Pharmacokinetics of Darunavir, Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir and Ribavirin in Adults Infected with Hepatitis C Virus (HCV) Genotype 1 and Human Immunodeficiency Virus (HIV)

Jennifer R King, Amit Khatri, Roger Trinh, Bifeng Ding, Jiuhong Zha and Rajeev Menon

AbbVie Inc.

17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

Washington D.C., June 8-10, 2016

abbvie

Disclaimers

- All the authors are AbbVie employees and may hold AbbVie stocks/options.
- The design, study conduct, analyses and financial support for the clinical trial were provided by AbbVie.

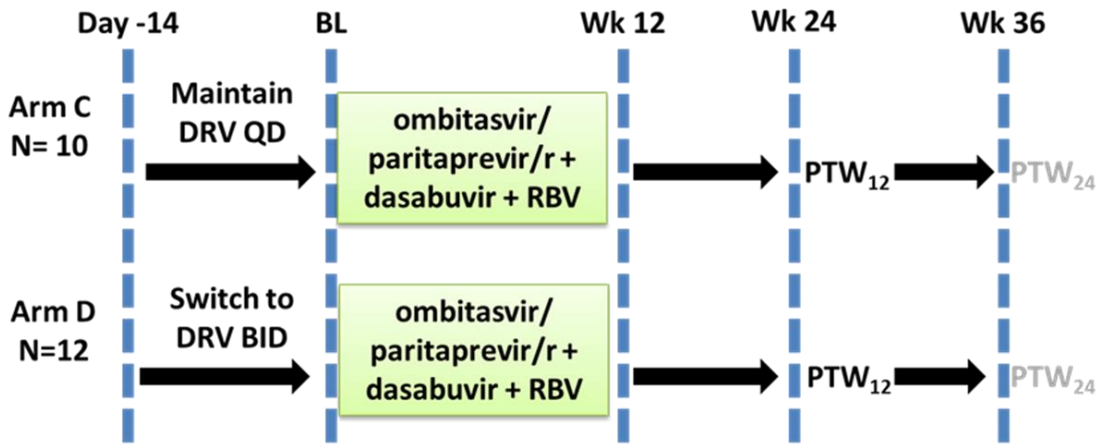
Background

- AbbVie's three direct acting antiviral (**3D**) regimen of ombitasvir (OBV), paritaprevir (PTV) co-dosed with ritonavir (r), and dasabuvir (DSV) with and without ribavirin (RBV) is approved for the treatment of chronic HCV genotype (GT) 1 infection in the US and EU among other countries/regions.
- The 2D regimen of OBV and PTV/r is approved for HCV GT1 in Japan and for the treatment of HCV GT4 among many countries/regions
- The 2D and 3D regimens are also approved for HCV/HIV-1 co-infected patients
- Co-administration of 3D with darunavir (DRV)
  - In healthy volunteers, decreased DRV C_{24} 48% with QD and DRV C_{12} 43% with BID; DRV AUC and C_{max} were comparable (≤ 24% difference)
  - Not recommended in **USPI**
  - 800 mg once daily administered at the same time as OBV/PTV/r + DSV can be used in the absence of extensive PI resistance in **EU SmPC**

TURQUOISE I (Study M14-004)

- Phase 2/3, randomized, open-label multicenter study to assess the safety and efficacy of 3D for 12 or 24 weeks in adults with HCV/HIV co-infection
- Part 1 evaluated a smaller group of subjects on various antiretroviral regimens to determine safety, efficacy and pharmacokinetics prior to dosing a larger group of subjects in Part 2 of the study
  - Part 1a evaluated atazanavir or raltegravir in combination with 3D
  - Part 1b evaluated darunavir 800 mg QD or 600 mg BID with 3D

Part1b: Phase 2 Pilot Cohort



Ombitasvir/paritaprevir/r 25/150/100 mg QD + dasabuvir 250 mg BID + weight based RBV BID

Intensive PK (0, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours post dose) collected at: BL (Day-1) and Week 4

