Ombitasvir/Paritaprevir/ Ritonavir + Dasabuvir: Drug Interactions with Antiretroviral Agents

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Disclaimers

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

Background

- AbbVie's three direct acting antiviral (**3D**) regimen (ombitasvir, paritaprevir/r, and dasabuvir) with and without ribavirin has been approved for the treatment of chronic hepatitis virus (HCV) genotype 1 infection in the US and EU.
  - Paritaprevir (ABT-450), identified as a lead compound by AbbVie and Enanta, is a HCV NS3/4A protease inhibitor that is co-administered daily (QD) with ritonavir (paritaprevir/r).
  - Ombitasvir (ABT-267) is a HCV NS5A inhibitor dosed QD.
  - Dasabuvir (ABT-333) is a non-nucleoside inhibitor of HCV NS5B polymerase dosed twice-daily (BID).
- In phase 3 clinical trials with HCV genotype 1-infected patients, the 3D regimen ± ribavirin demonstrated 12-week sustained virologic response (SVR_{12}) in 92% to 100% of cirrhotic and noncirrhotic patients.
- The **2D** regimen of ombitasvir/paritaprevir/ritonavir is being developed for in HCV GT4 subjects with ribavirin (GT4 approved in EU). This regimen is also being developed without ribavirin in HCV GT1b subjects and with ribavirin in HCV GT2 subjects in Japan.

HIV-HCV Co-infection

- Patients with HIV/HCV co-infection are 3 times more likely to develop cirrhosis or liver decompensation than those infected with HCV alone[1].

- Unlike the treatment of HIV, for which the goal is viral suppression, treatment of HCV is finite in duration, and the goal is to achieve SVR. Achieving SVR is associated with a significant decrease in subsequent decompensation of liver function, liver cancer, and all-cause mortality in persons with HIV co-infection[2].

- Treatment of patients with HIV/HCV co-infection can be complicated by drug interactions between ARTs and HCV DAAs. Understanding drug interactions between ARTs and HCV DAAs are important prior to coadministering these agents.

1. Graham et al, Clin Infect Dis 2001;33(4):562-569
2. Limketkai et al, JAMA 2012;308(4):370-378

ART Evaluated in Drug-Interaction Studies with the AbbVie DAA Regimen

	Regimen evaluated
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	Emtricitabine/Tenofovir* Abacavir/lamivudine
Integrase Inhibitor	Raltegravir* Dolutegravir
Protease Inhibitor (PI)	Atazanavir (with and without ritonavir)* Darunavir (with and without ritonavir)* Lopinavir/ritonavir*
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Efavirenz/Emtricitabine/Tenofovir Rilpivirine

** Also evaluated in the 2D regimen of ombitasvir/paritaprevir/ritonavir. The 2D regimen is being developed for in HCV GT4 subjects with ribavirin (GT4 approved in EU). This regimen is also being developed without ribavirin in HCV GT1b subjects and with ribavirin in HCV GT2 subjects in Japan.*

