EFFECT OF FALDAPREVIR ON ATAZANAVIR PHARMACOKINETICS IN PATIENTS WITH HIV/HCV CO-INFECTION

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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; ritonavir boosted atazanavir (ATV/r) is an inhibitor of CYP3A4
- In healthy subjects, FDV had no clinically relevant effect on the pharmacokinetics (PK) of tenofovir, darunavir, raltegravir, and efavirenz[3]
- 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 effect of FDV on the PK of ATV and the effect of ATV/r on FDV in STARTVerso4

OBJECTIVES

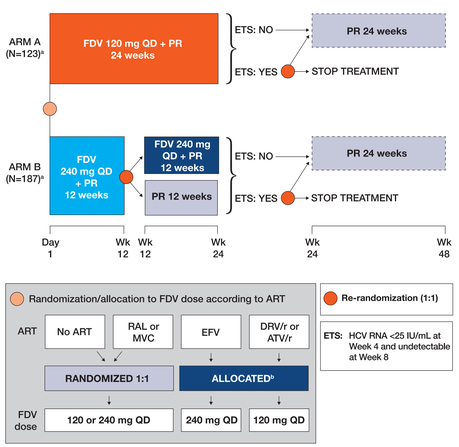
- To assess the effect of FDV on the steady-state PK of ATV in individuals co-infected with HCV and HIV

METHODS

TRIAL DESIGN

- STARTVerso4 was a multicenter, open-label, Phase III study in subjects co-infected with HCV GT-1 and HIV-1 (**Figure 1**)
- Individuals receiving ATV/r-based ART were assigned to receive FDV 120 mg QD + PR for 24 weeks
- Individuals on an ATV/r regimen with baseline bilirubin levels >2.5 x ULN were excluded since both ATV and FDV are inhibitors of UGT1A1
- The primary endpoint was SVR12
  - Primary results are presented in oral presentation 1493[4]

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

- Blood samples were collected for PK analyses over a 24-hour dosing interval on Day 1 (before HCV therapy) and after 2 weeks of treatment with FDV
- Concentrations of FDV, ATV, and ritonavir 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

SAFETY AND TOLERABILITY EVALUATION

- Safety and tolerability were evaluated throughout the study
- Safety endpoints included:
  - Occurrence of any adverse events (AEs), AEs leading to treatment discontinuation, and serious AEs
  - Changes from baseline in clinical laboratory parameters
  - HIV virologic failure (HIV RNA >200 copies/mL on 2 consecutive visits in individuals who had commenced FDV treatment with HIV RNA <40 c/mL or undetectable)

STATISTICAL ANALYSIS

- For the comparison of ATV PK with and without FDV, 90% confidence intervals (CIs) for the geometric mean (gMean) ratios were calculated for $AUC_{0-24h,ss}$ [area under the plasma concentration–time curve at steady state over a 24 hour dosing interval], $C_{max,ss}$ [maximum plasma concentration at steady state], and $C_{24h,ss}$ [plasma concentration at 24 hours post dose at steady state]
- The effect of ATV/r on FDV PK was evaluated by comparison with historical data from an HCV mono-infected population treated with FDV 120 mg + PR in a Phase II study (Study 1220.5)
- Safety data were analyzed using descriptive statistics

RESULTS

SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

- Among 308 individuals treated in STARTVerso4, 123 received FDV 120 mg + PR:
  - 12 of these were on ATV/r-based ART and were included in the ATV PK analysis
- Baseline characteristics are shown in **Table 1**