Sparse PK Sampling collected at Day 1 and Weeks 1, 2, 6, 8, 10 and 12

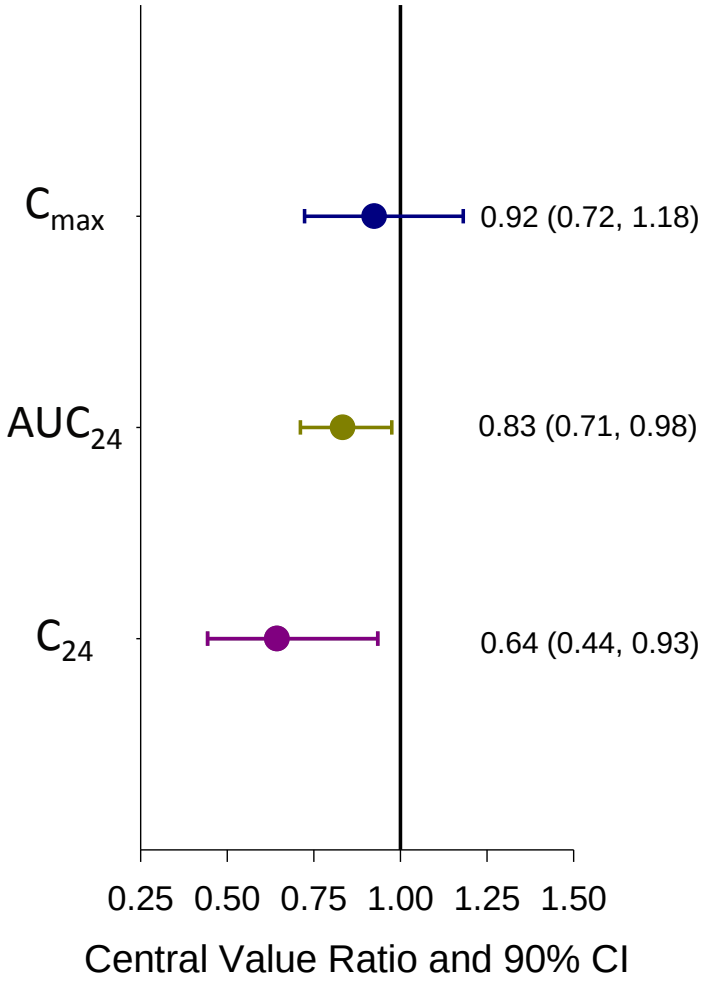
Plasma HIV RNA obtained at Day 1 and Weeks 1, 2, 4, 6, 8, 10 and 12

Patient Demographics

	Arm C: DRV QD (n=10)	Arm D: DRV BID (n=12)
Age (years), median (range)	56 (44-65)	53 (34-68)
Weight (kg), median (range)	77 (61-103)	81 (59-111)
Sex, n (%)	8 Males (80%) 2 Females (20%)	9 Males (75%) 3 Females (25%)
Race, n (%)	7 White (70%) 3 Black (30%)	5 White (42%) 6 Black (50%) 1 Asian (8%)
HCV GT 1 Subtype, n (%)	9 Subtype 1a (90%) 1 Subtype 1b (10%)	6 Subtype 1a (50%) 6 Subtype 1b (50%)
Cirrhosis, n (%)	0 (0%)	3 (25%)

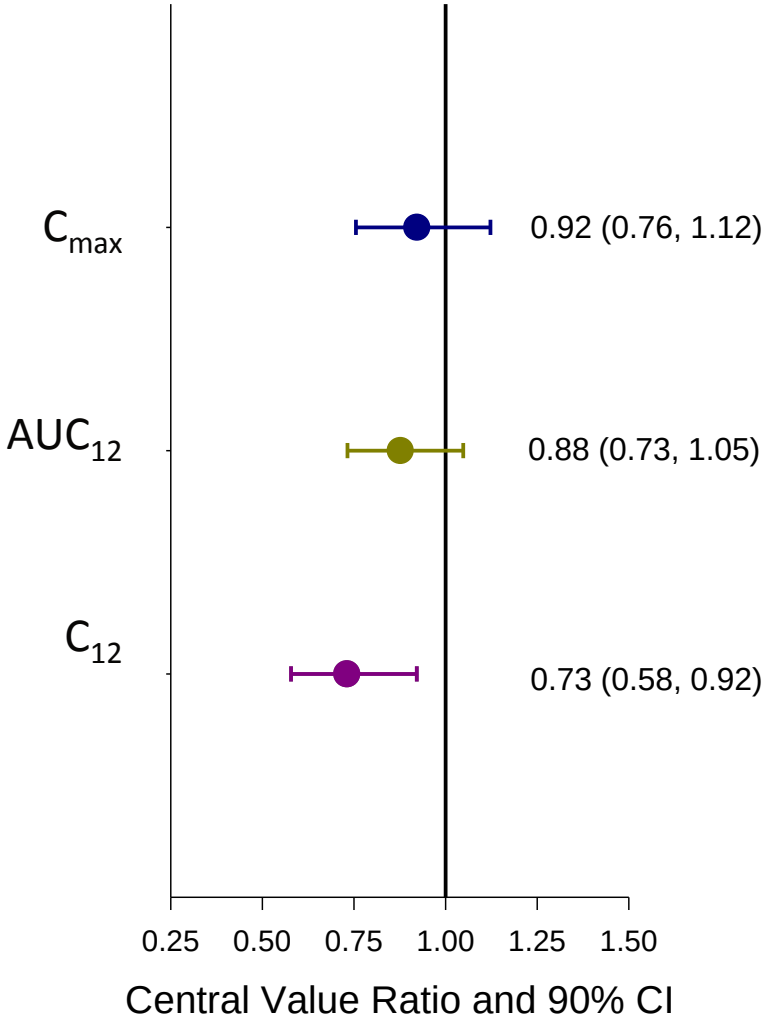
Darunavir 800 mg QD Pharmacokinetic Parameters

