Company Updates on Clinical Pharmacology and DDI Profile of HCV Drugs Recently Launched and in the Pipeline: Focus on DDIs between Daclatasvir and HIV Medicines

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Disclosures

- Timothy Eley is a full time employee and stockholder of Bristol-Myers Squibb

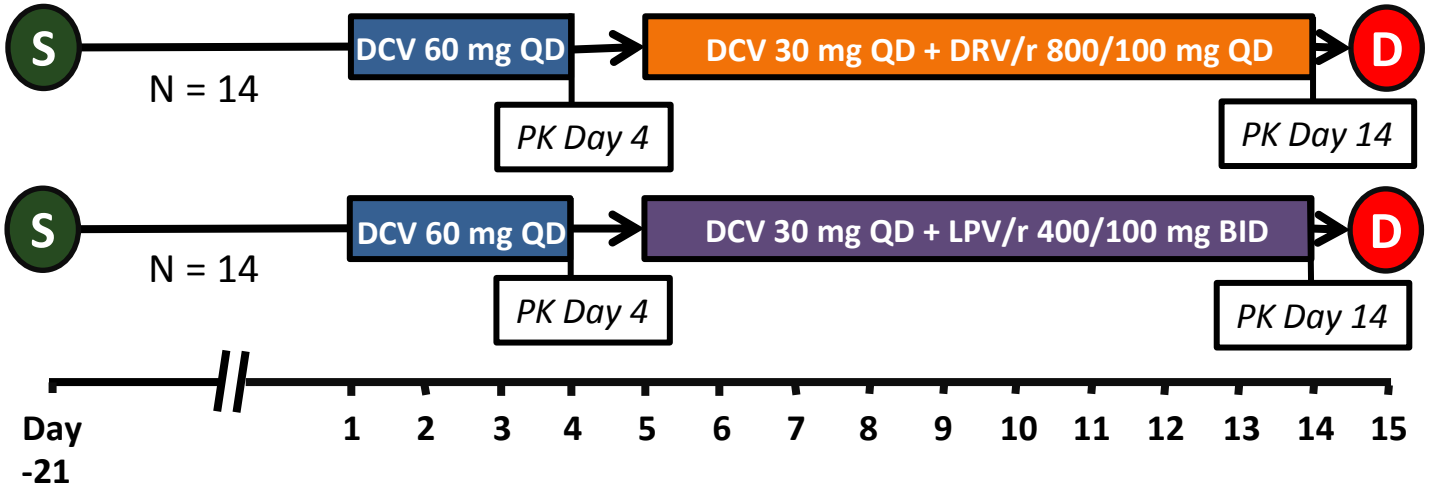
New DDI Data for Daclatasvir with HIV Meds

- AI444093 Effect of DRV/r and LPV/r on DCV in Healthy subjects
- AI444043 Effect of DCV on RTV-boosted DRV and LPV in HCV-HIV coinfected subjects (substudy)
  - Presented together at this meeting: Gandhi et al, Poster # 80
- AI444273 (ViiV/GSK Study #201102): 2 way DDI between DTG and DCV
  - Presented at this meeting: Song et al, Poster # 79

Background for AI444093/043

- Daclatasvir (DCV) is a pangenotypic, once-daily oral inhibitor of HCV NS5A approved in Europe, Japan, among multiple nations and under regulatory review in the US
- Daclatasvir has achieved high SVR rates and good tolerability in HCV combination treatment, and has been studied in HIV–HCV coinfection in all-oral regimens and with Peg-IFNα/RBV
- Daclatasvir has linear, time-independent pharmacokinetics (PK), is a substrate and inhibitor of P-glycoprotein, a substrate of cytochrome P450 3A4, and an inhibitor of BCRP
- Ritonavir-boosted HIV protease inhibitors well known for CYP3A- and Pgp-mediated drug interactions
- Atazanavir/ritonavir (ATV/r) increased DCV AUC_{tau} 2.1-fold; comparable effects were expected with DRV/r and LPV/r

