PHARMACOKINETICS OF FALDAPREVIR AND ANTIRETROVIRALS IN PATIENTS WITH HIV/HCV CO-INFECTION

497

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BACKGROUND

- Faldaprevir (FDV) is a potent inhibitor of HCV NS3/4A, with activity against HCV genotypes (GT) 1, 4, 5, and 6 in vitro[1]
- FDV is being developed for the treatment of chronic HCV infection in mono-infected and HIV co-infected populations and is therefore likely to be used in combination with antiretroviral therapy (ART)
- FDV is a substrate of CYP3A4, a moderate inhibitor of CYP3A4 at 240 mg[2], and a weak inhibitor of CYP3A4 at 120 mg
- In studies in healthy volunteers[3]
  - FDV increased raltegravir (RAL) AUC by approximately 2.5-fold and had no substantial effect on the pharmacokinetics (PK) of darunavir/ritonavir (DRV/r), efavirenz (EFV), or tenofovir (TDF)
  - EFV decreased FDV AUC by 35%
- In STARTVerso4, a Phase III trial in an HCV/HIV co-infected population, FDV + pegylated interferon α-2a and ribavirin (PR) was well tolerated and resulted in a sustained virologic response 12 weeks after the planned end of treatment (SVR12) in 72% of participants[4]
- We present an analysis of the PK interaction between FDV and antiretrovirals (ARV) used in STARTVerso4

OBJECTIVES

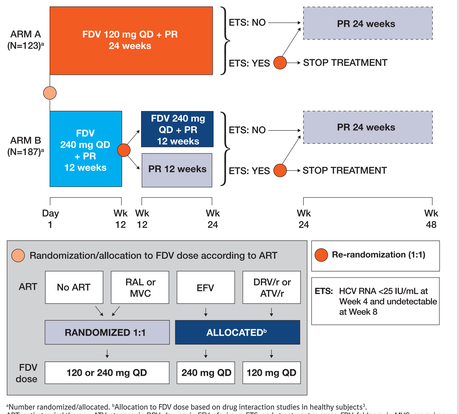
- To assess the effect of FDV on the steady-state trough concentrations of ARVs (EFV, DRV, atazanavir [ATV], RAL, and TDF) in patients co-infected with HCV and HIV
- To assess the effect of ART on the steady-state trough concentrations of FDV in patients co-infected with HCV and HIV

METHODS

TRIAL DESIGN

- STARTVerso4 was a multicenter, open-label, sponsor-blinded, randomized, Phase III study in patients co-infected with HCV GT-1 and HIV-1 (**Figure 1a**)
- Patients on DRV/r- or ATV/r-based ART were assigned to FDV 120 mg QD; those on EFV were assigned to FDV 240 mg QD (**Figure 1b**)
- The FDV dose for patients on other ARV regimens was randomly assigned
- The primary endpoint was SVR12
  - Primary results are presented in oral presentation 23[4]
- A substudy with intensive PK sampling was also carried out for patients receiving FDV with ATV/r
  - Results are presented in poster 499[5]

FIGURE 1. STARTVerso4 trial design



[a]Number randomized/allocated. [b]Allocation to FDV dose based on drug interaction studies in healthy subjects[3].
ART, antiretroviral therapy; ATV, atazanavir; DRV, darunavir; EFV, efavirenz; ETS, early treatment success; FDV, faldaprevir; MVC, maraviroc; PR, pegylated interferon α-2a and ribavirin; QD, once daily; r, ritonavir; RAL, raltegravir; SVR12, sustained virologic response (HCV RNA <25 IU/mL, not detected) 12 weeks after the planned end of treatment; Wk, week.

PHARMACOKINETIC EVALUATION

- Pre-dose blood samples were collected in the morning on Day 1 (before the start of FDV dosing) and Weeks 2, 4, 8, 24, and 36 (for patients who stopped at Week 24) for ARVs and on Day 1 and Weeks 1, 2, 4, 8, and 12 for FDV
- Concentrations of FDV and ARVs in plasma samples were determined at Tandem Labs (Salt Lake City, Utah, USA) using validated high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) assays