TABLE 1. Demographics and baseline characteristics

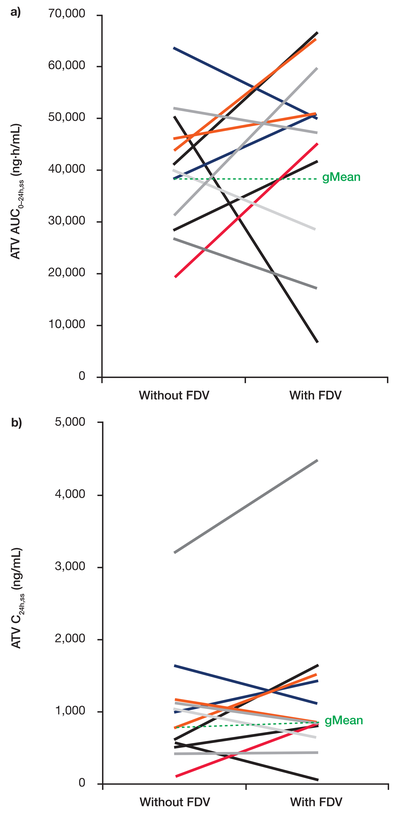
	PK substudy FDV 120 mg + PR with ATV/r (N=12)
Male, n (%)	9 (75)
Race, n (%)	
White	10 (83.3)
Black or African American	2 (16.7)
Mean age, years (SD)	48.1 (5.0)
Mean BMI, kg/m² (SD)	25.6 (6.8)
Cirrhosis,[a] n (%)	1 (8.3)
Mean baseline HCV RNA, log_{10} IU/mL (SD)	6.7 (0.59)
HIV RNA (copies/mL) ≥40, n (%)	1 (8.3)
Mean CD4+ cell count, cells/mm³ (SD)	498.1 (225.3)

[a]Cirrhosis was determined by the investigator based on fibroscan, biopsy, and/or other clinical parameters.
ATV/r, atazanavir/ritonavir; BMI, body mass index; FDV, faldaprevir; PK, pharmacokinetics; PR, pegylated interferon α-2a and ribavirin; SD, standard deviation.

PHARMACOKINETICS

- Steady-state PK parameters for ATV were comparable with and without FDV treatment (**Table 2** and **Figure 2**)
  - Inter-subject variability was higher with FDV vs without FDV
- Steady-state PK parameters for ritonavir were comparable with and without co-administration of FDV (**Table 3**)
- Steady-state FDV AUC_{0-24h}, C_{max}, and C_{24h} were higher in the presence of ATV/r than with FDV alone (**Table 4**)

FIGURE 2. Individual PK parameters for ATV without and with FDV 120 mg



ATV, atazanavir; $AUC_{0-24h,ss}$, area under the concentration–time curve from zero to 24 hours at steady state; $C_{24h,ss}$, plasma concentration at 24 hours at steady state; FDV, faldaprevir; gMean, geometric mean.

TABLE 2. Comparison of mean steady-state PK parameters of ATV before and after administration of FDV

ATV PK parameters (N=12)	Adjusted gMean					
	With FDV	Without FDV	Adjusted GMR (%)	90% CI (%)	gCV%	p-value
$AUC_{0-24h,ss}$, ng·h/mL	38,171	38,128	100.11	69.09, 145.07	56.8	0.158
$C_{max,ss}$, ng/mL	3,529	3,194	102.01	67.25, 154.75	65.1	0.206
$C_{24h,ss}$, ng/mL	863	789	109.33	65.64, 182.08	78.9	0.323
$T_{max,ss}$, h	3.3	2.6	Not determined			

ATV, atazanavir; $AUC_{0-24h,ss}$, area under the concentration–time curve from zero to 24 hours at steady state; $C_{24h,ss}$, plasma concentration at 24 hours at steady state; CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady state; gCV, intra-individual geometric coefficient of variation; FDV, faldaprevir; gMean, geometric mean; GMR, geometric mean ratio; $T_{max,ss}$, time to maximum plasma concentration at steady state.

TABLE 3. Comparison of mean steady-state PK parameters of ritonavir before and after administration of FDV

Ritonavir PK parameters (N=12)	Adjusted gMean					
	With FDV	Without FDV	Adjusted GMR (%)	90% CI (%)	gCV%	p-value
$AUC_{0-24h,ss}$, ng·h/mL	10,296	11,465	89.80	64.54, 124.95	47.4	0.271
$C_{max,ss}$, ng/mL	1,265	1,327	95.30	68.32, 132.94	50.3	0.188
$C_{24h,ss}$, ng/mL	95	87	109.58	72.86, 164.80	60.3	0.287
$T_{max,ss}$, h	3.0	2.7	Not determined			

$AUC_{0-24h,ss}$, area under the concentration–time curve from zero to 24 hours at steady state; $C_{24h,ss}$, plasma concentration at 24 hours at steady state; CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady state; gCV, intra-individual geometric coefficient of variation; FDV, faldaprevir; gMean, geometric mean; GMR, geometric mean ratio; $T_{max,ss}$, time to maximum plasma concentration at steady state.