Nucleoside Reverse Transcriptase Inhibitor

Emtricitabine/Tenofovir

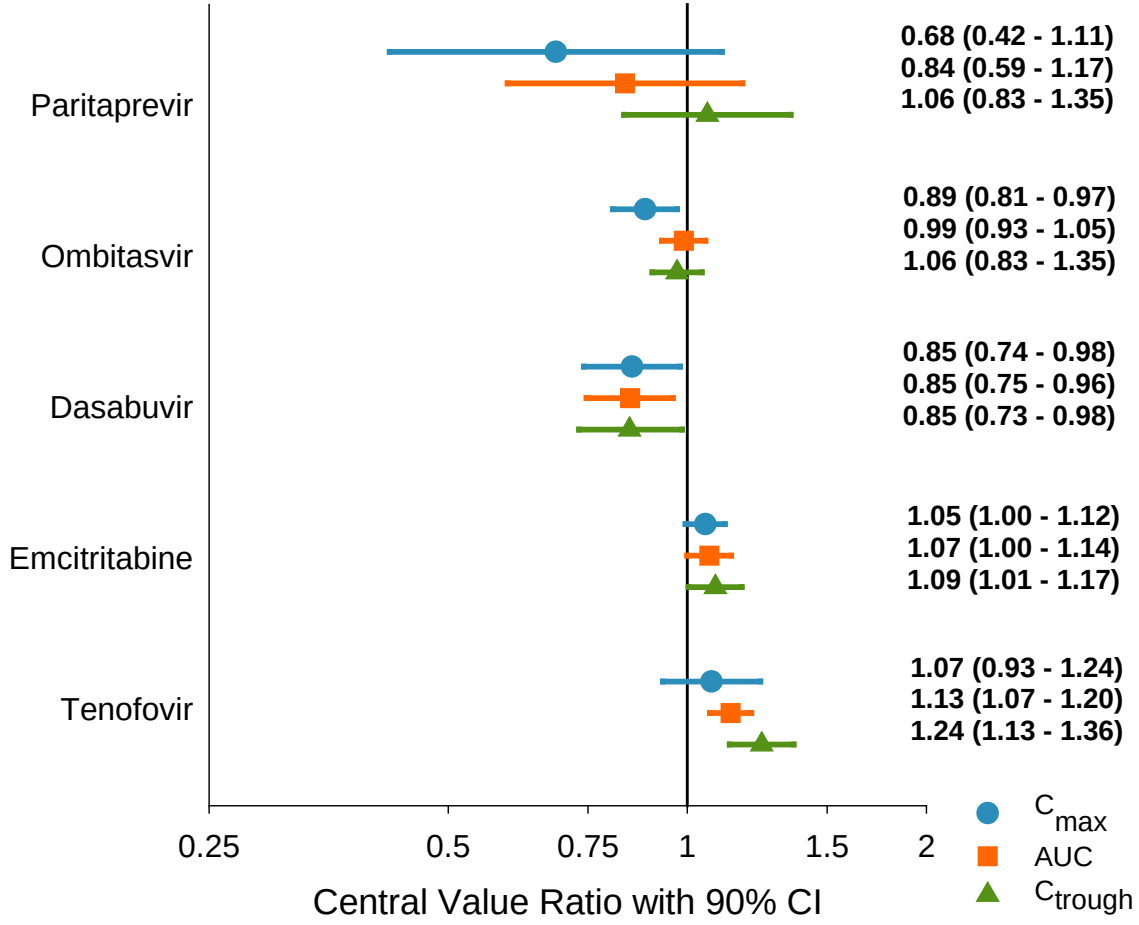
Abacavir/Lamivudine

Design: DDI with Emtricitabine/Tenofovir

	Days 1-14	Days 15-21
Cohort 1 (N=9)	3D	3D + Emtricitabine + Tenofovir disoproxil fumarate
	Days 1-7	**Days 8-21**
Cohort 2 (N=9)	Emtricitabine 200 mg QD + Tenofovir disoproxil fumarate 300 mg QD	3D + Emtricitabine + Tenofovir disoproxil fumarate

3D: Paritaprevir/ritonavir (150/100 mg QD)+ ombitasvir (25 mg QD) + dasabuvir (400 mg BID)

Results: DDI with Emtricitabine/Tenofovir



- No dose adjustment is required for the DAAs, emtricitabine or tenofovir when co-administered

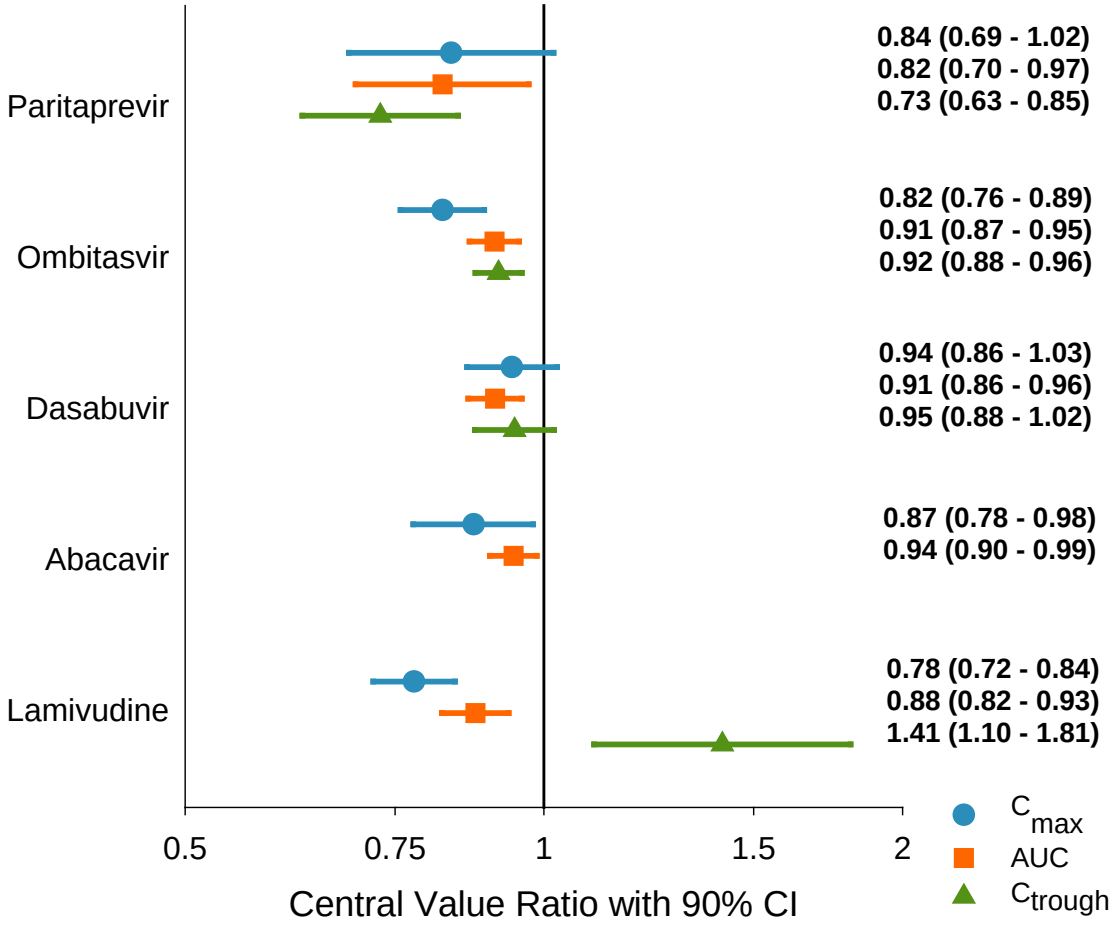
Design: DDI with Abacavir + Lamivudine

Period 1	Washout	Period 2	
Days 1-4	5 days	Days 1-14	Days 15-24
Abacavir 600 mg QD + Lamivudine 300 mg QD		3D	3D + Abacavir 600 mg QD + Lamivudine 300 mg QD