	Darunavir Geometric mean (CV%)		
Regimen (n=10)	**C_{max} ng/mL**	**AUC_{24} ng·h/mL**	**C_{24} ng/mL**
Day -1 DRV/r 800/100 mg QD	7376 (24)	86793 (25)	1625 (45)
Week 4 DRV QD + 3D regimen	6816 (30)	72269 (27)	1045 (63)

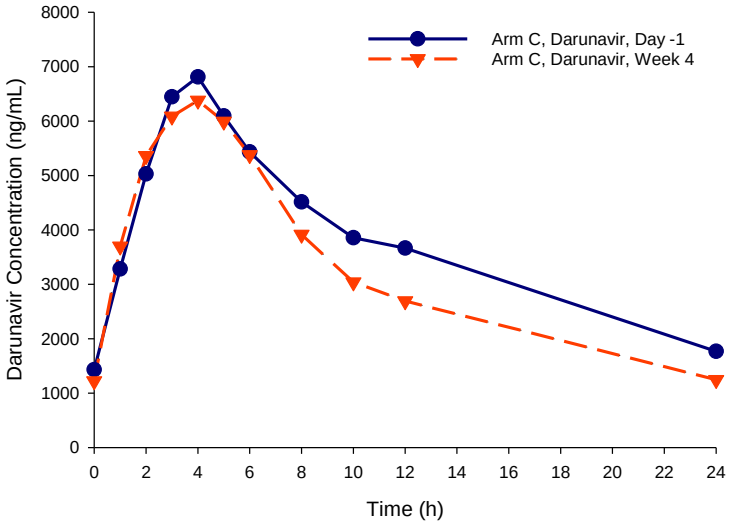


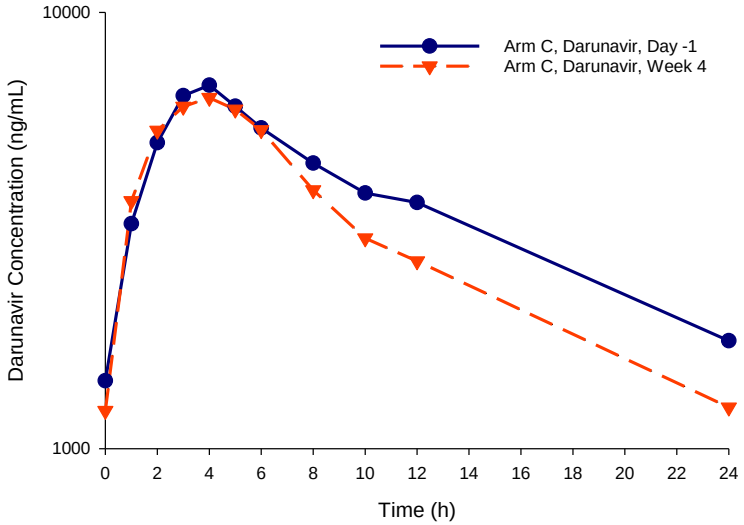
Darunavir 600 mg BID Pharmacokinetic Parameters