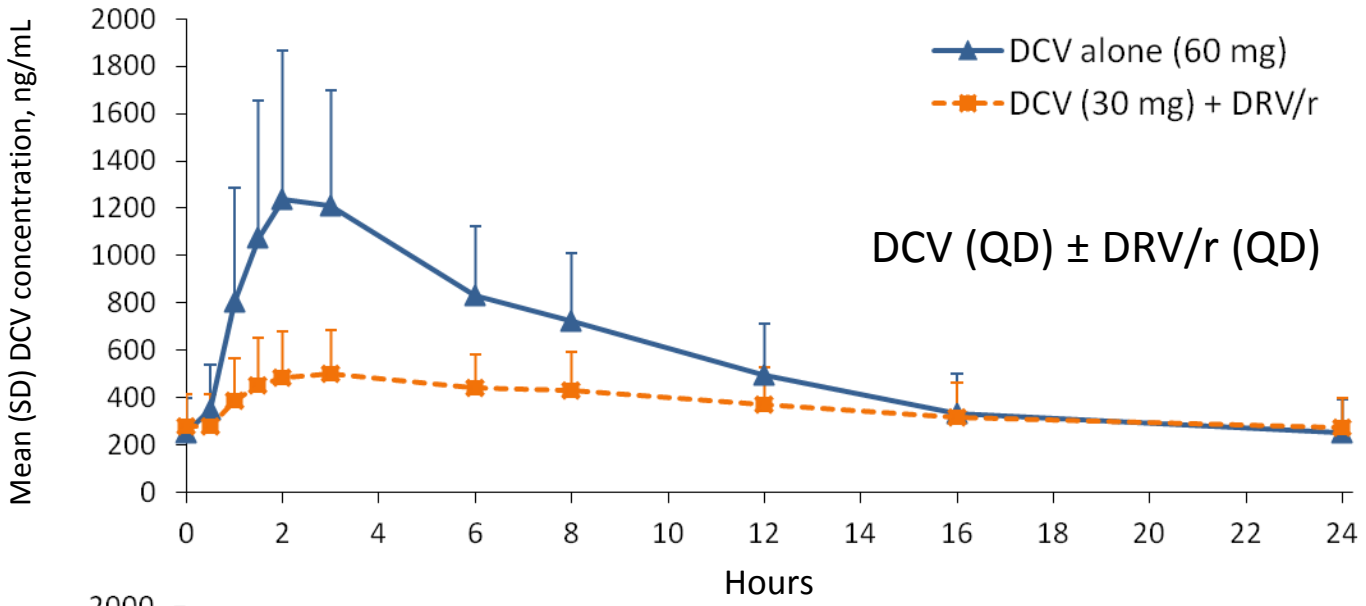
Effect of DRV/r or LPV/r on DCV PK: AI444-093 Study Design

