Poster
H-1245

Week 96 Virology Analysis of COL100758, a Study of Once-Daily (QD) Fosamprenavir (FPV) Boosted with 100 mg or 200 mg Ritonavir (/r) with Abacavir /Lamivudine (ABC/3TC) in Antiretroviral Naïve HIV-infected Patients

L. L. ROSS[1], E. DEJESUS[2], L. SLOAN[3], M. SENSION[4], Q. LIAO[1], K. OIE[1], B. WINE[1], K. PAPPA[1], C. HICKS[5]

[1]GlaxoSmithKline, Research Triangle Park, NC, [2]Orlando Immunology Cntr, Orlando, FL, [3]North Texas Infectious Disease Consultants, Dallas, TX, [4]Comprehensive Care Cntr, Ft. Lauderdale, FL, [5]Duke Univ Med Cntr, Durham, NC

Introduction

- Protease inhibitor (PI) mutations at virologic failure (VF) are rare with 200mg ritonavir (200mg/r) boosting, but emerge occasionally with unboosted PI regimens.
- COL100758 is a 96 week, open-label, multi-center randomized study which compared efficacy and safety of fosamprenavir/ritonavir (FPV/r) 1400/100mg (FPV/r100) to FPV/r 1400/200mg (FPV/r200) + ABC/3TC 600/300mg given QD in 115 ART-naïve subjects.
- This study compares the resistance detected in HIV from subjects who met virologic failure (VF) criteria when 100mg vs. 200mg /r is used over the course of this two year study, and examines whether baseline mutations impact resistance selected at VF.

Methods

- VF was defined as confirmed HIV-RNA ≥400 copies/mL after suppression or never suppressing to <400 copies/mL by Week 24.
- Population genotypes and phenotypes at baseline and on therapy were performed by Virco (Belgium) on plasma-derived HIV from subjects meeting VF criteria.
- Resistance was analyzed as per the 2008 IAS-USA guidelines (www.iasusa.org). In addition, the presence of thymidine analogue (TAMS) reversion mutations was also assessed.
- Between-treatment comparisons of these proportions were made using the Cochran-Mantel-Haenszel test stratified by baseline HIV-1 RNA. Differences were considered statistically significant if a P value was <0.05.

Table 1. Baseline Characteristics

	FPV/r100 arm N=58	FPV/r200 arm N=57	Total N=115
Male Gender	47 (81%)	46 (81%)	93 (81%)
Median Age in years (range)	39 (21-61)	40 (20-59)	39 (20-61)
Race, n (%)			
White	21 (36%)	26 (46%)	47 (41%)
Black	31 (53%)	30 (53%)	61 (53%)
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)
Median CD4+ cell count, cells/mm^3 (range)	259 (19-697)	179 (19-991)	211 (19-991)
CDC Class A (asymptomatic)	45 (78%)	38 (67%)	83 (72%)
CDC Class B (symptomatic, non-AIDS)	9 (16%)	8 (14%)	17 (15%)
CDC Class C (AIDS)	4 (7%)	11 (19%)	15 (13%)

Figure 1. Response Profiles for the 5 VFs on FPV/r100 + ABC/3TC

- NRTI, NNRTI and Major PI mutations and FC resistance to study drugs are shown. Mutations in red are major drug resistance-associated mutations that emerged during the study.

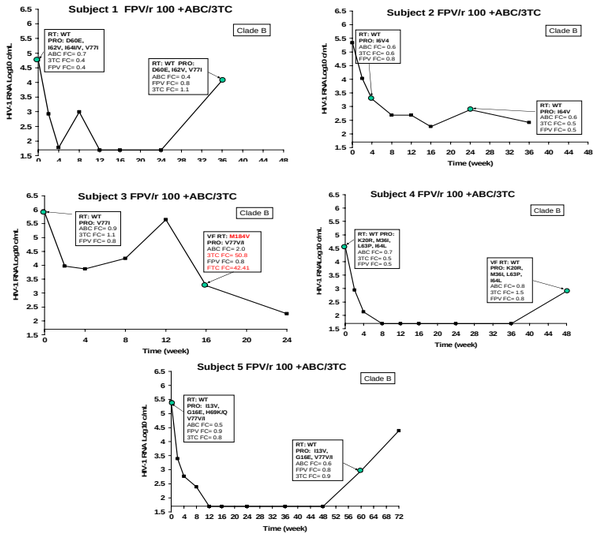
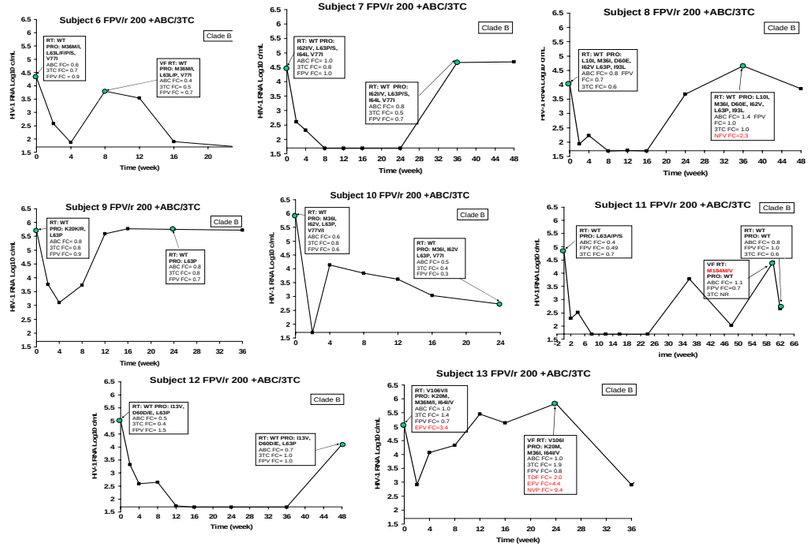


