Efficacy and Safety of Fosamprenavir + Ritonavir (FPV/RTV) 700mg/100mg Twice Daily (BID) Versus FPV/RTV 1400mg/100mg Once Daily (QD) with ABC/3TC QD over 24 Weeks

Poster Number

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Abstract

Background: Pilot PK and efficacy data on FPV/RTV 1400mg/100mg QD warrant further investigation in ART naives.
Methods: Study APV109141 is a 48 wk, randomized open-label study designed to demonstrate the virologic non-inferiority of FPV/RTV 1400mg/100mg QD to FPV/RTV 700mg/100mg BID with ABC/3TC QD in ART-naive adults (unscreened for HLA-B*5701). The study was also designed to show a superior non-HDL lipid profile of FPV/RTV QD. The group-sequential design included a first cohort of ~200 subjects to assess futility (with interim 24wk analysis); if study continuation criteria were met, enrolment of an additional 528 subjects would ensue with 48wk follow-up. The Stage 1 interim analysis is presented.
Results: Baseline demographics were similar between arms: median age 38 years; 74% male; 73% Caucasian; 6% CDC Class C; median VL 4.95 $\log_{10}$ c/mL and CD4+ count 247 cells/mm³. Responses (<400 c/mL) were similar in patients with BL VL <100K (101/115, 88%) and >100K (82/97, 85%).
Conclusion: Though changes in non-HDL lipids were lower in the QD arm, they did not meet criteria to proceed to Stage 2. High efficacy, however, was observed in both ABC/3TC-based treatment arms and in patients with both low and high viral loads. All subjects will be followed to 48 wks.

Introduction

- **In 2006, IAS Treatment Guidelines expanded the recommended regimens for initial therapy to include boosted PIs + 2NRTIs. FPV/RTV 700/ 100 mg BID (with 2 NRTIs) is now a recommended option for treatment naïve HIV-infected patients.**
- **Ritonavir-boosted protease inhibitors, however, are associated with dyslipidemia, particularly in the atherogenic non-HDL component of blood cholesterol.**
- **Reducing the dose of RTV to 100mg QD would be predicted to improve the lipid profile, reduce the pill burden, and to improve tolerability and regimen adherence.**
- **PK and pilot clinical data with FPV/RTV 1400/100mg QD has shown:**
  - **In a 14d crossover study, the APV Ctau was only modestly lower with RTV at 100 mg QD than with RTV at 200 mg QD, but remained six-fold higher than the protein-corrected 50% inhibitory concentration for wild-type virus. Fewer clinical adverse drug events and smaller increases in triglyceride levels were observed with the RTV 100 mg QD regimen (Ruane, 2007).**
  - **In a 96wk pilot study of ABC/3TC plus one of two FPV regimen, the proportion of subjects with viral loads <400 copies/mL (M=F analysis) was higher among subjects receiving FPV/RTV 1400/ 100 mg QD (78%) than 1400/ 200 mg QD (53%); LDL and TG changes were smaller on the 100 mg arm (DeJesus E, 2008).**
  - **In a separate 48wk pilot study of TDF/FTC plus either FPV/RTV 1400/100mg or ATV/RTV 300/100mgl, a M=F analysis showed similar responses to FPV and ATV (< 50 copies/mL: 75% [40/53] vs. 83% [44/53], p = 0.34); with fewer treatment-related Grade 2 to 4 adverse events on the FPV arm (Smith KY, 2008).**
- **This study (APV109141) was designed to demonstrate the virologic non-inferiority and superior non-HDL lipid profile of FPV/RTV 1400 mg/100 mg QD versus FPV/RTV 700 mg/ 100 mg BID with ABC/3TC QD over 48 Weeks.**

Methods

Endpoints and Sample Size

Primary

- **Proportion of subjects with HIV-1 RNA <400 c/mL over 48 weeks by ITT-E, TLOVR analysis**
  - **Assuming a 12% non-inferiority margin, a 72% response rate in each group and a one-sided 2.5% significance level, 95% power using a confidence interval based on a normal approximation required 364 evaluable subjects per arm.**

Key Powered Secondary

- **Change from Baseline in fasting non-HDL cholesterol over 48 weeks ITT-E, using Repeated Measures Mixed Model Analysis**
  - **Assuming a standard deviation of 45mg/dL and that 10% of subjects had no fasting samples (leaving 328 evaluable subjects per treatment arm), the study had 95% power at the two-sided 5% level of significance to detect a difference of 13mg/dL (0.34 mmol/L) for this endpoint.**