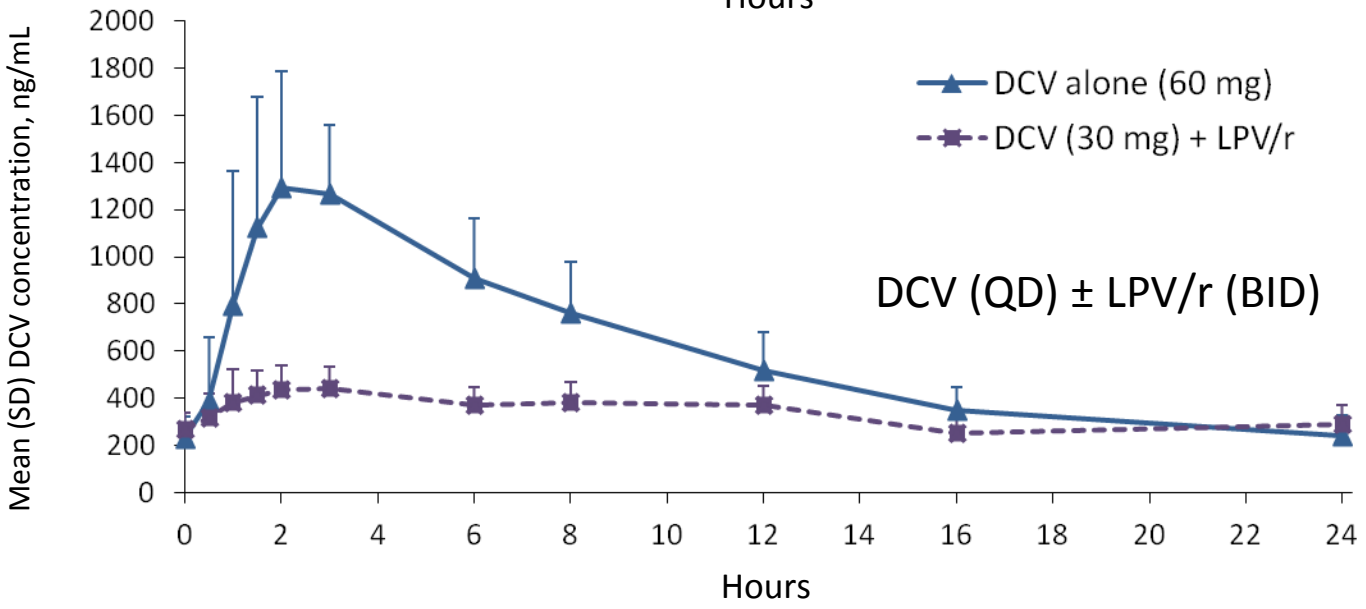


D, study discharge; PK, 12-hour or 24-hour intensive PK assessment; S, screening visit.

- A phase 1, non-randomized, open-label, one-way drug interaction study (AI444-093) in healthy volunteers
- Eligible subjects were healthy adults aged 18–49 years; body mass index 18.0–32.0
- Subjects received DCV 60 mg once daily for 4 days, then DCV 30 mg once daily with either DRV/r (800/100 mg once daily) or LPV/r (400/100 mg twice daily) on Days 5–14
- 24-hour PK sampling was conducted on Days 4 (DCV alone) and 14 (DCV + PI/r)