TABLE 4. Comparison of mean steady-state PK parameters of FDV with and without ATV/r

FDV PK parameters	With ATV/r (STARTVerso4) (N=11)[a] gMean (% gCV)	Without ATV/r[b] (Study 1220.5) (N=16) gMean (% gCV)	GMR (%)[c]	90% CI (%)[c]
$AUC_{0-24h,ss}$, ng·h/mL	85,100 (72.9)	48,400 (59.6)	176	(1.57, 1.97)
$C_{max,ss}$, ng/mL	6,090 (62.1)	3,640 (62.7)	167	(1.58, 1.78)
$C_{24h,ss}$, ng/mL	2,210 (91.8)	1,010 (82.2)	219	(1.96, 2.45)
$T_{max,ss}$, h	3.15 (79.8)	3.76 (25.7)	Not determined	

[a]For 1 subject no FDV PK data were available. [b]Data from the FDV 120 mg arm of study 1220.5. [c]GMR and CI are illustrative. Results of cross-study comparisons should be interpreted with caution.
ATV/r, atazanavir/ritonavir; $AUC_{0-24h,ss}$, area under the concentration–time curve from zero to 24 hours at steady state; $C_{24h,ss}$, plasma concentration at 24 hours at steady state; CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady state; gCV, intra-individual coefficient of variation; FDV, faldaprevir; gMean, geometric mean; GMR, geometric mean ratio; $T_{max,ss}$, time to maximum plasma concentration at steady state.

SAFETY AND TOLERABILITY

- The safety profile of FDV in this HIV/HCV co-infected population was similar to that observed in HCV mono-infected populations[4]
- The AE profile was generally comparable between the ATV/r subgroup and the FDV 120 mg study arm (**Table 5**)
- The incidence of bilirubin >2.5 x ULN was higher in the ATV/r subgroup than in the FDV 120 mg study arm (**Table 5**)
- However, mean increases in total bilirubin were not markedly different
  - Mean increase from baseline to Week 4, 0.9 mg/dL for the FDV 120 mg arm and 1.1 mg/dL in the ATV/r subgroup
  - Increases were mainly unconjugated bilirubin (0.7 mg/dL and 1.0 mg/dL, respectively)
- There were 5 cases of jaundice in the FDV 120 mg study arm and 2 in the ATV/r subgroup

TABLE 5. Summary of AEs

N (%)	ATV/r subgroup FDV 120 mg + PR with ATV/r (N=12)	FDV 120 mg + PR (with other ART or no ART) (N=111)
Any AE	11 (92)	108 (97)
Serious AEs	2 (17)	15 (14)
AEs leading to discontinuation of any HCV study medication	0	10 (9)
DAIDS grade 3 or 4 AEs	2 (17)	22 (20)
DAIDS grade 4 AEs	0	5 (4.5)
Total bilirubin (>2.5 x ULN)[a]	7 (58)	10 (10)
Jaundice	2 (17)	5 (45)

[a]DAIDS grade 3. Elevations in bilirubin were not associated with increases in ALT, AST, or other markers of liver injury.
AE, adverse event; ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; DAIDS, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; FDV, faldaprevir; PR, pegylated interferon α-2a and ribavirin; ULN, upper limit normal.

CONCLUSION

- Co-administration of FDV 120 mg with ATV/r:
  - Did not result in any clinically relevant change in the steady-state AUC_{0-24h}, C_{max}, or C_{24h} of ATV (GMR 1.00, 1.02, and 1.09, respectively)
  - Resulted in increased FDV steady-state AUC_{0-24h}, C_{max}, and C_{24h} (GMR 1.76, 1.67, and 2.19, respectively, based on cross-study comparison)
- The safety profile of FDV + PR with concomitant ATV/r therapy was consistent with the overall safety profile of FDV + PR
- These STARTVerso4 data show that FDV 120 mg QD and ATV/r can be safely co-administered without dose modification in HIV/HCV co-infected individuals
  - 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; Poster 35. **4.** Dieterich D, et al. CROI 2014; Oral 1493.

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