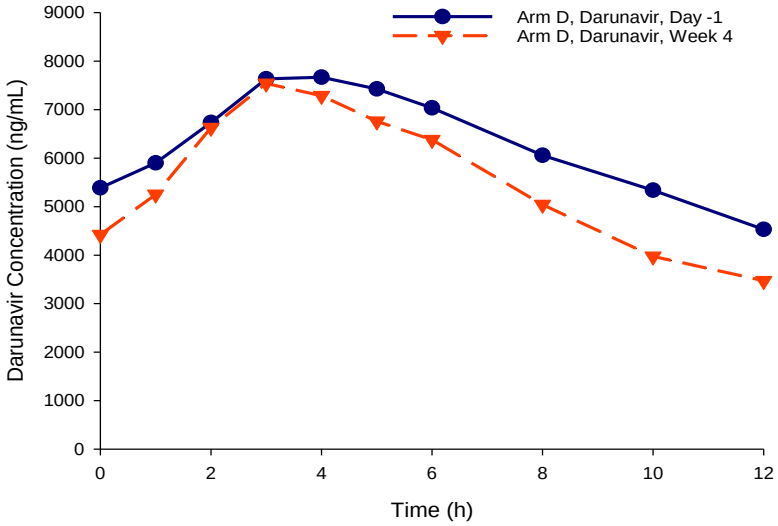
Regimen (n=12)	Darunavir Geometric mean (CV%) C_{max} ng/mL	AUC_{12} ng·h/mL	C_{12} ng/mL
Day -1 DRV/r 600/100 mg BID	8116 (35)	66097 (47)	3549 (62)
Week 4 DRV BID + 3D regimen	7471 (41)	57914 (49)	2590 (67)

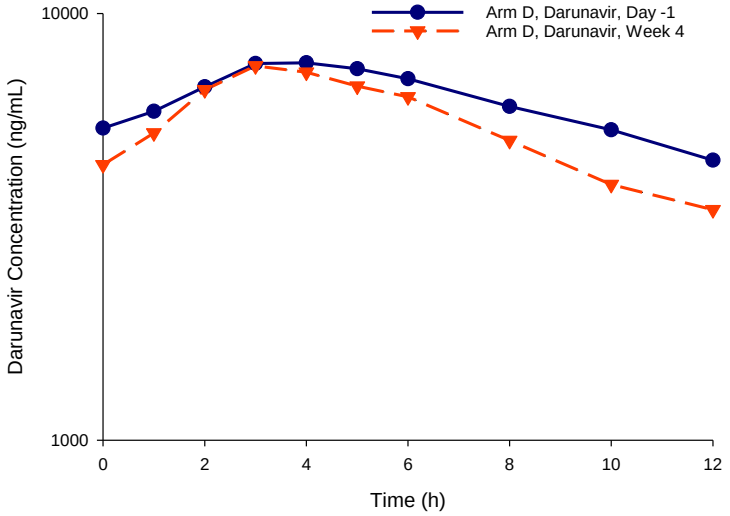


Steady-State DRV Concentration-Time Curves









DRV 800 mg QD with the 3D Regimen in HCV/HIV Co-Infected versus DRV/r 800/100 mg QD in HIV-1 Mono-Infected Adults

Patient Population	N	Darunavir 800 mg QD (Mean ± Standard Deviation)		
		C_{max} (ng/mL)	AUC_{24} (ngxh/mL)	C_{24} (ng/mL)
HCV/HIV co-infected M14-004 Part 1b	10	7211 ± 2155	74916 ± 20029	1244 ± 782
HIV mono-infected[1] (4 weeks of therapy)	9	5471 ± 1320	64230 ± 18210	1440 ± 514
HIV mono-infected[1] (24 weeks of therapy)	13	5804 ± 1558	66950 ± 18610	1644 ± 727
HIV mono-infected[1] (48 weeks of therapy)	10	6756 ± 1683	75620 ± 26440	1447 ± 706

[1]Kakuda et al. J Antimicrob Chemother 2014

- DRV C_{max}, AUC_{24} and C_{24} when administered with 3D in HCV/HIV co-infected patients were comparable (<25% difference) to parameters when DRV/r was administer to HIV mono-infected adults.

