ABT-450/Ritonavir +Ombitasvir + Dasabuvir: Drug Interactions Mediated by Transporters

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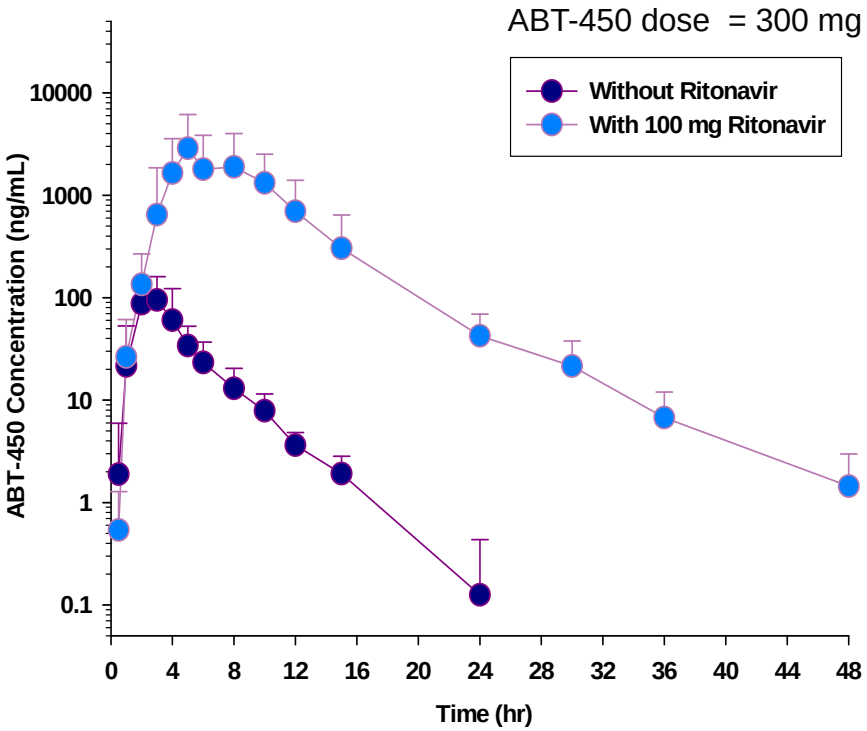
Disclaimers

- All authors are AbbVie employees and may hold AbbVie stocks or options.
- The design, study conduct, analyses and financial support for the clinical trials were provided by AbbVie.
- This presentation contains information on the investigational products ABT-450/r, ABT-267 and ABT-333.

Background

- ABT-267(ombitasvir) is a HCV nonstructural protein 5A (NS5A) inhibitor dosed once daily (QD) in Phase 3 clinical studies.
- ABT-333 (dasabuvir) is a non-nucleoside inhibitor of HCV NS5B polymerase dosed twice daily (BID) in Phase 3 clinical studies.
- ABT-450, identified as a lead compound by AbbVie and Enanta, is a HCV NS3/4A protease inhibitor that is co-administered with ritonavir (ABT-450/r) and dosed QD in Phase 3 clinical studies.

Why is ABT-450 Dosed with Ritonavir?



C_{max}	↑ 28-fold
AUC	↑ 48-fold
C_{12}	↑ 200-fold
C_{24}	↑ 340-fold
$t_{½}$	↑ from 3 hours to 5 hours

- Significant pharmacokinetic boosting allows for QD administration at lower ABT-450 doses while potentially improving the resistance profile.

- Changes in ABT-267 and ABT-333 exposures were ≤ ~50% when dosed with ABT-450 + ritonavir.

Clinical Pharmacology Program

- The final Phase 3 regimen for treatment of HCV genotype (GT) 1- infected subjects included the 3-DAA combination of ABT-450/r/ABT-267 + ABT-333 ± ribavirin (RBV).
- The 3-DAA combination regimen was used for Clinical Pharmacology studies including drug-drug interaction, special populations etc.
  - *Drug –Drug Interaction studies included:*
    - *Mechanism-based: CYPs, UGT and **Transporters***
    - *Special populations (e.g., HIV medications, immunosupressants)*
    - *Commonly used (e.g., antidepressants, sleep aids)*
  - *Hepatic Impairment, renal impairment*
  - *Thorough QT*

Drug-Drug Interaction Program

The drug-drug interaction program characterized the effect of the 3-DAA combination on concomitant medication and the effect of concomitant medication on the 3-DAA combination.