STATISTICAL ANALYSIS

- Steady-state ARV trough concentrations ($C_{pre,ss}$) are summarized with descriptive statistics for FDV and for ARVs (prior to FDV dosing, at FDV steady state, and after completion of FDV treatment)
  - Note that since EFV is taken in the evening, trough concentrations are substituted for concentration 12 hours post-dose (C_{12h}) for EFV
- Very few patients in STARTVerso4 were not taking ART; the effect of ARVs on FDV trough concentrations was evaluated by comparison with historical data from non-Asian HCV mono-infected patients treated with FDV + PR in a Phase III study (Study 1220.47) with similar demographics and baseline characteristics

RESULTS

SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

- Among 308 patients treated in STARTVerso4
  - 123 received FDV 120 mg + PR: 66 with ritonavir booster protease inhibitor (PI/r)-based ART
  - 185 received FDV 240 mg + PR: 82 with EFV-based ART
- Baseline characteristics were generally well balanced across FDV treatment groups and ART regimen (**Table 1**)

TABLE 1. Demographics and baseline characteristics

	FDV 120 mg + PR		FDV 240 mg + PR	
	Without PI/r (N=57)	With PI/r (N=66)	Without EFV (N=103)	With EFV (N=82)
Male, n (%)	49 (86)	54 (82)	85 (83)	60 (73)
Race, n (%)				
White	47 (83)	59 (89)	90 (87)	60 (73)
Black or African American	6 (11)	6 (9)	11 (11)	19 (23)
Other[a]	4 (7)	1 (2)	2 (2)	3 (4)
Ethnicity, n (%)				
Hispanic or Latino	6 (11)	8 (12)	3 (3)	10 (12)
Mean age, years (SD)	47.4 (7.7)	47.7 (7.7)	44.6 (7.8)	48.7 (8.5)
Mean BMI, kg/m^2 (SD)	24.5 (3.9)	24.6 (4.7)	25.0 (3.8)	24.7 (4.4)
Cirrhosis,[b] n (%)	8 (14)	16 (24)	10 (10)	11 (13)
Mean baseline HCV RNA, $\log_{10}$ IU/mL (SD)	6.3 (0.75)	6.6 (0.59)	6.3 (0.66)	6.4 (0.66)
HIV RNA (copies/mL) ≥40, n (%)	4 (7)	4 (6)	11 (11)	0
Mean CD4+ cell count cells/mm^3 (SD)	525 (199)	516 (263)	558 (242)	537[c] (219)
ART regimen, n (%)				
EFV	2 (4)[d]	0	0	82 (100)
ATV/r	0	12 (18)	0	0
DRV/r	0	54 (82)	1 (1)[d]	0
RAL	49 (86)	0	94 (91)	0
Other ART	0	0	3 (3)	0
No ART	6 (11)	0	5 (5)	0

[a]Other race includes Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and missing data. [b]Cirrhosis was determined by the investigator based on fibroscan, biopsy, and/or other clinical parameters. [c]N=81. [d]Randomization errors.
ART, antiretroviral therapy; ATV, atazanavir; BMI, body mass index; DRV, darunavir; EFV, efavirenz; FDV, faldaprevir; PI/r, ritonavir boosted protease inhibitor (atazanavir or daclatasvir); PR, pegylated interferon α-2a and ribavirin; r, ritonavir; RAL, raltegravir; SD, standard deviation

EFFECT OF FDV ON ARVs

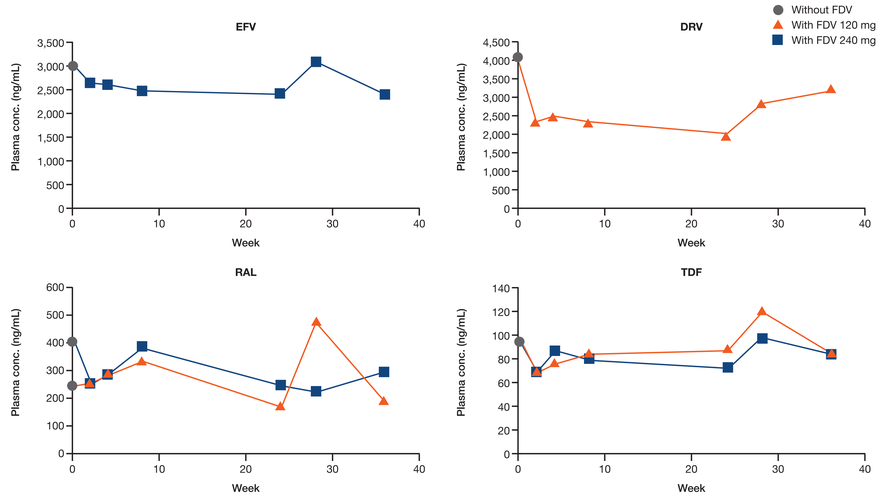
- The effects of FDV on ARV trough concentrations are summarized in **Figure 2** and **Table 2**
- There was no apparent effect of FDV on EFV $C_{12h,ss}$
- DRV gMean trough level was lower with FDV than without FDV
- RAL gMean trough level was similar with or without FDV in the 120 mg group but lower with FDV than without FDV in the 240 mg group
- TDF gMean trough levels were lower with than without FDV in the 120 mg group and in the 240 mg group in the absence of EFV
  - In the presence of EFV, TDF trough levels in the FDV 240 mg group were comparable with or without FDV