N=12

3D: ombitasvir/paritaprevir/ritonavir (25/150/100 mg QD)+ dasabuvir (250 mg BID)

Results: DDI with Abacavir + Lamivudine



- No dose adjustment is required for the DAAs, abacavir or lamivudine when co-administered

Safety: Discontinuations due to Adverse events during combination dosing

- No discontinuations due to AEs during combination dosing of 3D regimen with emtricitabine + tenofovir DF or abacavir + lamivudine

- No SAEs or any new or unexpected safety findings were observed.

Integrase Inhibitors

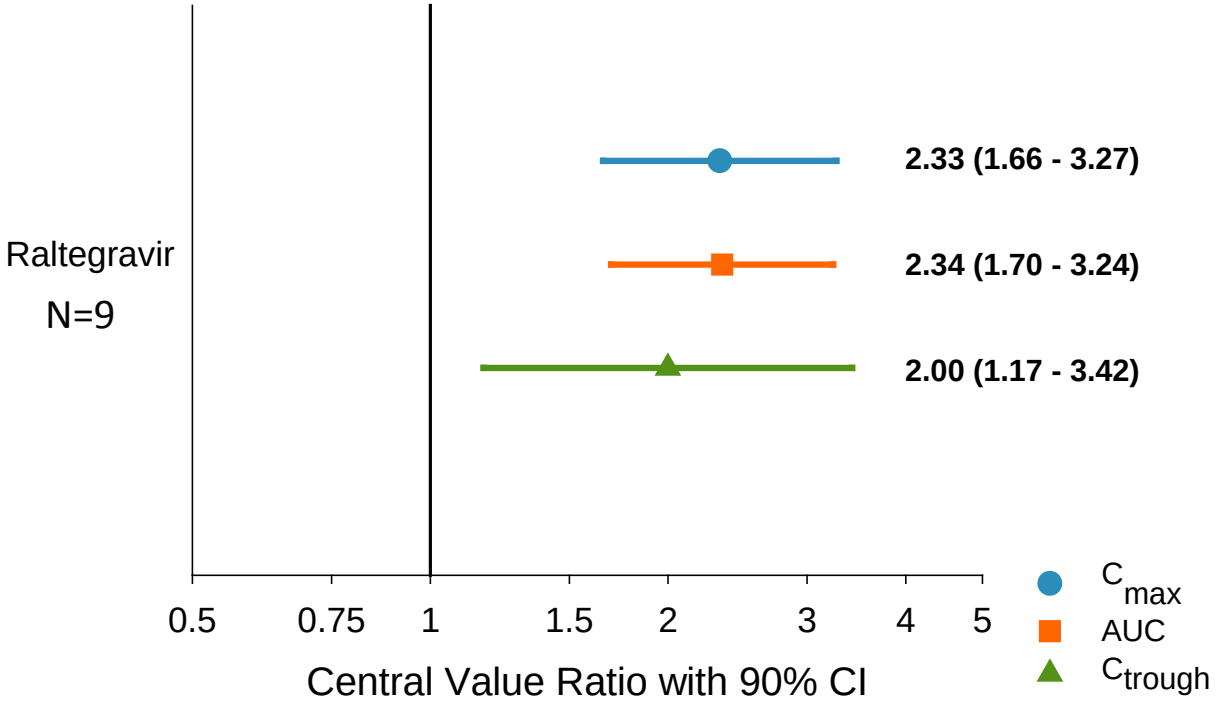
Raltegravir

Dolutegravir

Design and Results: DDI with Raltegravir

Days 1-3	Days 4-17
Raltegravir	3D + Raltegravir

3D: Paritaprevir/ritonavir (150/100 mg QD)+ ombitasvir (25 mg QD) + dasabuvir (400 mg BID)



- Cross-study comparisons indicate that DAA exposures were not affected by raltegravir coadministration

Recommendations with Raltegravir

According to the raltegravir prescribing information in the United States (Isentress®[raltegravir], Merck Prescribing Information, Isentress: European Public Assessment Reports Product Information), co-administration of raltegravir with omeprazole increases the raltegravir exposure 3-fold but no dose adjustment is needed.

