200 arm	p-value
FPV			
Median % compliance*	100%	100%	***
Proportion w/ ≥95% compliance, % (n/N)**	98% (54/55)	95% (52/55)	0.618
RTV			
Median % compliance*	94.5%	88.8%	***
Proportion w/ ≥95% compliance, % (n/N)**	47% (25/53)	27% (15/55)	0.046
ABC/3TC			
Median % compliance*	95.8%	92.1%	***
Proportion w/ ≥95% compliance, % (n/N)**	56% (31/55)	40% (22/55)	0.127

*Compliance = total number of pills taken/total number of pills prescribed
 **Percent of subjects who took 95% or more of the total pills dispensed to them
 ***Statistical testing not done

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Discussion

- Subjects in the FPV/r100 tended to have better virologic responses at both 48 weeks and 96 weeks than did subjects in the FPV/r200 arm. The response rates in the FPV/r100 arm were comparable to those seen in previous studies of shorter duration³ reinforcing the efficacy of a FPV regimen boosted with this lower dose (100 mg) of ritonavir. It's possible that differences between the two groups in their median baseline HIV viral load and CD4 count contributed to the improved virologic response in the FPV/r100 arm. Additionally, the higher rate of early withdrawals in the FPV/r200 arm would impact the results of the ITT, M=F virologic analysis.
- Early withdrawals in the FPV/r200 arm were twice the number in the FPV/r100 arm. Given the study was open-label, study subjects may have discontinued the FPV/r200 regimen at higher rate due to a desire to transition to a 100 mg r regimen. The data for lost to follow-up, noncompliance, and subject decided to withdraw are consistent with this observation.
- Lower compliance to RTV was observed in the FPV/r200 arm. This may have affected virologic response, and could possibly have contributed to the lack of a difference between the arms with regard to changes in lipid parameters and incidence of AEs.
- Likewise, small sample size may have also contributed to the inability to detect major differences in lipid parameters and AEs between the arms.
- The use of the lower-dose RTV boosting of FPV in clinical practice diminishes pill burden (thereby reducing cost), may enhance adherence, and provides excellent virologic and immunologic outcomes in antiretroviral-naïve, HIV-infected subjects.

Conclusions

- At week 96, the proportion of subjects with viral loads suppressed <400 copies/mL was statistically significantly higher in the FPV/r100 arm versus the FPV/r200 arm by ITT, M=F analysis.
- CD4+ cell counts continued to increase over 96 weeks in both arms, and these improvements did not differ between the two groups.
- Over 96 weeks, lipid values increased in both arms, although, with the exception of triglycerides, smaller median increases in lipid parameters were observed in the FPV/r100 arm.
- The incidence of Grade 2-4 AE's was similar between the two groups.
- By pill count, fewer subjects in the FPV/r200 arm took 95% or more of their prescribed ritonavir pills compared with the FPV/r100 group.

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