Drug-Drug Interactions of Commonly Used Medications with Direct Acting Antiviral HCV Combination Therapy of Paritaprevir/r, Ombitasvir and Dasabuvir

Akshanth R. Polepally, Jennifer R. King, Bifeng Ding, Diana L. Shuster, Emily O. Dumas, Amit Khatri, Jingtao Wu, Thomas J. Podsadecki, Rajeev M. Menon

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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 3 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 patients with or without cirrhosis.[1-4]
- Results from several drug-drug interaction studies (DDIs) in healthy volunteers for the 3D regimen have been previously reported.[5-7]

Current DDI Evaluations for the 3D Regimen with Commonly Used Medications

The following concomitant medications were selected for DDI evaluations based on their high frequency of use in clinical practice.[8]

Medication (Dose)	Drug Class	Metabolic Pathway
Diazepam (2 mg)	Benzodiazepine/anxiolytic	CYP3A4 and CYP2C19 substrate
Hydrocodone (5 mg)	Opioid analgesic	CYP2D6 substrate
Acetaminophen (300 mg)	Analgesic/antipyretic	Glucuronidation
Carisoprodol (250 mg)	Muscle relaxant	CYP2C19 substrate
Cyclobenzaprine (5 mg)	Muscle relaxant	CYP3A4, 1A2, and 2D6 substrate
Metformin (500 mg)	Antidiabetic	OCT1/OCT2 substrate
Sulfamethoxazole (800 mg BID)	Antimicrobial	CYP2C9 inhibitor
Trimethoprim (160 mg BID)	Antimicrobial	Weak CYP2C8 inhibitor; OCT2 inhibitor

Study Design: DDI with Diazepam and Hydrocodone bitartrate/Acetaminophen (HC/AP)

	Day 1	21 Days Washout	Days 22-35	Day 36	Days 37-45
N=15	Diazepam 2 mg		3D regimen	3D Regimen + Diazepam 2 mg	3D regimen

3D regimen : ombitasvir/paritaprevir/r 25/150/100 mg QD + dasabuvir 250 mg BID

Diazepam and nordiazepam PK sampling: on Day 1 and Day 36; pre-dose and up to 240 hours post dose

DAA PK sampling: on Day 35 and Day 36; pre-dose and up to 24 hours post dose

	Day 1	2 Days Washout	Days 3-16	Day 17	Day 18
N=15	HC/AP 5/300 mg		3D regimen	3D Regimen + HC/AP 5/300 mg	3D regimen

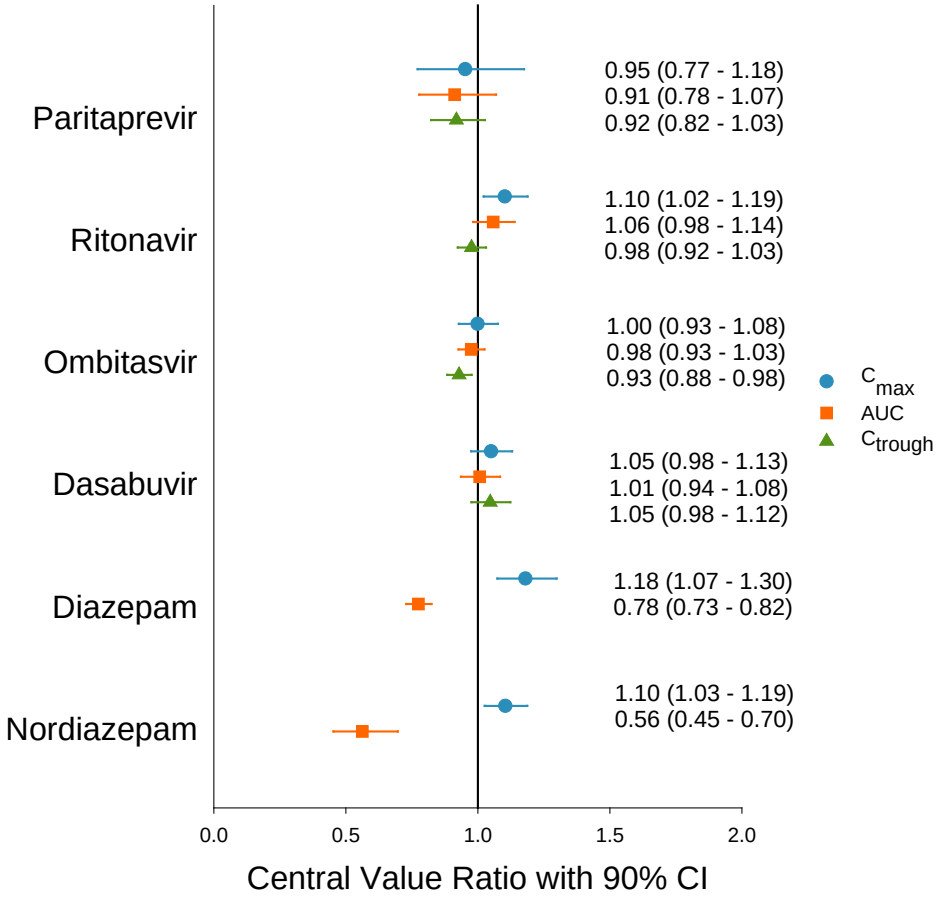
3D regimen : ombitasvir/paritaprevir/r 25/150/100 mg QD + dasabuvir 250 mg BID