AI444-093: DCV Concentration–Time Profiles



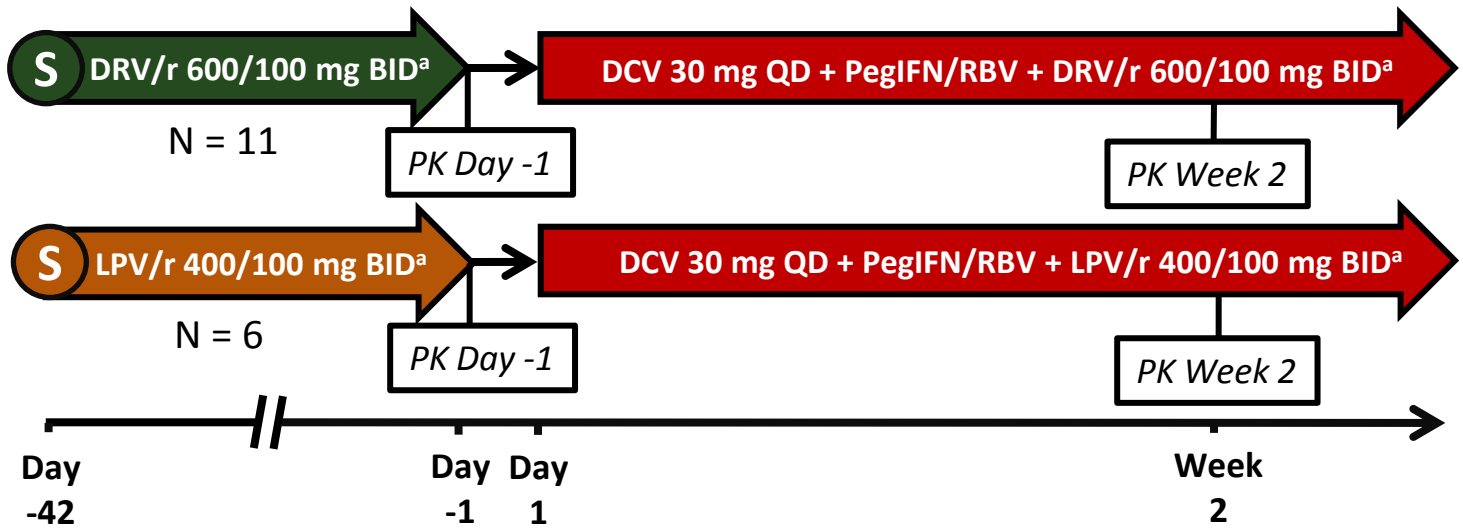


AI444-093: Statistical Analysis of DCV PK ± PI/r

Observed, adjusted GM (90% CI)	DRV/r (800/100 mg QD)			LPV/r (400/100 mg BID)		
	DCV 60 mg	DCV 30 mg + DRV/r	**Adjusted GMR (90% CI)**	DCV 60 mg	DCV 30 mg + LPV/r	**Adjusted GMR (90% CI)**
C_{max}, ng/mL	1335 (1121, 1589)	512 (433, 606)	**0.384 (0.348, 0.423)**	1412 (1249, 1596)	475 (427, 529)	**0.337 (0.306, 0.371)**
AUC_{tau}, ng·h/mL	12677 (10500, 15305)	8910 (7404, 10721)	**0.703 (0.658, 0.750)**	13799 (12168, 15649)	7961 (7132, 8886)	**0.577 (0.535, 0.622)**
Dose-normalized, adjusted GM (90% CI)						
C_{max}/D, ng/mL/mg	22.2 (18.7, 26.5)	17.1 (14.4, 20.2)	**0.768 (0.697, 0.846)**	23.5 (20.8, 26.6)	15.8 (14.2, 17.6)	**0.673 (0.611, 0.742)**
AUC_{tau}/D, (ng·h/mL)/mg	211 (175, 255)	297 (247, 357)	**1.406 (1.317, 1.501)**	230 (203, 261)	265 (238, 296)	**1.154 (1.070, 1.244)**

- Observed C_{max} and AUC_{tau} for 30 mg DCV administered with DRV/r or LPV/r were lower relative to 60 mg DCV administered alone
- Compared with DCV alone, modest decreases in dose-normalized DCV Cmax (23–33%) and modest increases in dose-normalized DCV AUC_{tau} (15–41%) were observed with concomitant DRV/r or LPV/r