DRV 600 mg BID with the 3D Regimen in HCV/HIV Co-Infected versus DRV/r 600/100 mg BID in HIV-1 Mono-Infected Adults

Patient Population	N	Darunavir 600 mg BID (Mean ± Standard Deviation)		
		C_{max} (ng/mL)	AUC_{12} (ngxh/mL)	C_{12} (ng/mL)
HCV/HIV co-infected M14-004 Part 1b	12	8037 ± 3291	65493 ± 32255	3470 ± 2339
HIV mono-infected[2]	32	NA	62360 ± 25020	3559 ± 2385[a]

a. n = 26

[2]*Kakuda et al. AIDS Research and Treatment 2011*

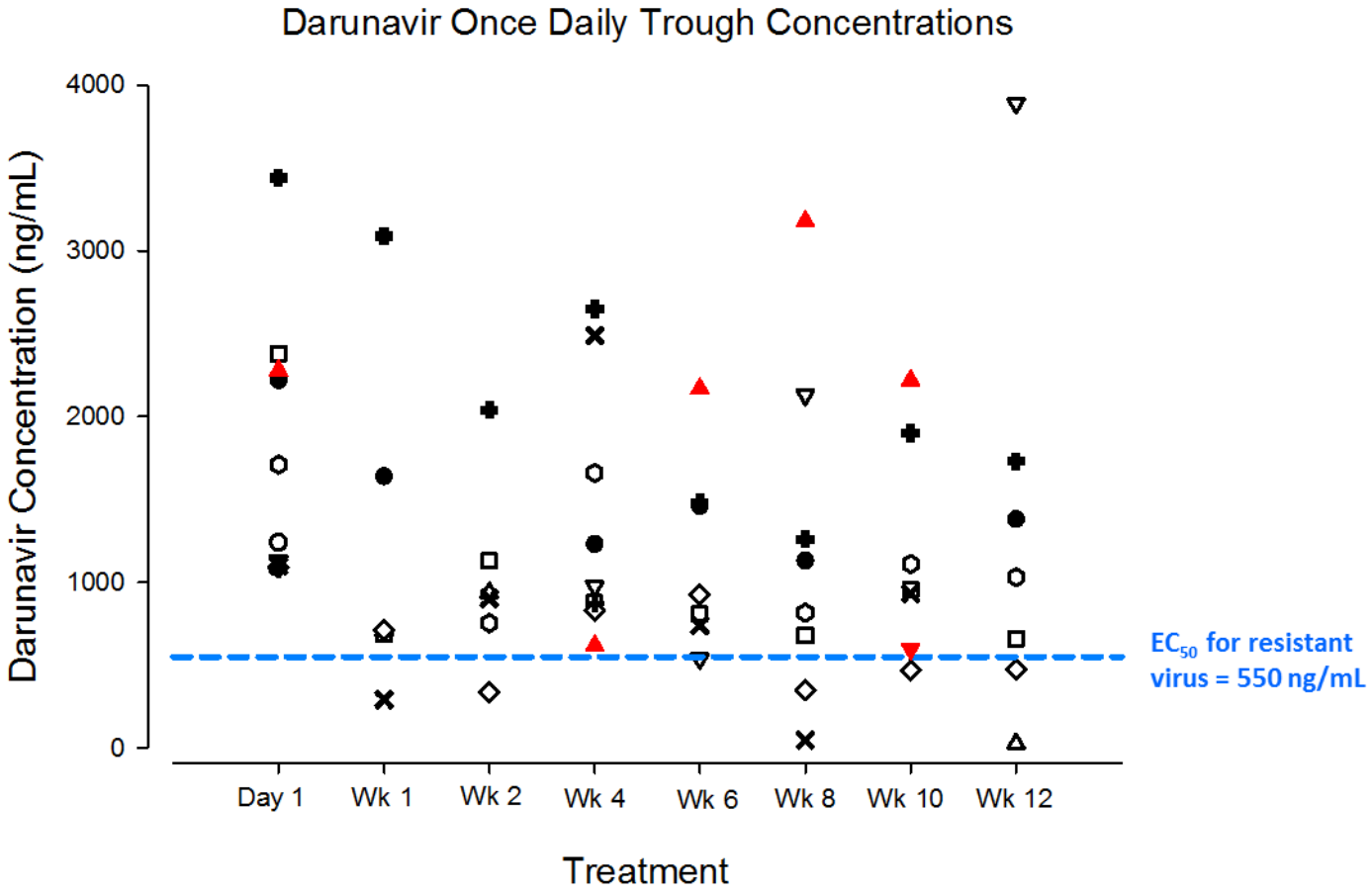
- DRV AUC_{12} and C_{12} when administered with 3D in HCV/HIV co-infected patients were comparable (≤ 5% difference) to parameters when DRV/r was administer to HIV mono-infected adults