HC and AP PK sampling: on Day 1 and Day 17; pre-dose and up to 48 hours post dose

DAA PK sampling: on Day 16 and Day 17; pre-dose and up to 24 hours post dose

Results: DDI with Diazepam

- No *a priori* dose adjustment required for diazepam; increase dose if clinically indicated
- No dose adjustment is needed for the DAAs when co-administered with diazepam

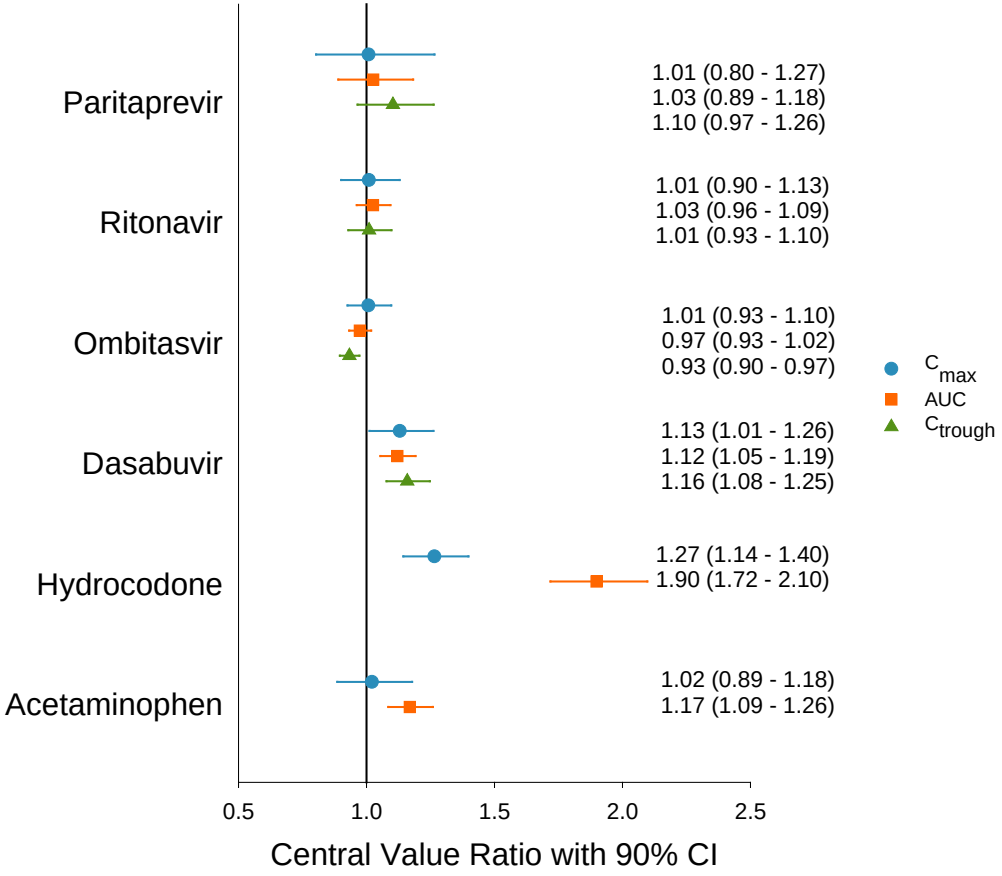


Note: Nordiazepam AUC_t was decreased only by 3%. Due its long half-life (137 hours), AUC_{inf} was not reliably estimated when diazepam was dosed alone.