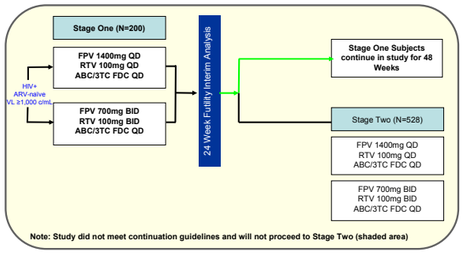
Protocol defined suspected and confirmed virological failure was any:

- **Subject who did not achieve a 1 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA by Week 4 (relative to baseline value, confirmed by a second plasma HIV-1 RNA determination 2-4 weeks later), OR**
- **Subject has two consecutive plasma HIV-1 RNA measures ≥400 copies/mL separated by at least 2-4 weeks after being previously <400 copies/mL on or after Week 4, OR**
- **Subject has two consecutive plasma HIV-1 RNA measures ≥400 copies/mL separated by at least 2-4 weeks on or after Week 24**

Study Design

- **This study utilized a group-sequential study design with two stages:**
  1. **A 24 week futility interim analysis of approximately 200 subjects (Stage 1), and**
  2. **If study continuation criteria were met at this interim the study would evaluate an additional 528 subjects for a total of 728 subjects, followed over a minimum of 48 weeks (Stage 2).**
- **Interim go/no-go futility criteria were based upon conditional power (see results in Table 1); assumptions have been previously described (Hughes, 2008). Conditional power is defined as the probability of proving the study hypotheses at the end of the trial assuming the observed current trend continues (Lan, 1988).**
- **Subjects were randomized 1:1 and were stratified by:**
  1. **Screening plasma HIV-1 RNA <100,000 c/mL or ≥100,000 c/mL**
  2. **Body mass index (BMI) <25 kg/m² or ≥25 kg/m²**
  3. **Screening non-HDL Cholesterol < 3.38 mmol/L (130 mg/dL) or ≥3.38 mmol/L**

Figure 1. Study Design



Note: Study did not meet continuation guidelines and will not proceed to Stage Two (shaded area)

Results

- **All results are presented on the intent-to-treat exposed population.**

Table 1. Conditional Power (Stopping Criteria and Results)

Interim analysis on Stage 1 population at Week 24 to assess Conditional power (CP) and to determine if study proceeds to Stage 2	Target Conditional Power	Actual Conditional Power
Efficacy Proportion <400 c/mL endpoint (MD=F*, ITT-E)	≥70%	96.7%
Safety Mean change from Baseline in fasting non-HDL cholesterol (ITT-E)	≥60%	56.6%

* MD=F was used to derive efficacy CP instead of TLOVR as per primary end-point as responders would have been falsely classified as failures by TLOVR due to the absence of a Week 16 visit by design and the need of confirmed success by TLOVR definition.

- **Conditional power go criterion for efficacy endpoint was met, but safety endpoint did not achieve go criterion; thus, study recruitment was discontinued. Subjects enrolled in Stage 1 were to be followed per protocol through Week 48.**

Table 2. Baseline Characteristics

		FPV/RTV 1400mg/100mg QD (N=106)	FPV/RTV 700mg/100mg BID (N=106)	Total (N=212)
Age (yrs)	Median (range)	37 (18 - 70)	38 (19 - 69)	38 (18 - 70)
Sex	Male	79 (75%)	77 (73%)	156 (74%)
Race	White	76 (72%)	79 (75%)	155 (73%)
	African American/ African Heritage	23 (22%)	22 (21%)	45 (21%)
	Other	9 (6%)	7 (4%)	16 (6%)
CDC Category	C: AIDS	8 (8%)	4 (4%)	12 (6%)
HIV-1 RNA, c/mL	Median $\log_{10}$ c/ml	4.95	4.94	4.95
	HIV-1 RNA <100,000 c/mL	56 (53%)	59 (56%)	115 (54%)
	HIV-1 RNA ≥100,000 c/mL	50 (47%)	47 (44%)	97 (46%)
CD4 count, cells/mm³	Median cells/mm³	250.5	242.0	247.0
	<250 cells/mm³	53 (50%)	54 (50%)	107 (51%)
	≥250 cells/mm³	53 (50%)	52 (49%)	105 (49%)

Table 3. Subject Disposition at 24 Weeks

	FPV/RTV 1400mg/100mg QD (N=106)	FPV/RTV 700mg/100mg BID (N=106)	Total (N=212)
Completion Status			
Prematurely discontinued	13 (12%)	9 (8%)	22 (10%)
Ongoing at time of analysis	93 (88%)	97 (92%)	190 (90%)
Reason for Discontinuation			
Adverse Events	4 (4%)	3 (3%)	7 (3%)
Lost to follow-up	4 (4%)	2 (2%)	6 (3%)
Protocol violation	1 (<1%)	1 (<1%)	2 (<1%)
Subject decided to withdraw from study	2 (2%)	2 (2%)	4 (2%)
Other	2 (2%)	1 (<1%)	3 (1%)