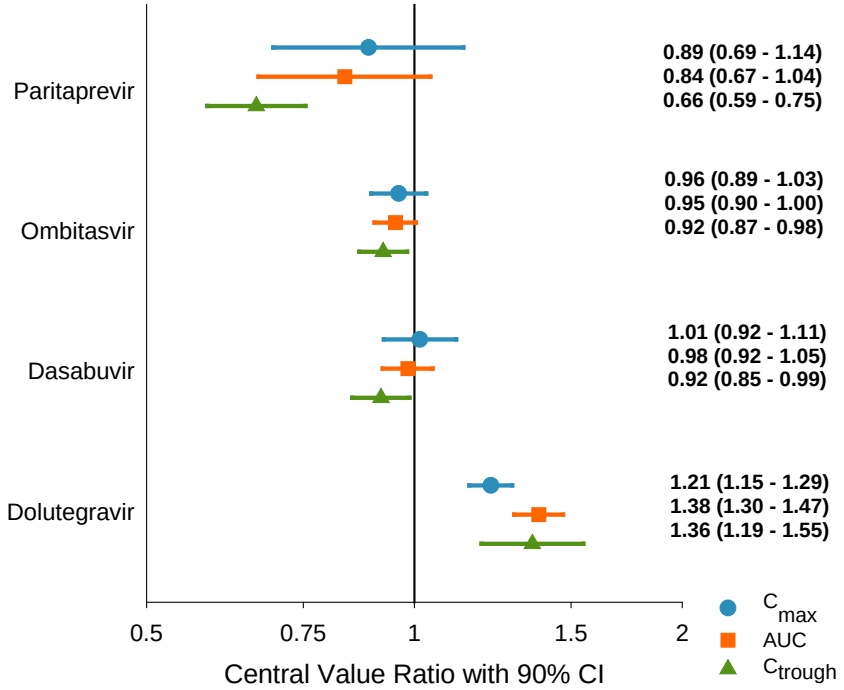
No dose adjustment is recommended for raltegravir when co-administered with the DAAs. Raltegravir based regimens were evaluated in the HCV-HIV co-infected study M14-004.

Design: DDI with Dolutegravir

Period 1	Washout	Period 2	
Days 1-7	7 days	Days 1-14	Days 15-24
Dolutegravir 50 mg QD		3D	3D + Dolutegravir 50 mg QD

N=12

3D: ombitasvir/paritaprevir/ritonavir (25/150/100 mg QD)+ dasabuvir (25 mg BID)



- No dose adjustment is required for the DAAs or dolutegravir when co-administered

Safety: Discontinuations due to Adverse events during combination dosing

- No discontinuations due to AEs during combination dosing of the 3D regimen with raltegravir or dolutegravir
- No SAEs or any new or unexpected safety findings were observed.

Protease Inhibitors

Atazanavir DDI Study Design

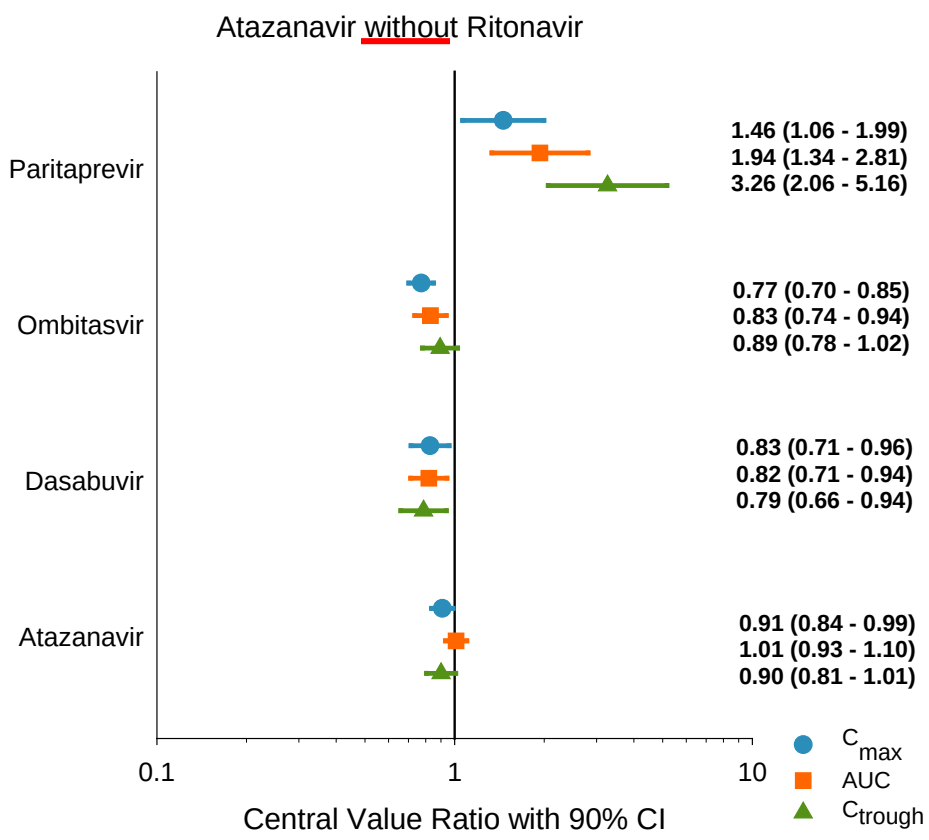
	Days 1-14	Days 15-28
Cohort 1	3D	3D + ATZ or 3D +ATZ/RTV*
Cohort 2	ATZ + RTV	3D + ATZ or 3D + ATZ/RTV*

