

# Switching to Fosamprenavir (FPV) Led to Similar Efficacy and Safety in HIV-1-infected Subjects on their First PI Regimen: a Prospective, Open-label, Multicenter, Randomized Trial (ESS100290)

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## Abstract

**Background:** Fosamprenavir (FPV) is an efficacious and well-tolerated protease inhibitor (PI); switching to FPV from another PI regimen may offer advantages in tolerability and virologic response.

**Methods:** Subjects on their first PI-regimen (HIV-1 RNA <400 copies/mL (c/mL) for 23 months) were randomized 1:1 to switch to FPV (± 200mgRTV) or continue their baseline (BL) PI-regimen (stable NRTI background). Subjects in the BL-PI-regimen arm were allowed to switch to FPV (± 200mgRTV) at Week 24. Primary efficacy endpoint was proportion of subjects with HIV-1 RNA <400 c/mL at 24 weeks (TLOVR, 12% non-inferiority margin).

**Results:** Baseline characteristics include median age 43 years in all arms; % males and African American subjects, respectively: FPV-switch (79%, 35%); BL-PI (78%, 34%); and Wk-24 FPV-switch (85%, 24%).

PI Strata*, ITT(E) Population, n (%)	ATV	IDV	LPV/r	NFV	RTV	SQV
BL FPV-switch, N=153	51 (33)	9 (6)	63 (41)	26 (17)	0	4 (3)
BL-PI, N=97	36 (37)	2 (2)	40 (41)	17 (18)	1 (1)	1 (1)
Wk-24 FPV-switch, N=54	14 (26)	6 (11)	25 (46)	7 (13)	0	2 (4)

\*PI Strata determined by active PI (RTV boosting was at the discretion of the investigator). Full details of boosted regimens will be presented.

TLOVR responders	Week 24		Week 48		
	BL FPV-switch (N=153)	Continue BL PI (N=151)	BL FPV-switch (N=153)	Continue BL PI (N=97)	Week 24 FPV-switch (N=54)
HIV-1 RNA <400 c/mL, n (%)	137 (90)*	140 (93)*	116 (76)	73 (75)	49 (91)
HIV-1 RNA <50 c/mL, n (%)	123 (80)	129 (85)	100 (65)	67 (69)	45 (83)
<b>Safety, Safety Population</b>					
Any drug-related Grade 2-4 AEs		20%	19%	20%	
Any drug-related Grade 2-4 GI Event		7%	3%	7%	

\*FPV was non-inferior to BL PI at Week 24 (95% CI = -9.8, 3.5)

Low rates of virologic failure (confirmed ≥400c/mL) were observed through Week 48 (BL FPV-switch, n=8, BL-PI, n=1; Wk-24 FPV-switch, n=0).

**Conclusions:** Virologic response was similar between the FPV switch and BL PI arms at 24 and 48 weeks; subjects who switched to FPV at Week 24 appeared to have higher virologic response rates. Adverse events were similar between groups; however subjects who switched regimens reported more GI AEs.

## Introduction

- Current DHHS Guidelines recommend a number of different options for protease inhibitor (PI)-based combination antiretroviral therapy (ART), including fosamprenavir (FPV).<sup>1</sup>
  - Since there are several efficacious PIs available, tolerability becomes an important consideration in making treatment decisions.
- We compared the safety, tolerability, and efficacy of switching subjects who were virologically stable on their current therapy of a protease inhibitor (PI) [± ritonavir (RTV)] + 2 nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) to a fosamprenavir based therapy versus those who maintained their baseline (BL) PI therapy.

## Methods

- ESS100290 was a Phase IIIb/IV, randomized, open-label, multicenter 48 week study conducted in the United States with a planned 24 week interim analysis.
- HIV-1 infected subjects with HIV-1 RNA <400copies/mL on their current PI regimen were randomized 1:1 to either switch their current PI for FPV (± 200mg RTV) for 48 weeks or to continue their current therapy for 24 weeks and then have the option of maintaining their current PI regimen or switching their PI regimen for FPV (± 200mg RTV) for an additional 24 weeks.
- Subjects were stratified, based on their primary PI therapy into the following groups at randomization – atazanavir (ATV or ATV/r), indinavir (IDV or IDV/r), LPV/r, NFV, RTV and saquinavir (SQV hard-gel capsule with or without RTV or SQV soft-gel capsule, with or without RTV).
- Virologic failure (VF) was defined as two consecutive HIV-1 RNA measures ≥400 copies/mL at any time during the study.
- Primary Efficacy Endpoint:
  - The proportion of subjects with HIV-1 RNA <400 copies/mL at Week 24 by the time to loss of virological response (TLOVR) algorithm.
- Secondary Endpoints:
  - Proportion of subjects with plasma HIV-1 RNA <400 copies/mL at 48 weeks
  - Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at 24 and 48 weeks
  - Incidence of Grade (G) 2-4 adverse events (AEs) and gastrointestinal (GI) AEs through Weeks 24 and 48