Note: AUC = AUC_{24} for paritaprevir, ritonavir and ombitasvir; AUC_{12} for dasabuvir; AUC_{inf} for diazepam and nordiazepam; C_{trough} = C_{24} for paritaprevir, ritonavir and ombitasvir; C_{12} for dasabuvir

Results: DDI with Hydrocodone/Acetaminophen Combination

- Reduce hydrocodone dose by half and/or monitor clinical response when co-administered with 3D regimen; no dose adjustment is required for the DAAs when co-administered with hydrocodone
- No dose adjustment is required for the DAAs or acetaminophen when co-administered



Note: AUC = AUC_{24} for paritaprevir, ritonavir and ombitasvir; AUC_{12} for dasabuvir; AUC_{inf} for hydrocodone and acetaminophen
C_{trough} = C_{24} for paritaprevir, ritonavir and ombitasvir; C_{12} for dasabuvir

Study Design: DDI with Carisoprodol and Cyclobenzaprine

	Day 1		Days 4-17	Day 18	Days 19-20
N=14	Carisoprodol 250 mg	3 Days Washout	3D regimen	3D Regimen + Carisoprodol 250 mg	3D regimen

3D regimen: ombitasvir/paritaprevir/r 25/150/100 mg QD + dasabuvir 250 mg BID

Carisoprodol and meprobomate PK sampling: on Day 1 and Day 18; pre-dose and up to 72 hours post dose

DAA PK sampling: on Day 17 and Day 18; pre-dose and up to 24 hours post dose

	Day 1		Days 6-19	Day 20	Days 21-25
N=14	Cyclobenzaprine 5 mg	5 Days Washout	3D regimen	3D Regimen + Cyclobenzaprine 5 mg	3D regimen

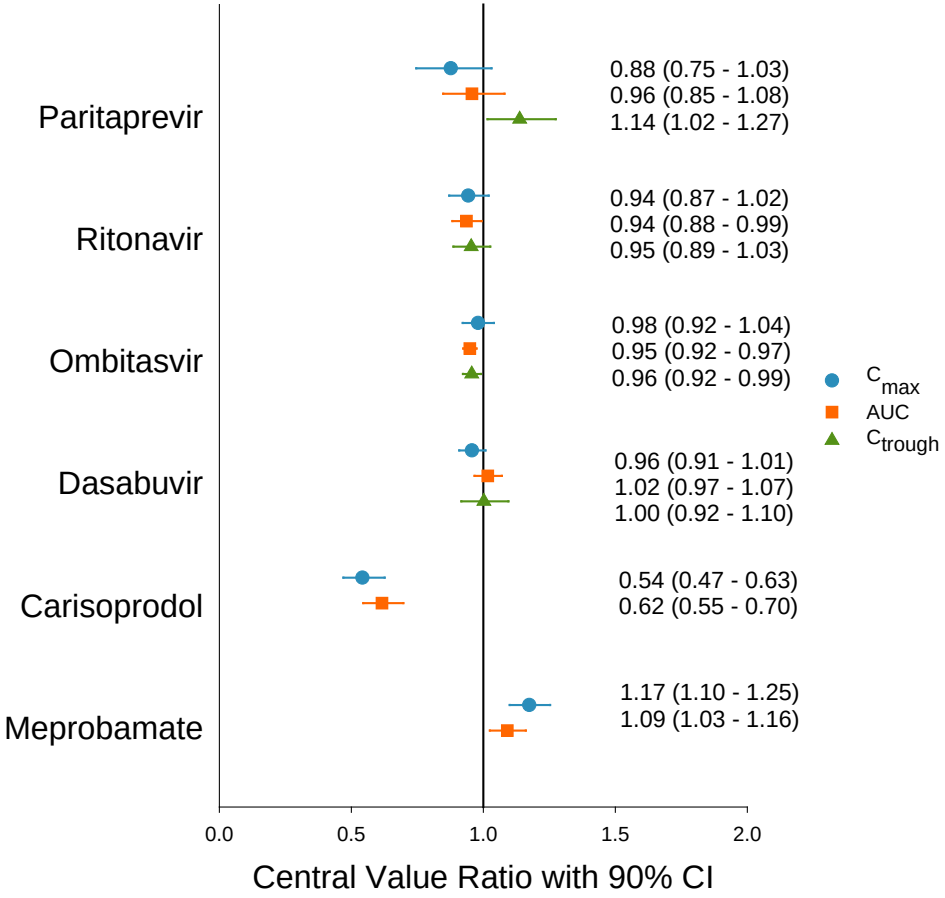
3D regimen : ombitasvir/paritaprevir/r 25/150/100 mg QD + dasabuvir 250 mg BID