Figure 2. Response Profiles for the 8 VFs on FPV/r200 + ABC/3TC

- NRTI, NNRTI and Major PI mutations and FC resistance to study drugs are shown. Mutations in red are major drug resistance-associated mutations that emerged during the study.



Results

- Baseline (BL) characteristics for the two study arms are shown in Table 1.
- At week 96, VF criteria were met by 13/115 (11%) enrolled subjects (5 subjects in the FPV/r100 arm, and 8 in the FPV/r200 arm).
- For the 13 VFs, the median HIV-1 RNA at baseline was 5.34 and 4.93 $\log_{10}$ copies/mL and median CD4 cells/mm^3 was 203 and 164 for the 100 mg arm and 200 mg arms, respectively.
- Rates of virologic suppression between the two arms was not significantly different (NS) in the Observed analysis at Week 96 (Table 2) using either the <50 or <400 copies/mL cut offs, with high rates of response. In the ITT-exposed, missing=failure (ITT-e, M=F) analysis, using the <50 copies/mL cut-off, there was NS, while by the <400 copies/mL cut-off, the response rate was significantly greater in the FPV/r100 arm (p<0.006).
- Response profiles for the 5 VF in the FPV/r100 arm are shown in Figure 1; response profiles for the 8 VF in the FPV/r200 arm are shown in Figure 2.

Table 2. Proportion of subjects at Week 96 with virologic suppression to <50 or <400 copies/mL by Observed and by ITT-e, M=F analyses

	FPV/r100 n/N (%)	FPV/r200 n/N (%)	p-value
<50 copies/mL, Observed	38/46 (83%)	30/32 (94%)	NS
<50 copies/mL, ITT-e, M=F	38/58 (66%)	30/57 (53%)	NS
<400 copies/mL, Observed	45/46 (98%)	30/32 (94%)	NS
<400 copies/mL, ITT-e, M=F	45/58 (78%)	30/57 (53%)	0.006

- At baseline, only 1 subject had a major mutation--Subject 13 (FPV/r200 arm) had the NNRTI resistance mutation V106I. This mutation was still present at VF.
- At VF, HIV from 2/13 VFs selected mutations (Mut): M184V (Subject 3; 100 mg arm) and M184M/V (Subject 11; FPV/r200 arm).

Acknowledgements

This study was funded by a grant from GlaxoSmithKline. We are grateful to all the patients, to the staff at all of the COL100758 sites, and the other COL100758 investigators-Rafael Campo, Beata Casanas, Jason Flamm, Jeffrey Lennox, Rodger MacArthur, Jeffrey Nadler, John Schrank, Jr., Jeffrey Stephens, David Wohl and to Beth Rouse at GSK for her help with data analysis.

Discussion

- Transmission of drug resistant HIV has been increasing in United States and globally. The current DHHS guidelines now recommend genotyping antiviral-naïve patients prior to antiviral treatment initiation.[1] These revisions occurred after the start of the COL100758 study, so genotyping was not performed at the time of study screening and was not a randomization criteria.
- Both arms had high virologic efficacy rates at 96 weeks, with protocol-defined virologic failure occurring in 11% (13/115) of study subjects overall--9% (5/58) for subjects in the FPV/r100 arm, and 14% (8/57) for subjects in the FPV/r200 arm. These results confirm other recent data that have demonstrated good activity using FPV in combination with a 100mg ritonavir dose.[2,3]
- These results were also similar to what was observed in the SOLO study[4] in which ART-naïve HIV-infected subjects received FPV 1400mg once daily + ritonavir 200mg once daily + ABC 300mg twice daily + 3TC 150mg twice daily. Subjects meeting the SOLO Study VF criteria did not select for FPV mutations at VF, and selection for NRTI mutations was low (2/13 VFs; 15%).

Conclusions

- **After 2 years on therapy, 13/115 (11%) of the subjects met VF criteria.**
- **None of these subjects with VF selected for any major PI resistance mutation.**
- **Only 2/13 patients experiencing VF (one in each of the study arms) developed a significant new resistance mutation in RT (M184V or M184M/V mixtures).**
- **These results support and reaffirm the low long term risk of resistance selection with initial FPV/r-boosted regimens observed in other studies.**

References

1. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. January 29, 2008 http://AIDSinfo.nih.gov
2. Smith K. *et al*. 2007 IAS, Sydney, AU Abstract WEPEB023.
3. DeWit S. *et al*. *8th International Congress on Drug Therapy in HIV Infection*, Glasgow, UK, November 12-16, 2006. Abstract/Poster P17.
4. MacManus S. *et al*. *Aids* 2004; 18(4):651-655.