Maintenance of Plasma HIV-RNA Suppression

- At least one plasma HIV-1 RNA value ≥ 40 copies/mL and < 200 copies/mL occurred during the treatment period in:
  - 2 of 10 (20%) of subjects receiving DRV QD
  - 3 of 12 (25%) of subjects receiving DRV BID
- The highest HIV-1 RNA during the treatment period was 79 copies/mL in a subject enrolled into DRV QD
- All but one patient (in the DRV BID arm) had HIV-1 RNA suppression at the end of treatment; however, this patient maintained HIV-1 RNA <40 copies/mL at all other visits.
- No subjects in either treatment arm required a switch of their HIV-1 antiretroviral regimen due to loss of plasma HIV-1 RNA suppression.

DRV QD: DRV Trough Concentrations (C_{trough}) Relative to Plasma HIV RNA

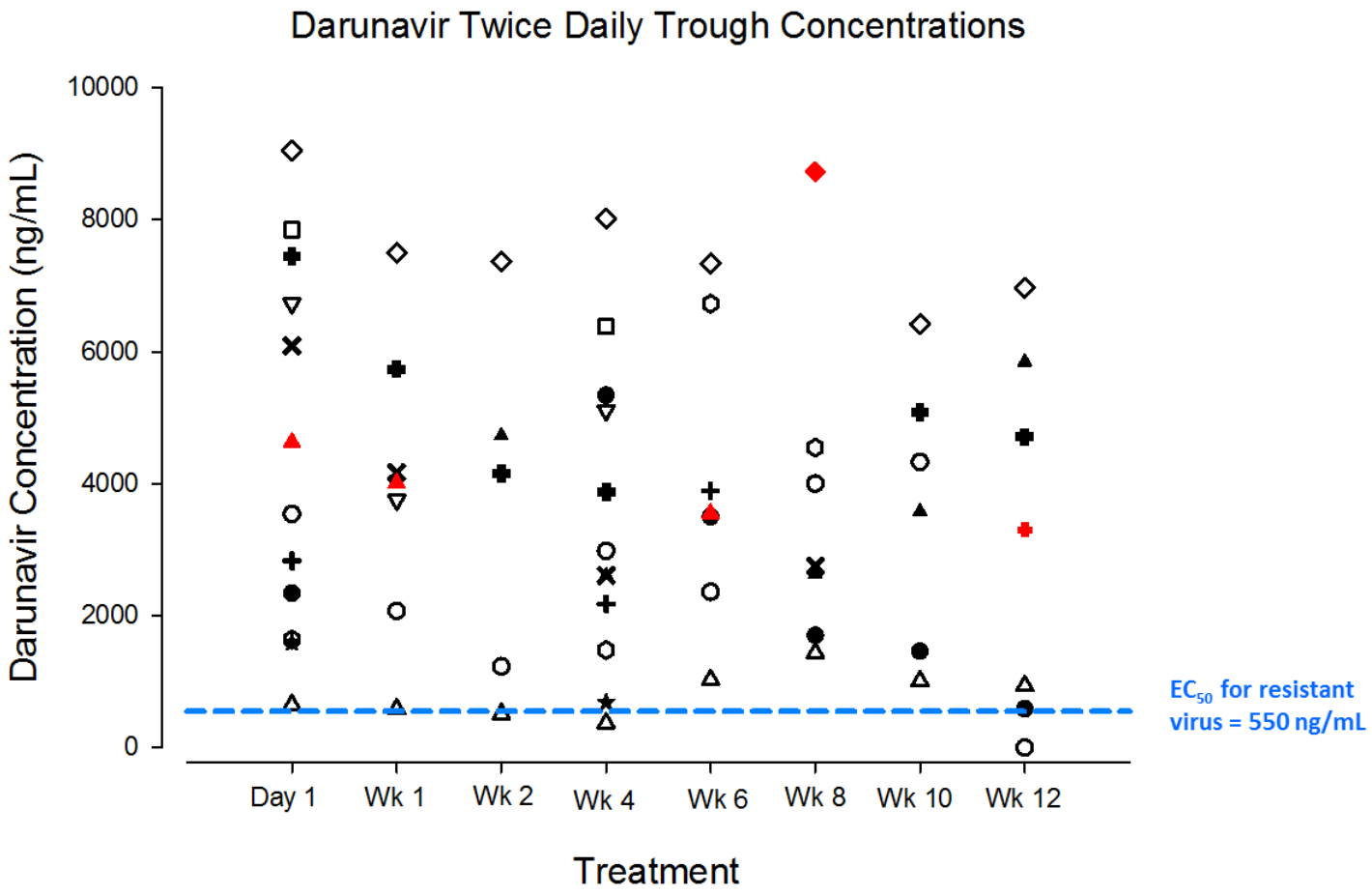
- 60 DRV $C_{troughs}$ were available from 10 subjects over the treatment period