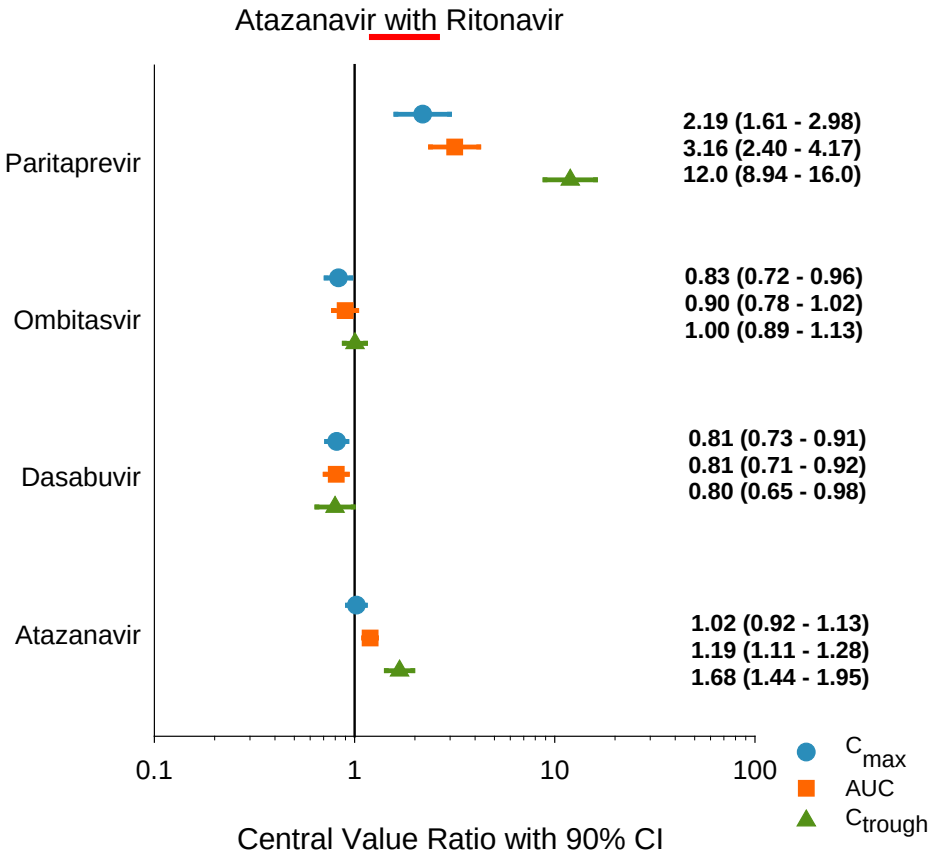
3D: Paritaprevir/ritonavir (150/100 mg QD)+ ombitasvir (25 mg QD) + dasabuvir (400 mg BID)

*Additional ritonavir was coadministered when dosed PM

PI	N	Dose	Dosing
Atazanavir	24	300	Dosed AM
Atazanavir/RTV	24	300/100	Dosed PM

Results and Recommendations: Atazanavir with and without RTV





- Atazanavir **without** additional RTV can be coadministered the 3D regimen. Atazanavir should be coadministered with ombitasvir/ paritaprevir/ritonavir

Darunavir with and without RTV

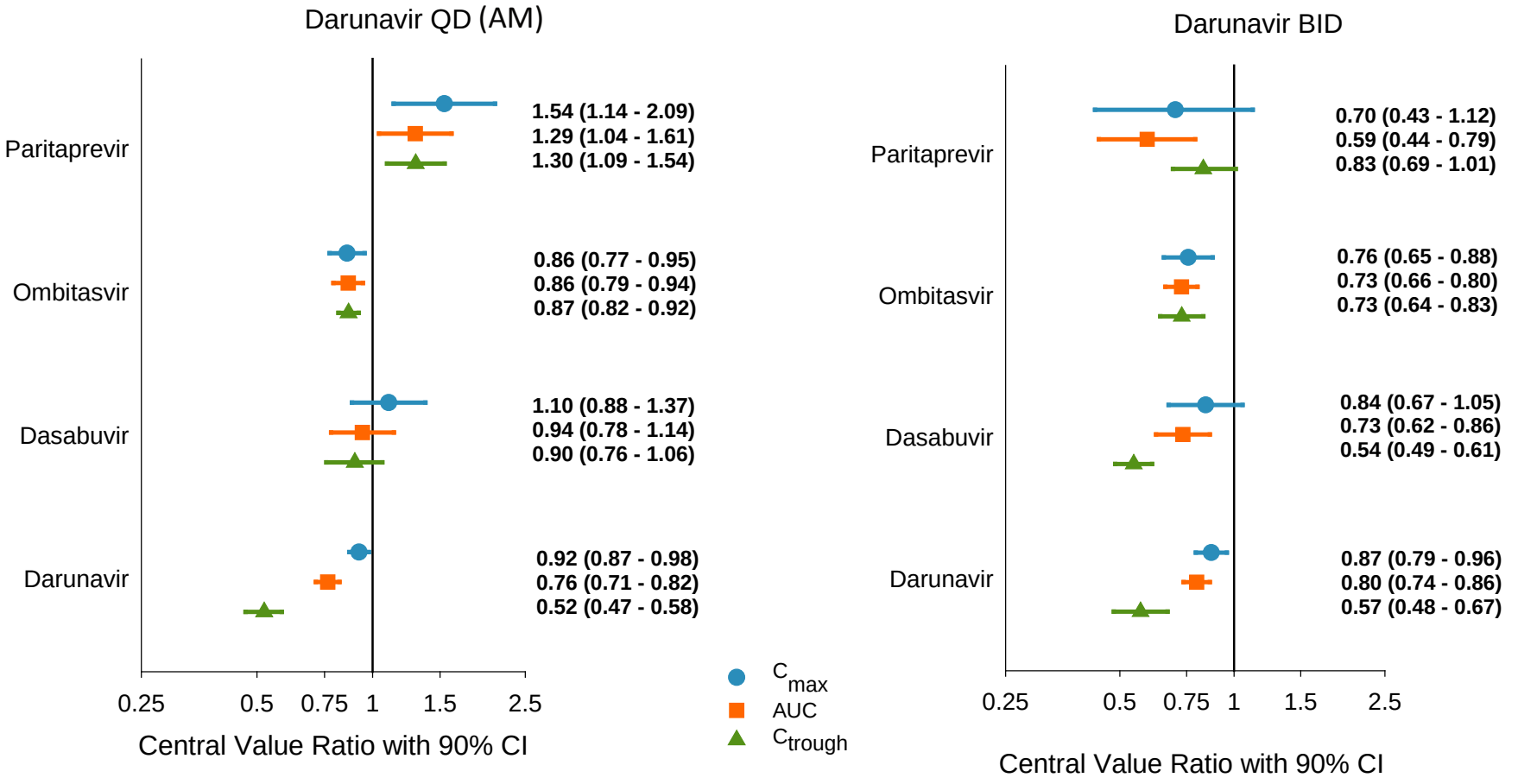
	Days 1-14	Days 15-28
Cohort 1	3D	3D + DRV 3D + DRV/RTV*
Cohort 2	DRV + RTV	3D + DRV 3D + DRV/RTV