Effect of DCV on DRV or LPV PK: AI444-043 Substudy Design

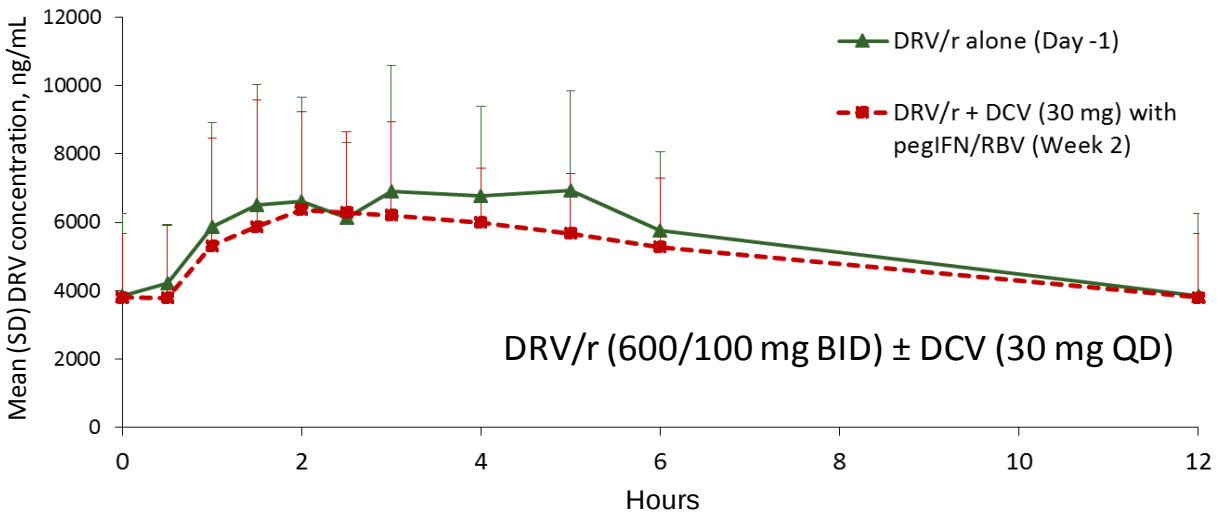


PK, 12-hour or 24-hour intensive PK assessment; S, screening visit.
[a] with nucleoside analogs.

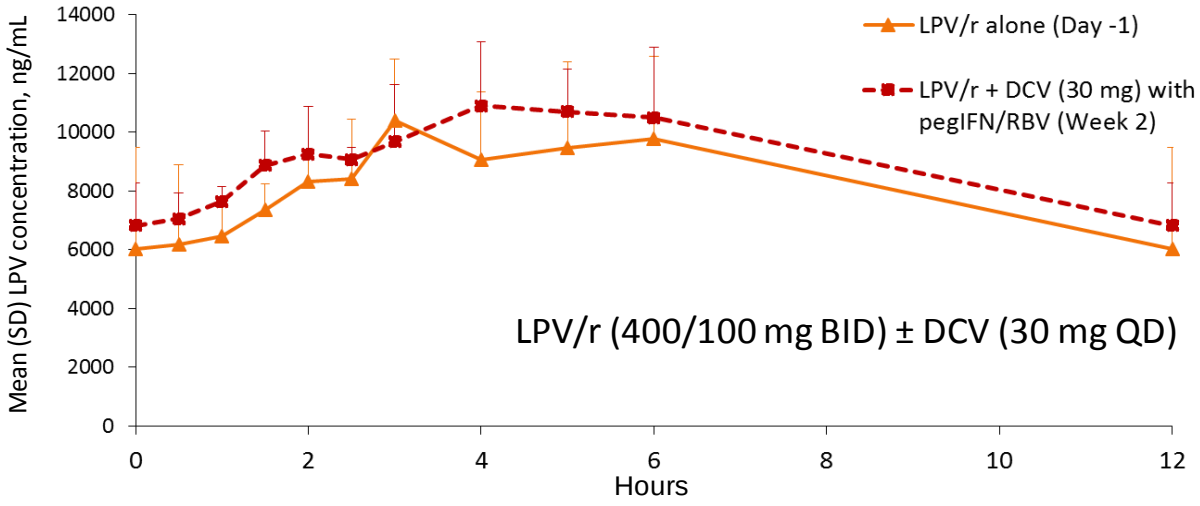
- A site-specific substudy of study AI444-043 in HIV–HCV (GT 1) coinfected adults naive to HCV therapy
- Eligible patients for AI444-043 were either
  - on suppressive cART (< 40 HIV RNA copies/mL at screening) with CD4 ≥ 100 cells/mm^3,or
  - not on cART with CD4 ≥ 350 cells/mm^3
- Patients receiving DRV/r (600/100 mg BID) or LPV/r (400/100 mg BID) were separately consented to 12-hour PK sampling on study Day -1 (before study therapy) and at the Week 2 study visit after receiving ≈14 days of DCV 30 mg plus pegIFN/RBV

AI444-043: Concentration–Time Profiles

(A)



(B)