## Results

- Overall, 304 subjects were randomized and included in the ITT(E) population. Approximately 20% of the population was female and 33% was Black.

**Table 1. Baseline (BL) Characteristics, ITT(E) Population**

	Switch BL PI to FPV (N = 153)	Continue BL regimen (N = 97)	Switch BL PI to FPV at Week 24 (N = 54)
Median age (range), years	43 (23 – 71)	43 (21 – 66)	43 (23 – 67)
Male, n (%)	121 (79)	76 (78)	46 (85)
Race, n (%)			
Black	53 (35)	33 (34)	13 (24)
White	96 (63)	60 (62)	40 (74)
Other	4 (3)	4 (4)	1 (2)
Median BL HIV-1 RNA log <sub>10</sub> copies/mL (range)	1.69 (1.69–4.39)	1.69 (1.69–4.73)	1.69 (1.69–2.93)
n	412	403	439
Median CD4+ (range)	(87-2303)	(23-1410)	(78-1331)

**Table 2. Subject Disposition, ITT(E) Population**

	Switch BL PI to FPV (N = 153)	Continue PI regimen (N = 97)	Switch BL PI to FPV at Week 24 (N = 54)	Total (N = 304)
Completed through Week 48, n (%)	125 (82)	81 (84)	52 (96)*	258 (85)
Withdrawn due to AE, n (%)	7 (5)	5 (5)	1 (2)	13 (4)
Withdrawn due to lack of efficacy, n (%)	1 (<1)	3 (3)	0	4 (1)
Withdrawn for other reasons†, n (%)	20 (13)	8 (8)	1 (2)	29 (10)

\*Note: Subjects switched from BL PI regimen to FPV at Wk 24 and then completed Wk 48

†Other reasons included lost-to-follow-up (n=10); protocol violation (n=1); non-compliance (n=2); subject decision to withdraw (n=11); subject translocation (n=3); incarceration (n=1); and pregnancy (n=1) as reported by the investigator.

- The most commonly used NRTIs during the study were zidovudine (ZDV)/lamivudine (3TC) and abacavir (ABC)/3TC in all three PI arms. Four subjects continued to use NRTIs as their background therapy.

**Table 3. PI Strata, ITT(E) Population**

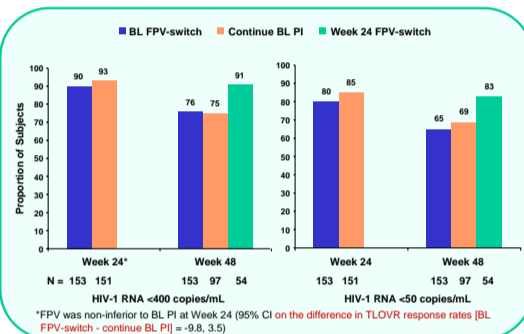
PI Strata*, ITT(E) Population, n (%)	BL FPV-switch N=153	BL-PI N=97	Wk-24 FPV-switch N=54
ATV	51 (33)	36 (37)	14 (26)
IDV	9 (6)	2 (2)	6 (11)
LPV/r	63 (41)	40 (41)	25 (46)
NFV	26 (17)	17 (18)	7 (13)
RTV	0	1 (1)	0
SQV	4 (3)	1 (1)	2 (4)
RTV Boosting after FPV switch	90 (59) <sup>†</sup>	NA	35 (65) <sup>‡</sup>

\*PI strata determined by active PI (RTV boosting was at the discretion of the investigator).

<sup>†</sup>FPV/RTV dosing: FPV/RTV 700/100mg BID: 36, 24%; FPV/RTV 1400/200mg QD: 53, 35%; Mixed dosing: 1, <1%.

<sup>‡</sup>FPV/RTV dosing: FPV/RTV 700/100mg BID: 17, 31%; FPV/RTV 1400/200mg QD: 18, 33%.