Cyclobenzaprine and norcyclobenzaprine PK sampling: on Day 1 and Day 20; pre-dose and up to 144 hours post dose

DAA PK sampling: on Day 19 and Day 20; pre-dose up to 24 hours post dose

Results: DDI with Carisoprodol

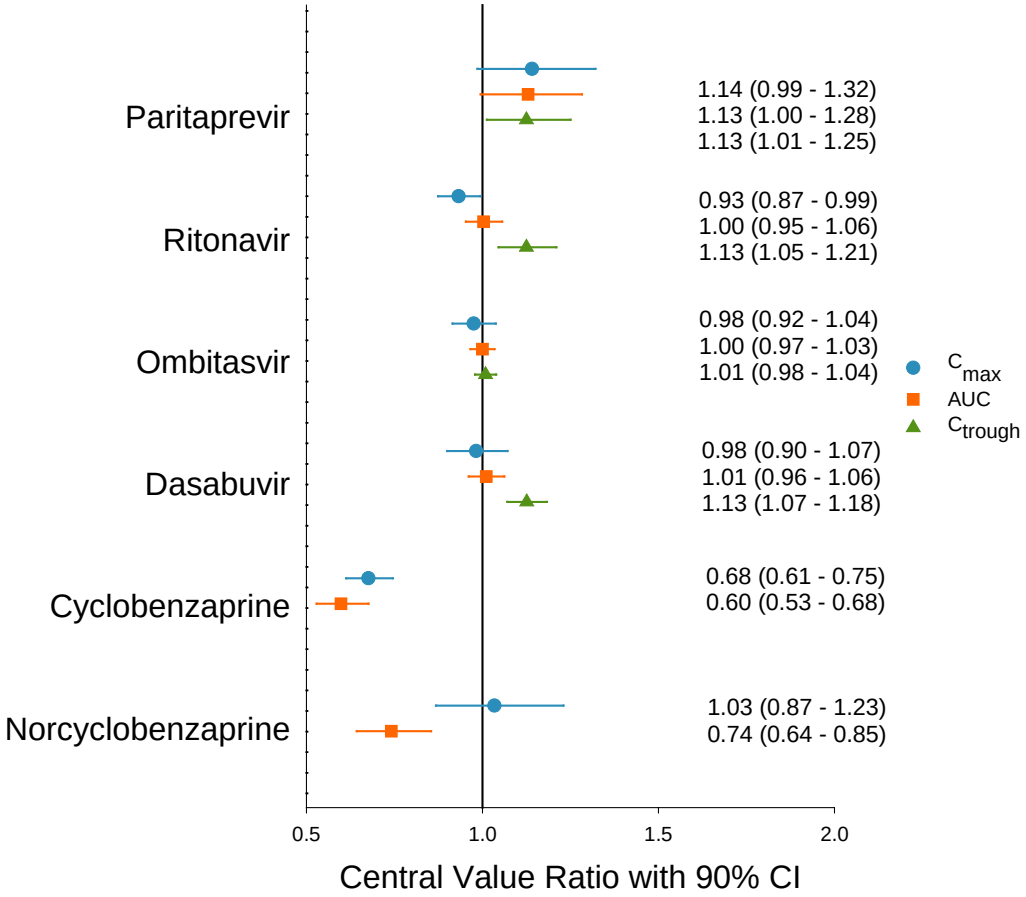
- No *a priori* dose adjustment required for carisoprodol; increase dose if clinically indicated
- No dose adjustment is needed for the DAAs when co-administered with carisoprodol



Note: AUC = AUC_{24} for paritaprevir, ritonavir and ombitasvir; AUC_{12} for dasabuvir; AUC_{inf} for carisoprodol and meprobamate
C_{trough} = C_{24} for paritaprevir, ritonavir and ombitasvir; C_{12} for dasabuvir

Results: DDI with Cyclobenzaprine

- No *a priori* dose adjustment required for cyclobenzaprine; increase dose if clinically indicated
- No dose adjustment is needed for the DAAs when co-administered with cyclobenzaprine



Note: AUC = AUC_{24} for paritaprevir, ritonavir and ombitasvir; AUC_{12} for dasabuvir; AUC_{inf} for cyclobenzaprine and norcyclobenzaprine; C_{trough} = C_{24} for paritaprevir, ritonavir and ombitasvir; C_{12} for dasabuvir

