Interactions Between ABT-493 plus ABT-530 combination and Rilpivirine or Raltegravir

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INTRODUCTION

- The therapy with direct-acting antivirals (DAA) have become standard of care for the treatment of chronic Hepatitis C virus (HCV) infection, allowing shorter treatment duration, higher efficacy, and better tolerability and safety than previous PEG-interferon/ribavirin therapy.
- AbbVie is developing an all oral, ribavirin and interferon-free next generation DAA regimen of ABT-493 (a non-structural [NS] 3/4 protease inhibitor discovered by AbbVie and Enanta) and ABT-530 (a NS5A inhibitor) for the treatment of chronic HCV infection with genotypes 1-6.
- ABT-493 and ABT-530 are characterized by potent antiviral activity across all major HCV GTs and common DAA treatment-emergent resistant variants, as well as high barriers to development of resistance.
- Liver disease is a leading cause of non-AIDS-related mortality among HIV-infected patients. HCV and HIV co-infection is associated with accelerated HCV disease progression with higher rates of liver decompensation and death. Treatment with antiretroviral therapy for HIV and treatment of HCV have independently been shown to delay the progression of liver fibrosis and reduce complications from end-stage liver disease among co-infected patients.
- Drug-drug interaction (DDI) studies were conducted between ABT-493 and ABT-530 with antiretroviral drugs, rilpivirine (a HIV-1 specific, non-nucleoside reverse transcriptase inhibitor [NNRTI]) or raltegravir (a HIV-1 integrase strand transfer inhibitor [HIV-1 INSTI]) in healthy subjects.

OBJECTIVE

- These studies were designed to evaluate the pharmacokinetics, tolerability, and safety of the combination of ABT-493 + ABT-530 co-administered with rilpivirine or raltegravir.

METHODS

- Phase 1, randomized, single-center, multiple-dose, non-fasting, open label studies evaluated DDI between DAAs (ABT-493 + ABT-530) and rilpivirine or raltegravir (Figures 1 and 2)
- Pharmacokinetic parameters for ABT-493, ABT-530, rilpivirine and raltegravir including C_{max}, AUC_{τ} (AUC_{0-24} and AUC_{0-12} for drugs administered QD and BID, respectively) and C_{trough} (C_{24} and C_{12} for drugs administered QD and BID, respectively) were determined by non-compartmental analysis using Phoenix™ WinNonlin®, Version 6.2 or higher (Pharsight Corporation, St. Louis, MO).
- Effect of ABT-493 + ABT-530 on rilpivirine or raltegravir pharmacokinetics and vice versa was evaluated from central value ratios and 90% confidence intervals (CI) of C_{max}, AUC_{τ} and C_{trough} estimated using SAS, Version 9.3 (Cary, NC).
- Adverse events (AE) monitoring, vital signs, physical examinations, ECGs, and laboratory test assessments were conducted throughout each study.

METHODS (CONTINUED)

MAIN INCLUSION CRITERIA

- Male or female between the ages of 18 and 55, inclusive, in general good health
- Female subjects were of non-childbearing potential.

MAIN EXCLUSION CRITERA

- Positive test for HIV antibody (HIV Ab) at Screening

Figure 1: Rilpivirine Study Design

	Period 1 (Days 1 – 7)	Period 2 (Days 1-14)
Cohort I N=12	ABT-493 300 mg QD + ABT-530 120 mg QD	
		Rilpivirine 25 mg QD
	Period 1 (Days 1-14)	**Period 2 (Days 1-7)**
Cohort II N=12		ABT-493 300 mg QD + ABT-530 120 mg QD
	Rilpivirine 25 mg QD	

Intensive PK sampling for DAAs: Cohort I - Period 1/Day 7, Period 2/Day 1 and Period 2/Day 14; Cohort II – Period 2/Day 1 and Period 2/Day 7

Intensive PK sampling for Rilpivirine: Cohort I - Period 2/Day 1 and Period 2/Day 14; Cohort II - Period 1/Day 14, Period 2/Day1 and Period 2/Day 7

Figure 2: Raltegravir Study Design

Period 1	Period 2		
Days 1-3	Day 1	Days 2-7	Days 8-10
Raltegravir (400 mg BID)			Raltegravir (400 mg BID)
	ABT-493 300 mg QD + ABT-530 120 mg QD		