3D: Paritaprevir/ritonavir (150/100 mg QD), ombitasvir (25 mg QD), dasabuvir (250 or 400 mg BID)

*Additional ritonavir was coadministered when dosed PM

PI	N	Dose	Dosing
Darunavir QD	18	800	Dosed AM
Darunavir/RTV QD	24	800/100	Dosed PM
Darunavir/RTV BID	18	600/100	No RTV with AM dose

Results and Recommendations: Darunavir with and without RTV



- Darunavir C_{trough} is lower when coadministered with the 3D regimen
- Similar C_{trough} and C_{max} results were observed for darunavir though AUC increased by 34% when darunavir/ritonavir (PM) was administered with the 3D regimen

Can Darunavir be dosed with the 3D regimen?

- Up to 50% lower Ctrough exposures without a significant impact on Cmax or AUC DRV exposures are unlikely to result in a negatively impact HIV treatment efficacy (in the maintenance of plasma HIV-1 RNA suppression for patients on a stable DRV-based ART regimen during treatment with 3D)
- This is being verified in the M14-004 study in HCV-HIV co-infected subjects
- **USPI**: Coadministration not recommended
- **EU SPC**: 800 mg once daily administered at the same time as ombitasvir/paritaprevir/ritonavir + dasabuvir can be used in the absence of extensive PI resistance

Ref:
PK-PD analyses of darunavir from two Phase 3 trials (ODIN and ARTEMIS) (Sekar V et al., 2008, 15th Conference on Retroviruses and Opportunistic Infections (CROI); Sekar V et al., 2010, 10th International Conference on Drug Therapy in HIV)

Molto J, Valle M, Ferrer E, et al. Reduced darunavir dose is as effective in maintaining HIV suppression as the standard dose in virologically suppressed HIV-infected patients. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. 19- 21 May 2014. Washington, DC. Abstract O_02

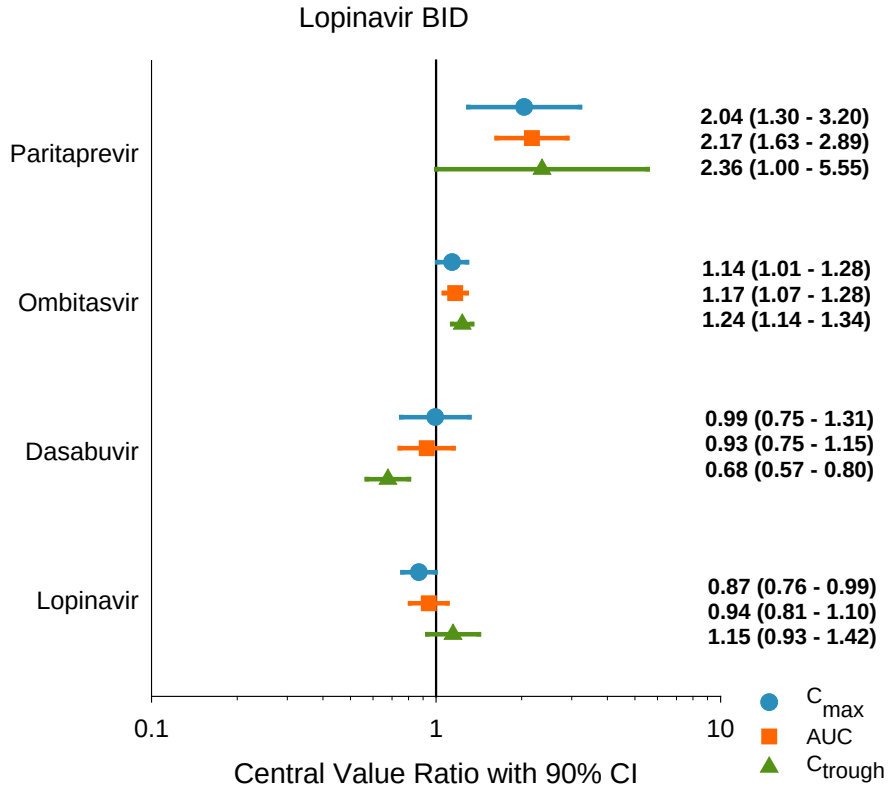
Lopinavir with RTV QD and BID

	Days 1-14	Days 15-28
Cohort 1	3D	3D + LPV/r
Cohort 2	LPV/r	3D + LPV/r

3D: Paritaprevir/ritonavir (150/100 mg QD)+ ombitasvir (25 mg QD) + dasabuvir (400 mg BID)