Day 1 is without the 3-DAA regimen
Each symbol represents concentrations for each subject
Red symbols represent concentrations associated with plasma HIV RNA > 40 copies/mL

DRV BID: DRV C_{trough} Relative to Plasma HIV RNA

- 63 DRV $C_{troughs}$ were available from 12 subjects over the treatment period



Day 1 is without the 3-DAA regimen
Each symbol represents concentrations for each subject
Red symbols represent concentrations associated with plasma HIV RNA > 40 copies/mL

Geometric Mean (CV%) PK Parameters of DAAs, Ritonavir and Ribavirin

	DRV 800 mg QD (n=10)	DRV 600 mg BID (n=12)	Phase 1 Studies (n=113)
Ombitasvir			
C_{max} (ng/mL)	92.6 (35)	71.7 (38)	83-130
AUC_{24} (ng·h/mL)	1118 (36)	944 (40)	1050-1560
Paritaprevir			
C_{max} (ng/mL)	1440 (106)	1244 (109)	771-3360
AUC_{24} (ng·h/mL)	7653 (139)	6714 (124)	3819-18600
Ritonavir			
C_{max} (ng/mL)	881 (46)	941 (59)	1289-2240
AUC_{24} (ng·h/mL)	6909 (32)	15034 [a]	7571-14400
Dasabuvir			
C_{max} (ng/mL)	725 (45)	572 (39)	826-1460
AUC_{12} (ng·h/mL)	4403 (48)	3509 (40)	5624-9790
Ribavirin			
C_{max} (ng/mL)	2208 (25)	2813 (31)	NA
AUC_{12} (ng·h/mL)	21506 (27)	27373 (36)	NA

[a] Value is 2*AUC_{12} to get estimated AUC_{24}

Geometric Mean (CV%) PK Parameters of DAAs, Ritonavir and Ribavirin

	DRV 800 mg QD (n=10)	DRV 600 mg BID (n=12)	Phase 3 Studies (n=1277)[1]
Ombitasvir			
C_{trough} (ng/mL)	20 (70)	21 (45)	24-33
Paritaprevir			
C_{trough}(ng/mL)	19 (218)	44 (133)	16-36
Ritonavir			
C_{trough}(ng/mL)	48 (76)	NA	40-50
Dasabuvir			
C_{trough}(ng/mL)	198 (33)	118 (46)	175-270[a]
Ribavirin			
C_{trough}(ng/mL)	1606 (34)	1969 (44)	2060-2330[b]

C_{trough} = C_{24} for OBV, PTV and RTV; C_{12} for DSV and RBV

Plasma C_{trough} from Phase 3 studies were determined using binned time intervals of >22-26 hours for OBV, PTV and RTV and >10-14 hours for DSV and RBV

a. n=1253
b. n = 897

[1]*Pockros K et al. Gastroenterology2016*

Conclusions

- In the presence of the 3D regimen in HCV/HIV co-infected adults
  - DRV AUC and C_{max} were comparable to DRV/ritonavir 800/100 mg QD or 600/100 mg BID alone
  - DRV C_{24} after DRV 800 mg QD decreased 36% and DRV C_{12} after 600 mg BID decreased 27% when administered with the 3D regimen
- 87% of DRV C_{trough} values in subjects taking DRV QD and 95% in DRV BID were above 550 ng/mL (EC_{50} for resistant virus).
  - None of the concentrations below the EC_{50} were associated with a plasma HIV RNA >40 copies/mL
- Exposures of DAAs and RBV in combination with DRV are similar compared to exposures reported in healthy volunteers and HCV mono-infected adults

Acknowledgements

- Volunteers
- Investigators
- Study staff
- AbbVie personnel involved in study conduct, sample analyses, data analyses