- **All patients prematurely withdrawn from the study for any reason were considered failures in the Intent-to-Treat, Missing or Discontinuation=Failure (MD=F) analysis.**

Table 4. Efficacy at Week 24

	FPV/RTV 1400mg/100mg QD (N=106)	FPV/RTV 700mg/100mg BID (N=106)	Total (N=212)
Plasma HIV-1 RNA <400 c/mL			
MD=F (ITT-E)	91 / 106 (86%)	92 / 106 (87%)	183 / 212 (86%)
Observed (ITT-E)	91 / 93 (98%)	92 / 94 (98%)	183 / 187 (98%)
Plasma HIV-1 RNA <50 c/mL			
MD=F (ITT-E)	77 / 106 (73%)	81 / 106 (76%)	158 / 212 (75%)
Observed (ITT-E)	77 / 93 (83%)	81 / 94 (86%)	158 / 187 (84%)
Median ΔCD4+ (cells/mm³) from Baseline (Q1-Q3)			
Observed (ITT-E)	114 (48, 198)	99 (35, 189)	107 (46, 191)
Median Δ from Baseline in Plasma HIV-1 RNA ($\log_{10}$ c/mL) (Q1-Q3)			
Observed (ITT-E)	-3.2 (-3.5, -2.7)	-3.2 (-3.6, -2.8)	-3.2 (-3.6 -2.7)

Note: MD=F analysis used at Week 24 in preference to TLOVR given limited number of viral load measurements prior to Week 24.

- **Protocol-defined suspected virologic failure was low in both arms (13% [14/106] in QD, 9% [10/106] in BID).**
- **Virologic responses (<400 c/mL) were similar in subjects with Baseline viral load <100K (101/115, 88%) and ≥100K (82/97, 85%) (MD=F [ITT-E]).**
- **By Week 24, the median change in CD4+ cell count from Baseline was 107 cells/mm³ and median change from Baseline in log viral load was -3.2 $\log_{10}$ c/mL.**
- **Treatment-emergent mutations in confirmed virological failures (n=2) included: M184V, Q334D/H, A360V, R211S, R277K, V381I (RT); R57K (PRO).**

Figure 2. Adjusted Mean Change from Baseline in Non-HDL Cholesterol (mmol/L) by Visit - Repeated Measures Mixed Model Analysis

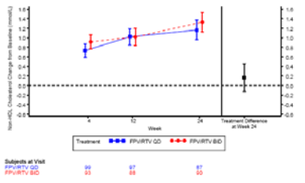


Table 5. Adjusted Mean Change from Baseline in Non-HDL Cholesterol (mmol/L) at Week 24 - Repeated Measures Mixed Model Analysis

	n	Adjusted Mean	S.E.	Difference	95% CI for Difference	p-value
Effect of Treatment						
FPV/RTV QD	102	1.161	0.1033			
FPV/RTV BID	100	1.327	0.1031	0.1663	(-0.1234, 0.4561)	0.259
Independent effect of Baseline non-HDL cholesterol						
<2.6 mmol/L	56	1.098	0.1372			
≥2.6 - <3.38 mmol/L	66	1.213	0.1267	0.1143	(-0.2536, 0.4821)	0.540
≥3.38 - <3.9 mmol/L	41	1.355	0.1593	0.2563	(-0.1622, 0.6748)	0.228
≥3.9 mmol/L	39	1.383	0.1742	0.2849	(-0.1551, 0.7248)	0.203
Independent effect of Baseline BMI						
<21 kg/m²	53	0.966	0.1411			
≥21 - <23 kg/m²	40	1.261	0.1664	0.2951	(-0.1337, 0.7238)	0.176
≥23 - <25 kg/m²	43	1.281	0.1601	0.3148	(-0.1074, 0.7370)	0.143
≥25 kg/m²	66	1.429	0.1269	0.4624	(0.0866, 0.8383)	0.016
Independent effect of Metabolic Status						
Diabetic	6	1.954	0.2978			
Not Diabetic	196	1.221	0.0731	-0.7327	(-1.3182, -0.1473)	0.014

Note: Values are estimated from a repeated measures model adjusting for treatment, visit, baseline non-HDL cholesterol, baseline BMI, metabolic status, treatment*visit, baseline non-HDL*visit and baseline BMI*visitStudy did not meet continuation guidelines and will not proceed to Stage Two