Intensive PK sampling for DAAs: Period 2/Day 1 and Period 2/Day 10

Intensive PK sampling for Raltegravir: Period 1/Day 3, Period 2/Day 1 and Period 2/Day 10

RESULTS

Table 1. Demographics and Subject Disposition

	Rilpivirine DDI		Raltegravir DDI
	Cohort 1 (N = 12)[a]	Cohort II (N = 12)	(N = 12)
Age (years)	36.5 (24 - 52)	29.8 (21 – 47)	32.8 (22 – 56)
Weight (kg)	77.0 (54 – 91)	72.1(53 – 91)	76.2 (62 – 92)
Height (cm)	170 (151 – 186)	169 (154 – 177)	174 (165 – 193)
Sex			
N (male %)	12 (58%)	12 (66%)	12 (92%)
Race			
White	6	5	3
Black	5	6	8
Asian/ Multi-Race	1	1	1
Subjects that completed study (N)	12	12	12

Age, weight, height presented as mean (minimum – maximum)

a. One subject in Cohort I of the rilpivirine DDI study demonstrated atypical concentration-time profiles and was excluded from PK analysis for DAAs

RESULTS (CONTINUED)

Figure 3. Rilpivirine DDI: ABT-493, ABT-530 (Cohort I), and Rilpivirine (Cohort II) Plasma Concentration-Time Profiles

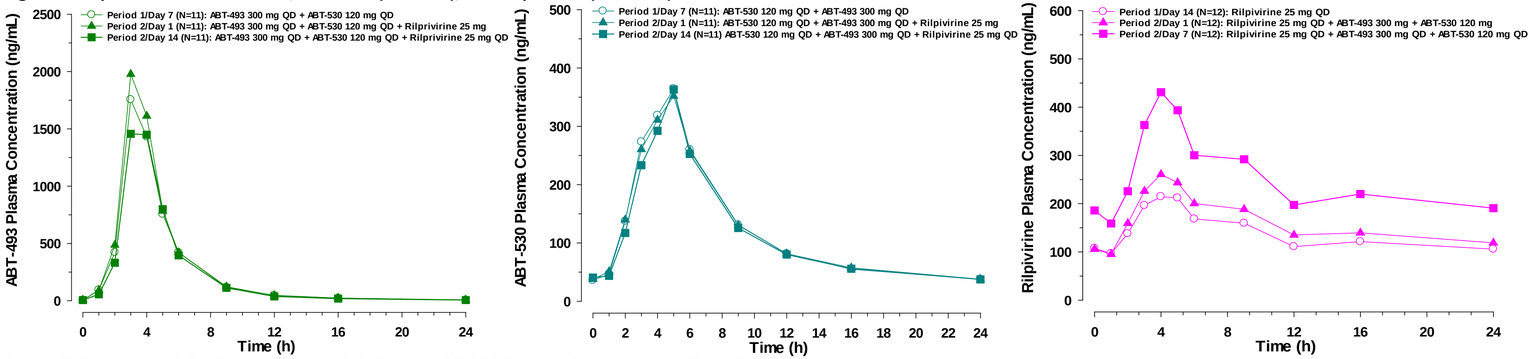


Figure 7. Raltegravir DDI: Raltegravir, ABT-493, and ABT-530 Plasma Concentration-Time Profiles

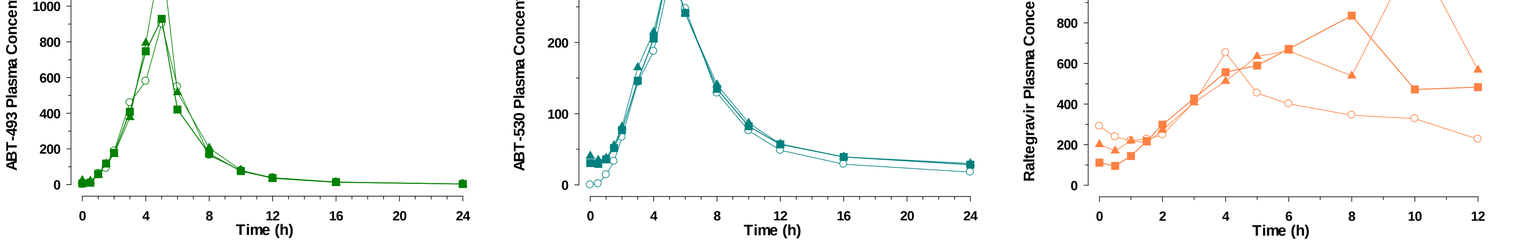
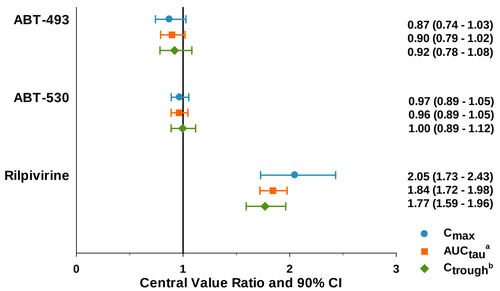