TABLE 2. Summary of the effect of FDV on ARV trough concentrations

ARV	FDV dose, mg	gMean with FDV[b] (n)	gMean without FDV[c] (n)	Adjusted GMR, % (90% CI)
EFV[a]	240	2,756.9 (46)	2,914.8 (43)	94.58 (86.31, 103.66)
DRV	120	2,309.71 (16)	4,122.71 (14)	56.02 (35.96, 87.27)
RAL	120	279.31 (32)	268.58 (22)	103.99 (58.65, 184.40)
	240	275.05 (45)	423.17 (21)	65.00 (38.41, 110.00)
TDF	120	66.92 (33)	90.29 (29)	74.11 (62.99, 87.21)
– EFV	240	69.36 (44)	95.90 (16)	72.33 (51.41, 101.77)
+ EFV	240	82.53 (50)	82.17 (41)	100.44 (90.27, 111.77)

[a]EFV is taken in the evening, so C_{12h} concentrations are presented instead of C_{pre} concentrations. [b]At Week 2. [c]At Week 0.
ARV, antiretrovirals; CI, confidence interval; DRV, darunavir; EFV, efavirenz; FDV, faldaprevir; gMean, geometric mean; GMR, geometric mean ratio; RAL, raltegravir; TDF, tenofovir.

FIGURE 2. ARV trough concentrations over time



DRV, darunavir; EFV, efavirenz; FDV, faldaprevir; RAL, raltegravir; TDF, tenofovir.

EFFECT OF ARVs ON FDV

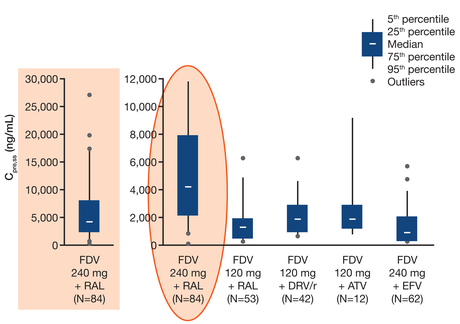
- The effects of ARVs on steady-state FDV trough concentrations are summarized in **Table 3** and **Figure 3**
- No consistent effects on FDV trough concentrations were observed in patients who received RAL-based ART
- FDV trough levels in patients who received FDV 120 mg with a DRV/r- or ATV/r-based ARV regimen were 1.8–1.9-fold higher than trough levels in patients who received RAL-based ART or in HCV mono-infected patients with similar demographic characteristics
- FDV trough levels in patients who received FDV 240 mg with an EFV-based ARV regimen
  - Were lower compared with trough levels in patients who received FDV 240 mg with RAL-based ART (GMR 0.19) or HCV mono-infected patients (GMR 0.25) with similar demographic characteristics
  - Appeared to be comparable with FDV trough levels in patients who received FDV 120 mg with RAL-based ART

TABLE 3. Comparison of mean steady-state $C_{pre,ss}$ of FDV with and without ARVs

FDV dose ARV	FDV$_{pre,ss}$, ng/mL[a] STARTVerso4, with ARV, gMean (% gCV)	FDV$_{pre,ss}$, ng/mL[a] Study 1220.47, without ARV,[b] gMean (% gCV)	GMR vs with RAL	GMR vs no ARV[b]
FDV 120 mg			NA	NA
DRV/r (N=42)	1,920 (72)	1,100 (103) [N=736]	1.8	1.8
ATV/r (N=12)	2,110 (71)		1.9	1.9
RAL (N=53)	1,240 (92)		NA	1.1
FDV 240 mg			NA	NA
EFV (N=62)	1,050 (114)	5,580 (125) [N=630]	0.25	0.19
RAL (N=84)	4,260 (122)		NA	0.76