- **The difference between the FPV/RTV QD arm and the FPV/RTV BID arm in fasting non-HDL cholesterol was 0.1663 mmol/L (6.4 mg/dL), 95% CI: -0.1234, 0.4561.**
- **Compared to subjects with low BMI, subjects with a high BMI had a greater increase in non-HDL cholesterol from Baseline. The interaction with treatment was not significant.**
- **Patients with diabetes had a greater increase in non-HDL cholesterol from Baseline. The interaction with treatment was not significant.**

Table 6. Median Changes and Interquartile Range (IQR) from Baseline Values in Clinical Chemistry Parameters of Special Interest

	FPV/RTV 1400mg/100mg QD (N=106)		FPV/RTV 700mg/100mg BID (N=106)	
	Median Baseline (IQR)	Median change from Baseline (IQR)	Median Baseline (IQR)	Median change from Baseline (IQR)
Triglycerides (mg/dL)*	108 (89, 146)	40 (12, 100)	108 (84, 165)	75 (35, 143)
Cholesterol (mg/dL)*	163 (139, 187)	46 (32, 77)	156 (134, 179)	55 (32, 85)
HDL cholesterol (mg/dL)	40 (34, 50)	7 (2, 14)	37 (30, 45)	7 (1, 14)
LDL cholesterol (mg/dL)	96 (74, 120)	28 (10, 57)	92 (75, 117)	31 (7, 54)
Non-HDL cholesterol (mg/dL)	119 (102, 146)	167 (138, 199)	116 (95, 146)	160 (125, 199)

*** For triglycerides and cholesterol only fasting data is included**

Table 7. Grade 3/4 Treatment-emergent Laboratory Abnormalities

Laboratory parameter	FPV/RTV 1400mg/100mg QD		FPV/RTV 700mg/100mg BID	
	Grade 3	Grade 4	Grade 3	Grade 4
Cholesterol*	8/102 (8%)	0	6/102 (6%)	0
Triglycerides*	2/102 (2%)	0	3/101 (3%)	3/103 (3%)
LDL	8/101 (8%)	0	8/96 (8%)	0
Non-HDL	17/102 (17%)	0	19/100 (19%)	0

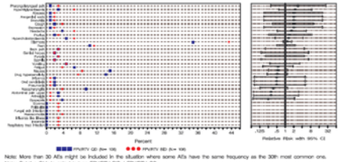
***For triglycerides and total cholesterol only fasting data is included**

Table 8. Grade 2-4 Drug-related Adverse Experiences Occurring in ≥3% of Subjects

Preferred Term	FPV/RTV 1400mg/100mg QD (N=106)	FPV/RTV 700mg/100mg BID (N=106)	Total (N=212)
Drug-Related Grade 2-4 AEs	22 (21%)	31 (29%)	53 (25%)
Drug hypersensitivity*	12 (11%)	7 (7%)	19 (9%)
Diarrhoea	1 (<1%)	12 (11%)	13 (6%)
Hypercholesterolaemia	2 (2%)	4 (4%)	6 (3%)

***All drug hypersensitivity events were attributable to ABC**

Figure 5. Most Frequent AEs by Relative Ris



Note: More than 30 AEs might be included in the situation where some AEs have the same frequency as the 30th most common one.
Note: Relative Risk is calculated as FPV/RTV BID / FPV/RTV QD.

Discussion

- **High and comparable levels of virologic efficacy were observed with both FPV/RTV 700 /100 mg BID and 1400 /100 mg QD.**
- **However, changes from baseline in non-HDL cholesterol were lower in the QD arm than the BID arm, the difference between the two arm did not reach the predefined criteria for pregression to Stage 2 of this group-sequential design study.**
- **Interestingly, in the 'Repeated Measures Mixed Model Analysis' of the adjusted mean Week 24 change from Baseline in non-HDL cholesterol of the whole study population, Baseline non-HDL cholesterol was not associated change from Baseline in non-HDL cholesterol, high BMI and a diabetes status was associated with a higher change from Baseline in non-HDL cholesterol.**

Conclusions

- **Full Week 24 analysis showed high antiviral efficacy, good safety and tolerability in both treatment arms and no increased risk of virological failure or development of resistance in the FPV/RTV 1400 /100 mg QD arm, allowing continuation of randomised treatment through Week 48.**
- **Treatment efficacy was high and comparable in patients with both low and high viral loads.**
- **Consistent with previous observations, once daily FPV/RTV was associated with a lower incidence of treatment-related diarrhoea.**
- **Though changes baseline in non-HDL cholesterol were also lower in the QD arm, they did not meet criteria to proceed to Stage 2 of the group-sequential design.**
- **All subjects in APV109141 have now been followed through 48 weeks; full analysis of safety and efficacy data will be the subject of a future publication.**

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