PI	N	Dose	Dosing
Lopinavir/RTV BID	12	400/100	BID
Lopinavir/RTV QD	24	800/200	Dosed PM

Results and Recommendations: LPV/r with and without RTV



- Similar higher paritaprevir AUC values were observed during coadministration with the 800/200 QD dose of LPV/r. C_{max} values were not affected while C_{trough} values were higher (due to the PM dose of LPV/r)
- Due to higher paritaprevir exposures and higher ritonavir dose, LPV/r is not recommended with the 3D regimen (USPI) or contraindicated (SMPC).
- Coadministration of the 3D or 2D regimen was tolerated in over 100 subjects for 14 days. If considered for coadministration, the possibility of a greater incidence of gastrointestinal AEs due to increased daily dose of ritonavir (300 mg) for 12 to 24 weeks should be considered.

Safety: Discontinuations due to Adverse events during combination dosing

- No SAEs or new safety events were identified in these studies

Regimen	Number of Subjects in the 3D Cohorts	Discontinuations due to AE on combination (3D + ARV) regimen
ATZ ± RTV*	48	2 (1st degree AV block and macular rash)
DRV ± RTV	60	0
LPV/r	36	0

* Bilirubin elevations occurred commonly during ATZ+ RTV dosing alone and did not worsen during coadministration with 3D regimen. No AE of jaundice reported.

  - Elevation in indirect bilirubin without increases in aminotransferases, was the most common laboratory abnormality; however, no premature discontinuation was observed due to bilirubin elevations. No subject met Hy's Law criteria.

Non-Nucleoside Reverse Transcriptase Inhibitor

Efavirenz/Emtricitabine/Tenofovir

Rilpivirine

Efavirenz/Emtricitabine/Tenofovir

	Days 1-14	Days 15-28
Cohort 1 (N=9)	*Paritaprevir/ritonavir (150/100 mg QD)+ dasabuvir (400 mg BID)*	*Paritaprevir/ritonavir + dasabuvir* + Efavirenz/Emtricitabine/Tenofovir
Cohort 2 (N=9)	Efavirenz/Emtricitabine/Tenofovir 600/200/300 mg QD	*Paritaprevir/ritonavir + dasabuvir* + Efavirenz/Emtricitabine/Tenofovir

- Study was discontinued due to safety & tolerability issues: nausea, vomiting, liver enzyme elevations
- Similar results have been reported with other enzyme inducers (rifampin) and LPV/r or Saquinavir/r
- PK profile was not collected as study discontinued
- Efavirenz containing regimens are contraindicated with the 3D (and 2D) regimen

Design: DDI with Rilpivirine

	Days 1-14	Days 15-28
Cohort 1 (N=12)	3D	3D + **Rilpivirine 25 mg**
Cohort 2 (N=12)	**Rilpivirine 25 mg**	3D + **Rilpivirine 25 mg**

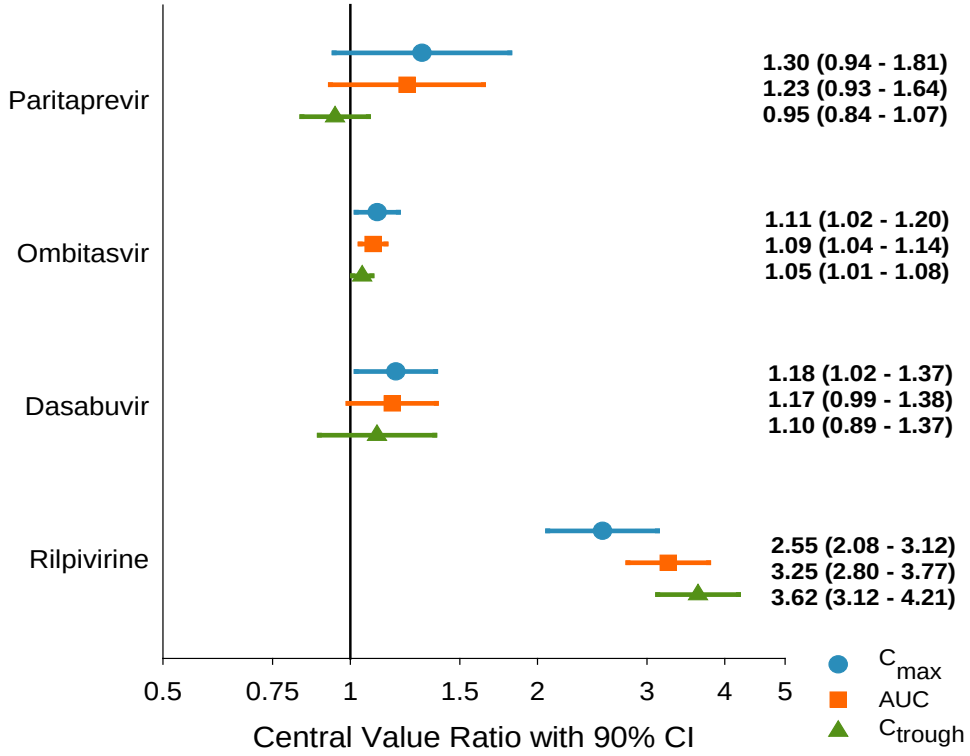
3D: Paritaprevir/ritonavir (150/100 mg QD)+ ombitasvir (25 mg QD) + dasabuvir (400 mg BID)