AI444-043 Substudy: Statistical Analysis of DRV and LPV PK ± DCV

Adjusted GM	DRV/r (600/100 mg BID)			LPV/r (400/100 mg BID)		
	Without DCV	With DCV	**Adjusted GMR (90% CI)**	Without DCV	With DCV	**Adjusted GMR (90% CI)**
C_{max}, ng/mL	7582	7366	**0.972 (0.80, 1.17)**	10123	12332	**1.218 (1.06, 1.41)**
AUC_{tau}, ng·h/mL	59020	53112	**0.900 (0.73, 1.11)**	92599	106517	**1.150 (0.77, 1.72)**
C_{tau}, ng/mL	3062	3011	**0.983 (0.67, 1.44)**	4430	6801	**1.535 (0.46, 5.07)**

CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio.

- No clinically relevant changes in DRV or LPV parameters were noted
  - The estimated effect of DCV on LPV C_{max} and AUC_{tau} is less than that reported for LPV/r administration with food[1]
- Confidence intervals for LPV parameters are broad due to small sample size
  - Mean LPV concentration–time plot does not indicate a substantial effect of DCV on LPV C_{tau}

1. Kaletra EU Summary of Product Characteristics. Jan 2015

Background for DTG-DCV DDI

- Dolutegravir (DTG) is an HIV integrase strand transfer inhibitor approved for use in combination with other antiretrovirals for the treatment of HIV-1 infection in adults and adolescents[1]
- DTG is metabolized primarily through UGT1A1 with a minor component (~10%) via cytochrome P450 (CYP) 3A4 and is a substrate P-gp and BCRP
- *In vitro*, DTG demonstrates minimal or no direct inhibition of CYP isozymes and P-gp and is not an inducer of CYP3A4
- DCV is a substrate of CYP3A4 and P-gp and an inhibitor of P-gp and BCRP

Two-Way DDI Between DCV and DTG: AI444-273 Study Design

Sequence	Period 1	Period 2	Period 3
1 (N=6)	DTG 50 mg q24h for 5 days	DCV 60 mg q24h for 5 days	DTG 50 mg + DCV 60 mg q24h for 5 days
2 (N=6)	DCV 60 mg q24h for 5 days	DTG 50 mg q24h for 5 days	DTG 50 mg + DCV 60 mg q24h for 5 days

- Single-center, open-label, 3-period crossover study in healthy adult subjects
- Twelve eligible subjects were randomized into 1 of 2 sequences
- Washout period of ≥7 days between Period 1 and Period 2; none between Period 2 and Period 3
- 24-hour PK sampling was conducted on the last day of each period