[a]Pooled $C_{pre,ss}$ from Week 1 to Week 12 samples; [b]Data from non-Asian HCV mono-infected patients in study 1220.47. Results of cross-study comparisons should be interpreted with caution.
ARV, antiretrovirals; ATV, atazanavir; $C_{pre,ss}$, steady-state pre-dose concentration; gCV, coefficient of variation; DRV, darunavir; EFV, efavirenz; FDV, faldaprevir; gMean, geometric mean; GMR, geometric mean ratio; NA, not applicable; RAL, raltegravir.

FIGURE 3. Pooled FDV steady-state trough concentrations by treatment group and ARV backbone



ARV, antiretrovirals; ATV, atazanavir; $C_{pre,ss}$, steady-state pre-dose concentration; DRV, darunavir; EFV, efavirenz; FDV, faldaprevir; r, ritonavir; RAL, raltegravir.

IMPACT OF PK EFFECTS ON SAFETY AND EFFICACY

- Overall, the safety profile of FDV in HIV and HCV GT-1 co-infected patients was similar to that observed in HCV GT-1 mono-infected patients
  - Results are presented in oral presentation 23[4]
- There was no apparent increase in the incidence of gastrointestinal events with the addition of FDV to DRV/r- or ATV/r-based ART
- Among patients receiving FDV 240 mg with EFV, 62% achieved SVR12 compared with 81% of patients receiving FDV 240 mg without EFV and 71% of patients receiving FDV 120 mg
  - Exploratory multivariate logistic regression did not identify any statistically significant association between ART and SVR12 after adjusting for GT-1 subtype, IL28B, baseline viral load, and age category

CONCLUSIONS

- In this analysis of data from STARTVerso4, consistent with observations from studies in healthy volunteers[3], FDV had no clinically relevant effect on the studied ARVs in patients co-infected with HIV and HCV
- The safety profile of FDV + PR with concomitant ART was consistent with the overall safety profile of FDV + PR and with the safety profile of the studied ARVs
- These STARTVerso4 data indicate that FDV 120 mg or 240 mg can be safely co-administered in combination with ART in HIV/HCV co-infected patients without the need for ARV dose modification
  - These results support the use of the FDV 120 mg dose in this population

REFERENCES: 1. White PW, et al. *Antimicrob Agents Chemother* 2010;54:4611–4618. **2.** Sabo J, et al. ICAAC 2012; Poster A-1248. **3.** Sabo J, et al. CROI 2013; Oral 35. **4.** Dieterich D, et al. CROI 2014; Oral 23. **5.** Nelson M, et al. CROI 2014; Poster 499.

ACKNOWLEDGMENTS

We thank the patients, the investigators, and all of our colleagues at Boehringer Ingelheim who worked to provide the data reported here

Brazil
Carlos Eduardo Brandão Mello
Raymundo Ferreira Filho
Paulo Ferreira
Juvencio Furtado
Beatriz Grinsztejn
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Gerald Pierone
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Michael Somero
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Andrew Talal
Kristen Marks

Medical writing assistance, supported by Boehringer Ingelheim, was provided by Esther Race of Choice Healthcare Solutions during preparation of this poster

DISCLOSURES

The authors report the following disclosures: Abbtile (JKR, JAP, PI, DD), BI (JKR, M-AV, JM, MP, JAP, PI, PM, RV, DD), Bioxxo (JKR), BMS (JKR, M-AV, MP, JAP, PI, DD), Gilead (JKR, M-AV, JM, MP, JAP, PI, DD), GSK (M-AV, MP, JAP), Ionnis (DD), Janssen (JKR, M-AV, JM, MP, JAP, PI), Medscape (JKR), Merck (JKR, M-AV, MP, JAP, PI, DD), Novartis (MP), Pfizer (JAP), Roche (M-AV, MP, JAP, PI), Tobira (JKR), Vertex (JKR, MP), VIV (JKR, MP, JAP), and ViroBlock (DK)

This study was funded by Boehringer Ingelheim

This presentation includes discussion of investigational drugs not approved for use in humans