Rilpivirine was administered:

- AM with 3D regimen (n=24)
- PM before a meal (n=24)
- PM after a meal (n=24)

Overall 72 subjects were dosed in the study

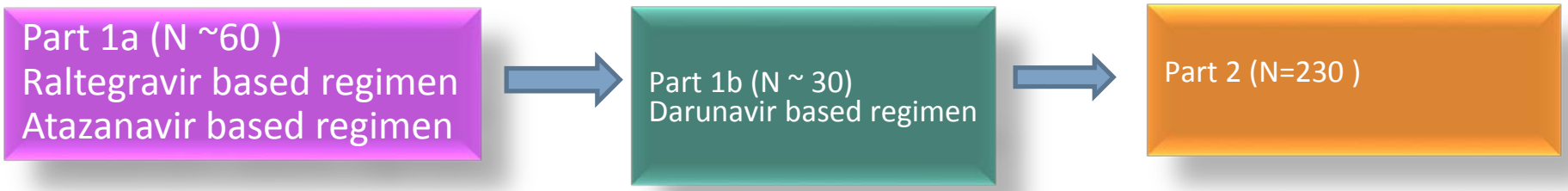
Results: DDI with Rilpivirine



Results from all 3 Arms were similar

- 2 of 72 subjects discontinued due to AEs (maculopapular rash (N=1) and blood creating phosphokinase and AST increase (N=1))
- The reported QTc prolongation associated with 2.6-fold increase in rilpivirine exposure from the rilpivirine 25 mg QD regimen is ~11 msec (Edurant® [rilpivirine], Janssen Prescribing information), co-administration of rilpivirine with the 3-DAA combination is not recommended at the labeled rilpivirine dose of 25 mg QD.
- USPI: not recommended, EU SPC: Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring.

ART Regimens evaluated in the HCV-HIV Co-infected Study M14-004 (ClinicalTrials.gov Identifier: NCT01939197)



In addition the following HIV-ART regimens were allowed

- Tenofovir disoproxil fumarate (TDF) PO
- Emtricitabine (FTC) PO
- Lamivudine (3TC) PO

Results from Part 1a

- SVR12 was achieved by :
  - 29 of 31 (94%) in the 12 week arm
  - 29 of 32 patients (91%) in the 24 week arms
- Of the 5 patients who did not achieve SVR , only 2 of 63 were true virologic failures
  - 1 subject with on treatment breakthrough, 1 subject with PT relapse
  - 1 subject withdrew consent (HCV RNA <LLOD at TW10),
  - 2 patients had clinical history and phylogenetic evidence consistent with HCV reinfection.

Ref: Mark S. Sulkowski et al, Ombitasvir, Paritaprevir Co-dosed With Ritonavir, Dasabuvir, and Ribavirin for Hepatitis C in Patients Co-infected With HIV-1 A Randomized Trial, JAMA. Published online February 23, 2015. doi:10.1001/jama.2015.1328

Recommendations for ART with the AbbVie 3-DAA Regimen

	Regimen evaluated	Recommendation
Nucleoside Reverse Transcriptase Inhibitor	Emtricitabine/Tenofovir Abacavir/lamivudine	No dose adjustment required No dose adjustment required
Integrase Inhibitors	Raltegravir Dolutegravir Elvitegravir/cobicistat	No dose adjustment required No dose adjustment required Not evaluated
Protease Inhibitors	Atazanavir Darunavir Lopinavir	No dose adjustment required[1] No dose adjustment required[1,2] Not recommended/Contraindicated[3]
Non-Nucleoside Reverse Transcriptase Inhibitor	Efavirenz/Emtricitabine/Tenofovir Rilpivirine	Contraindicated Not recommended[4]

[1]Dose PI at the same time as OBV/PTV/RTV without additional RTV
[1,2] Not recommended per USPI. Being evaluated in the HCV-HIV coinfected study
Not recommended (USPI) or contraindicated.(EU SPC). Coadministration of the 3D or 2D was tolerated in over 100 subjects for 14 days.
[3]EU SPC: Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring. Please refer to the SPC for additional details.

References

Khatri et al, *Drug-Drug Interactions of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir and Dasabuvir with HIV Protease Inhibitors*, ICAAC 2014 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 5-9, 2014, Washington, DC

Khatri et al, *Drug-Drug Interactions of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir and Dasabuvir with Emtricitabine + Tenofovir, Raltegravir, Rilpivirine and Efavirenz,* ICAAC 2014 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 5-9, 2014, Washington, DC

Khatri et al, *Drug-Drug Interactions of Ombitasvir/Paritaprevir/r plus Dasabuvir with Dolutegravir or Abacavir plus Lamivudine,* 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, May 26-28, 2015

Sulkowski et al, *Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial*. JAMA. 2015 Mar 24-31;313(12):1223-31. doi: 10.1001/jama.2015.1328.

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