AI444-273: DTG and DCV Concentration–Time Profiles

Figure 1. Mean (±SD) DTG Concentration-Time Profiles

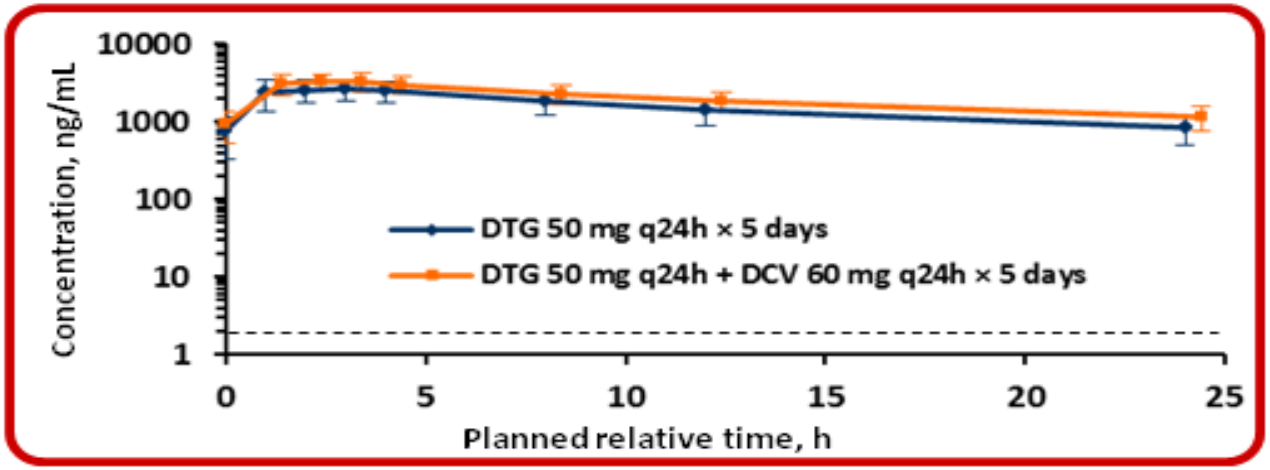
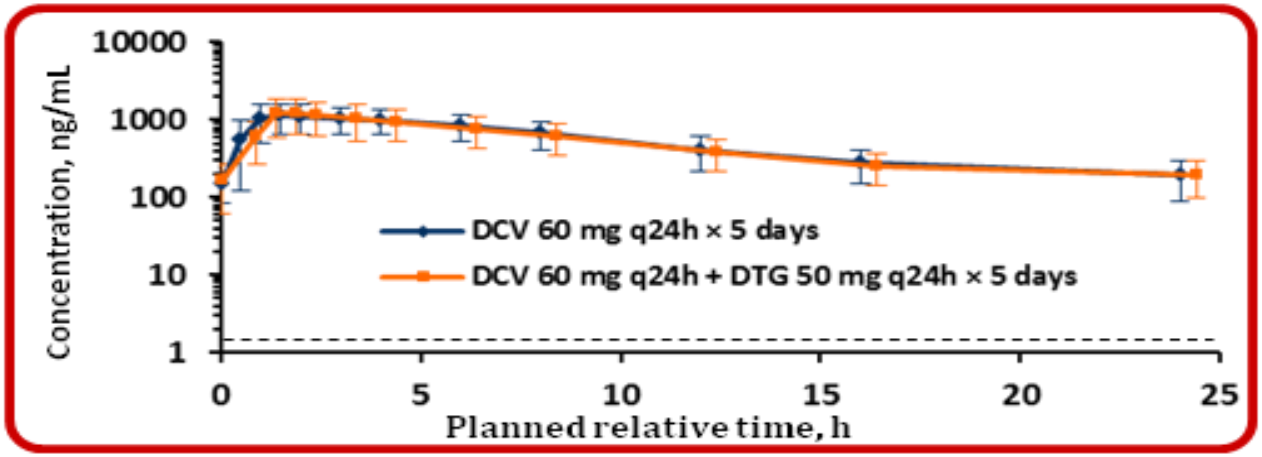


Figure 2. Mean (±SD) DCV Concentration-Time Profiles



AI444273: Statistical Analysis

PK Parameter	GLS Mean Ratio (90% CI)	
	DTG + DCV vs DTG alone	DCV + DTG vs DCV alone
AUC(0-τ) (µg*hr/mL)	1.33 (1.11, 1.59)	0.978 (0.831, 1.15)
Cmax (µg/mL)	1.29 (1.07, 1.57)	1.03 (0.843, 1.25)
Cτ (µg/mL)	1.45 (1.25, 1.68)	1.06 (0.876, 1.29)

Conclusions

- **The standard 60 mg once-daily DCV dose is optimal for patients receiving DRV/r or LPV/r**
  - Dose-normalized increases in DCV AUCtau were observed when DCV was coadministered with DRV/r (41%) or LPV/r (15%)
  - DCV had no clinically relevant effect on the PK of DRV/r or LPV/r in HIV–HCV coinfected patients on cART

- **DTG and DCV can be coadministered without dose adjustment**
  - DTG had no apparent effect on DCV and DCV increased DTG AUC ~33%
  - DCV and DTG had no clinically relevant effect on the PK of the other when coadministered

Acknowledgments

- All study participants and investigation site staff

- Authors of Gandhi, Adamczyk, Wang et al, Poster 80

- Authors of Song, Jerva, Zong, et al, Poster 79