**Figure 1. Efficacy Results, ITT(E) Population, TLOVR**



\*FPV was non-inferior to BL PI at Week 24 (95% CI on the difference in TLOVR response rates [BL FPV-switch - continue BL PI] = -9.8, 3.5)

- A total of 19 subjects met the protocol definition of virologic failure (confirmed HIV-1 RNA ≥400 copies/mL); BL-FPV-switch: 8 (4%); baseline-PI arm: 11 (11%); Wk-24 FPV-switch arm: 0.
  - Eight of these subjects chose to remain in the study and were able to achieve virologic re-suppression and had HIV-1 RNA <400 copies/mL at last study visit (Week 48 or beyond), including four subjects from the BL-FPV-switch and four from the PI continue study arm.
- At Week 48, the median change in CD4+ cell count was similar in the two FPV-switch arms (BL-FPV-switch +54 cells/mm<sup>3</sup>, Wk 24 FPV-switch +64 cells/mm<sup>3</sup>) but lower in the baseline PI arm (+30 cells/mm<sup>3</sup>).

**Table 4. Week 48 Safety Results, Safety Population**

	BL FPV-switch (N=153)	Continue BL PI (N=97)	Week 24 FPV-switch (N=54)
<b>Treatment-related Grade 2-4 Adverse Events (≥25%), n (%)</b>			
Subjects with Any Event	31 (20)	18 (19)	11 (20)
Diarrhea	9 (6)	2 (2)	3 (6)
Blood triglycerides increased	7 (5)	8 (8)	0
Blood bilirubin increased	0	7 (7)	2 (4)
<b>Treatment-Related Grade 2-4 GI Event (occurring in &gt;1 subject, any treatment group), n (%)</b>			
Subjects with Any Event	11 (7)	3 (3)	4 (7)
Diarrhea	9 (6)	2 (2)	3 (6)
<b>Summary of Fasting Lipids, n (range)</b>			
BL Total Cholesterol, mg/dL	199 (100-516)	197 (118-281)	194 (86-365)
Change from BL to Wk 48	2 (-380-160)	-7 (-108-80)	-2 (-146-78)
BL LDL Cholesterol, mg/dL	113 (38-207)	108 (32-201)	108 (37-248)
Change from BL to Wk 48	2 (-92-79)	-8 (-85-54)	-10 (-118-31)
BL HDL Cholesterol, mg/dL	44 (13-98)	44 (9-112)	43 (23-98)
Change from BL to Wk 48	2 (-39-31)	2 (-61-21)	4 (-32-24)
BL Triglycerides, mg/dL	174 (43-1986)	161 (56-680)	182 (58-691)
Change from BL to Wk 48	1 (-1793-535)	-1 (-489-196)	-4 (-243-448)

- There were no deaths and only one treatment-related SAE (cerebrovascular accident) in the baseline-PI group through Week 48. At the time of the event, the subject had prolonged and untreated elevated cholesterol levels for approximately one year.

## Discussion

- Over 48 weeks, virologic response (HIV-1 RNA levels <400 and <50 copies/mL) was similar in subjects who switched to FPV at baseline and those who continued on their baseline PI regimen. Those subjects who switched from their baseline PI to FPV at Week 24 appeared to have higher virologic response rates by Week 48.
- There were 19 subjects who met the protocol definition of virologic failure (BL FPV-switch arm 8 (4%); baseline-PI arm 11 (11%). Of these, eight subjects chose to remain in the study and re-suppressed to HIV-1 RNA <400 copies/mL (BL FPV-switch: 4; baseline-PI: 4).
- The current study design involved a comparison between subjects who remained on their baseline PI regimen to those who were switched to a new FPV regimen. The proportion of subjects who had any AEs through Week 48 was slightly higher in the switch arms than in the baseline PI arm. Overall, diarrhea was the most frequently reported AE and the only treatment-related grade 2-4 GI AE occurring in more than one subject per treatment arm.

## Conclusions

- Subjects who were switched to FPV from another PI regimen had favorable virologic, immunologic, and safety outcomes.
- Low rates of virologic failure were observed for subjects in the BL FPV-switch (4%) baseline PI (11%) arms.
- Similar tolerability was noted for subjects who switched to a FPV-based PI regimen compared to those who continued on their baseline PI regimen. Adverse events in the three PI arms were generally mild to moderate.

## References

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. January 28, 2008; 1-128. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

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