Study Design: DDI with Metformin and Sulfamethoxazole/Trimethoprim (SMZ/TMP)

	Day 1		Days 5-18	Day 19	Days 20 & 21
N=12	Metformin 500 mg	4 Days Washout	3D regimen	3D Regimen + Metformin 500 mg	3D regimen

DAAs: ombitasvir/paritaprevir/r 25/150/100 mg QD + dasabuvir 250 mg BID

Metformin PK sampling: on Day 1 and Day 19; pre-dose and up to 48 hours post dose

DAA PK sampling: on Day 18 and Day 19; pre-dose and up to 24 hours post dose

	Day 1		Days 9-10	Day 11	Days 12-14
N=12	3D Regimen	8 Days Washout	SMZ/TMP 800/160 mg BID	3D Regimen + SMZ/TMP 800/160 mg BID	SMZ/TMP 800/160 mg BID

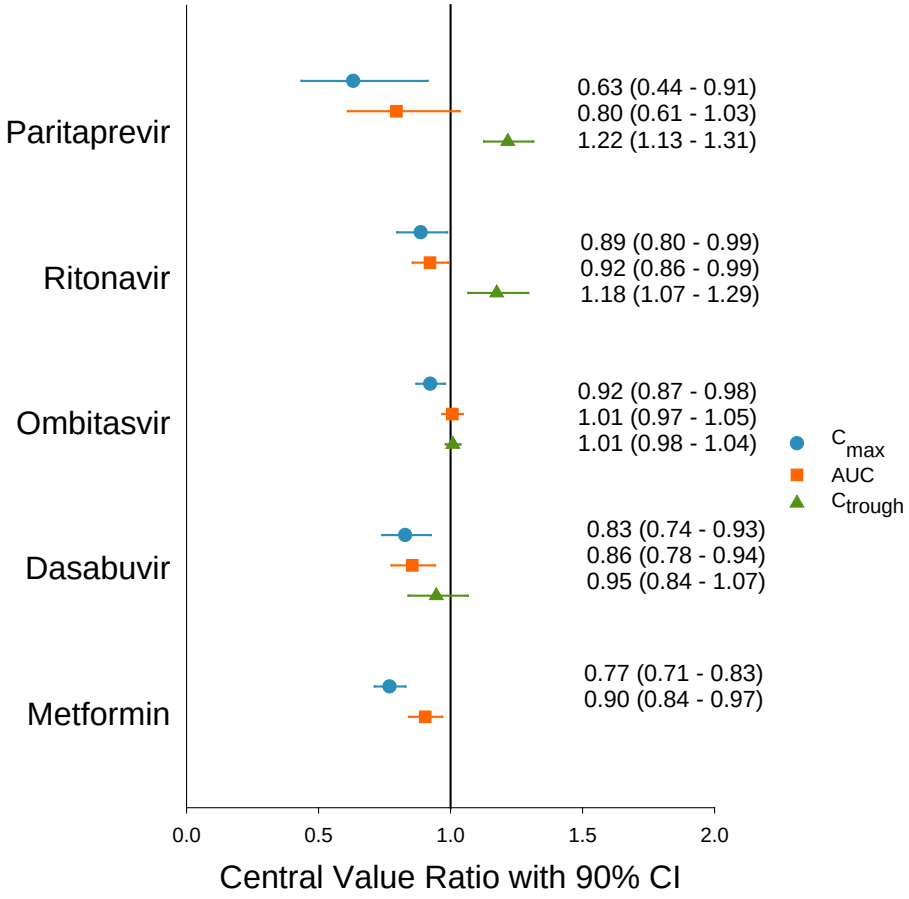
DAAs: ombitasvir/paritaprevir/r 25/150/100 mg *single dose* + dasabuvir 250 mg *single dose*

SMZ and TMP PK sampling: on Day 10 and Day 11; pre-dose and up to 24 hours post dose