Figure 3. Interaction between ABT-493 and ABT-530 with Rilpivirine (Central Value Ratios and 90% CIs)

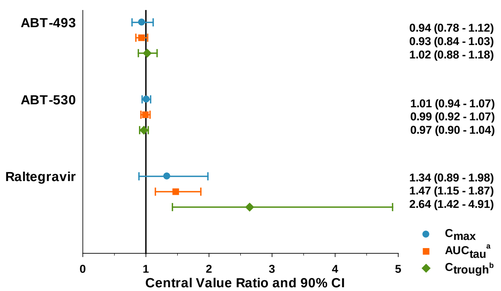


ABT-493 and ABT-530: Cohort I, Period 2 Day 14 (Test)/ Period 2 Day 7 (Reference)
Rilpivirine: Cohort II, Period 2 Day 7 (Test)/Period 1 Day 14 (Reference)

[a]$AUC_{\tau} = AUC_{24}$ for ABT-530, ABT-493, and rilpivirine
[b]$C_{trough} = C_{24}$ for ABT-530, ABT-493, and rilpivirine

- Following co-administration with multiple rilpivirine doses, ABT-493 and ABT-530 C_{max}, AUC_{24}, and C_{24} were similar to when the DAA combination was given alone (≤ 13% change).
- Compared to rilpivirine alone, co-administration with ABT-493 + ABT-530, increased rilpivirine C_{max}, AUC_{24}, and C_{24} by 105%, 84%, and 77%, respectively.

Figure 4. Interaction between ABT-493 and ABT-530 with Raltegravir (Central Value Ratios and 90% CIs)



ABT-493 and ABT-530: Period 2 Day 10 (Test)/Period 1 Day 7 (Reference)
Raltegravir: Period 2 Day 10 (Test)/Period 1 Day 3 (Reference)

[a]$AUC_{\tau} = AUC_{24}$ for ABT-493 and ABT-530. $AUC_{\tau} = AUC_{12}$ for raltegravir
[b]$C_{trough} = C_{24}$ for ABT-493 and ABT-530. $C_{trough} = C_{12}$ for raltegravir

- Following co-administration with raltegravir, ABT-493 and ABT-530 C_{max}, AUC_{24}, and C_{24} were minimally affected (≤ 7% change in central values) compared to administration of the DAA combination alone.
- Compared to raltegravir alone, co-administration with the DAAs increased raltegravir C_{max} and AUC_{12} central values by 34% and 47%, respectively, and C_{12} central values by 164%, compared to administration of raltegravir alone.

SAFETY AND TOLERABILITY

- No clinically significant vital signs, laboratory measurements, or severe adverse events were observed in either study.
- There was no pattern to the reported adverse events and no new safety issues were identified in either study.

CONCLUSIONS

- For ABT-493 and ABT-530 as victims of drug-drug interactions, exposures of both DAAs were minimally affected (≤13% change in exposures) when co-administered with rilpivirine or raltegravir.
- For ABT-493 and ABT-530 as perpetrators of drug-drug interactions, the DAAs increased exposures of rilpivirine and raltegravir.
- Consistent with rilpivirine and raltegravir label recommendations for coadministration with other drugs that caused similar magnitude of increase in rilpivirine and raltegravir exposures, no dose adjustment is needed when ABT-493 and ABT-530 are coadministered with rilpivirine or raltegravir.
- No new safety signals were identified when ABT-493 and ABT-530 were coadministered with rilpivirine or raltegravir.

DISCLOSURES

Both the studies were funded by AbbVie. AbbVie contributed to the study designs, research, and interpretation of data, writing, reviewing, and approving the publications. All authors are AbbVie employees and may hold AbbVie stocks or options.

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