DAA PK sampling: on Day 1 and Day 11; pre-dose and up to 72 hours post dose

Results: DDI with Metformin

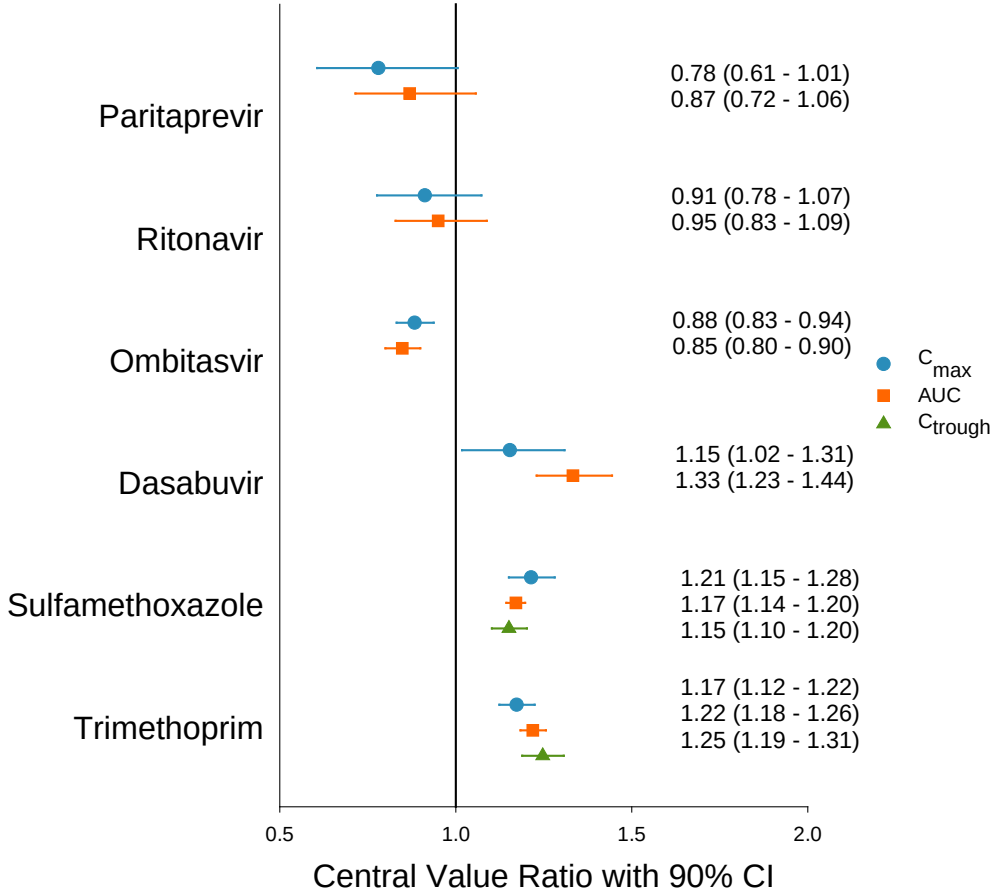
- No dose adjustment is required for the DAAs or metformin when co-administered



Note: AUC = AUC_{24} for paritaprevir, ritonavir and ombitasvir; AUC_{12} for dasabuvir; AUC_{inf} for metformin; C_{trough} = C_{24} for paritaprevir, ritonavir and ombitasvir; C_{12} for dasabuvir

Results: DDI with Sulfamethoxazole/Trimethoprim Combination

- No dose adjustment is required for the DAAs or sulfamethoxazole/trimethoprim when co-administered



Note: AUC = AUC_{inf} for paritaprevir, ritonavir, ombitasvir and dasabuvir; AUC_{12} for sulfamethoxazole and trimethoprim; $C_{trough} = C_{12}$ for sulfamethoxazole and trimethoprim

Safety Results

Across the DDI studies,

- co-administration of the 3D regimen with the comedications was generally well tolerated by the subjects
- no related SAEs or any new or unexpected safety findings were observed.
- no clinically meaningful changes in vital signs values, electrocardiogram parameters, or other laboratory values were observed.

Dosing Recommendations Based on Drug-drug Interactions

Medication (Dose)	Drug Class	Recommendation
Acetaminophen (300 mg)	Analgesic/antipyretic	**No dose adjustment**
Metformin (500 mg)	Antidiabetic	
Sulfamethoxazole (800 mg BID)	Antimicrobial	
Trimethoprim (160 mg BID)	Antimicrobial	
Carisoprodol (250 mg)	Muscle relaxant	**No *a priori* dose adjustment required; increase dose if clinically indicated**
Cyclobenzaprine (5 mg)	Muscle relaxant	
Diazepam (2 mg)	Benzodiazepine/anxiolytic	
Hydrocodone (5 mg)	Opioid analgesic	**Reduce dose by half and/or monitor clinical response**

No dose adjustment is required for the DAAs when co-administered with above commonly used medications

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