In vitro Transporter Characteristics of DAAs

	Substrate	Inhibitor
Efflux transporters		
P-glycoprotein	X	X
BCRP	X	X
MRP2	X	X
Uptake Transporters		
OATP1B1/B3	X	X
Renal transporters		
OAT1	Neither Substrate nor Inhibitor at clinically relevant concentrations	
OAT3		
OCT2		
MATE1		
MATE2K		

DAAs as Inhibitors of Transporters

The following substrates were used to evaluate the role of DAAs as inhibitors of transporters:

- Digoxin: P-gp
- Pravastatin: OATP1B1/1B3
- Rosuvastatin: BCRP + OATP1B1/B3
- Tenofovir: OAT1

Efflux Transporter P-gp: Effect of the 3-DAA Combination on Digoxin

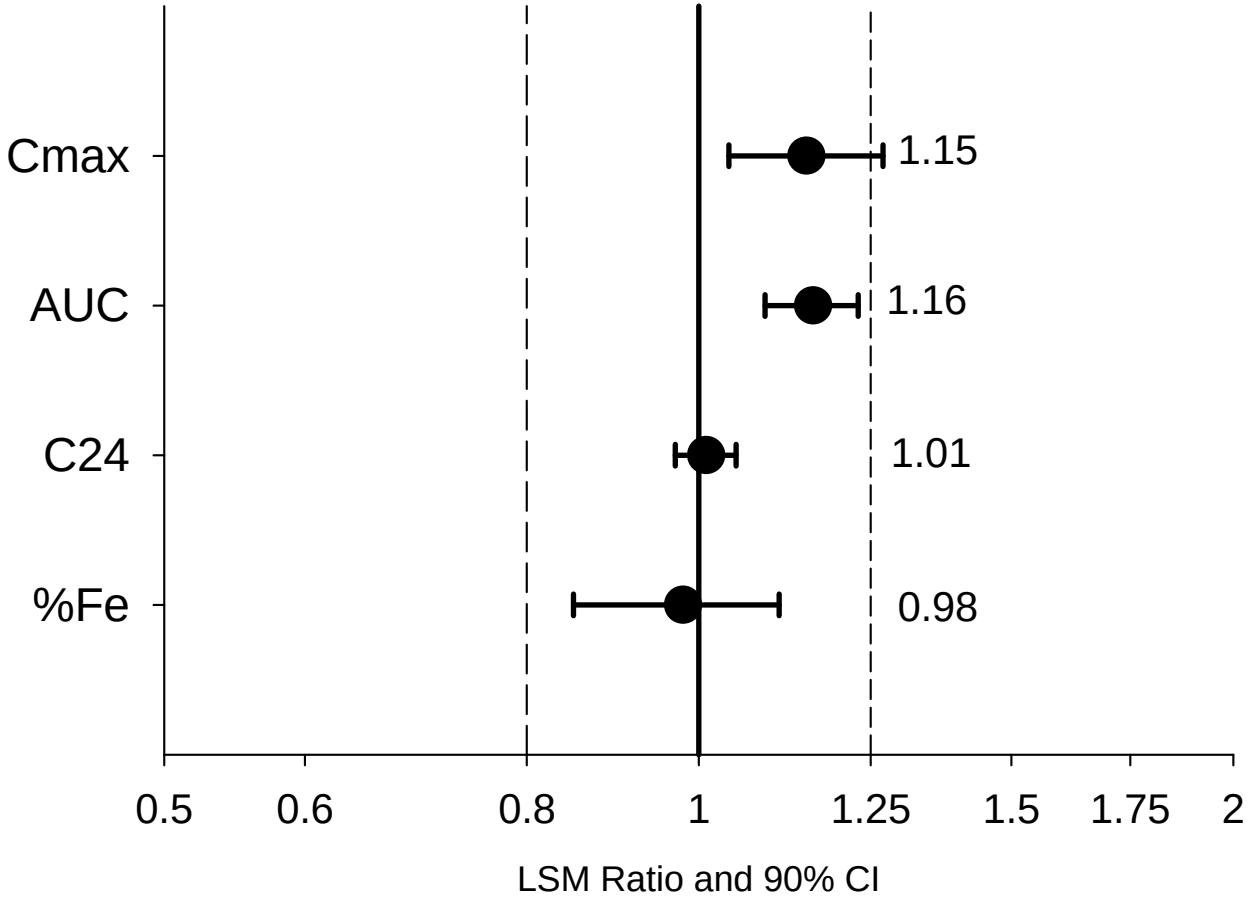
	Period 1		Period 2		
N=12	Day 1	10 Day Washout	Day 1 to 14	Day 15	Day 16 to 19
	Digoxin 0.5 mg		DAAs	DAAs + Digoxin 0.5 mg	DAAs

DAAs: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID

Digoxin plasma and urine sampling: Period 1, Day 1 and Period 2, Day 15

DAA plasma sampling: Period 2, Day 14 and Day 15

Effect of the 3-DAA combination on Digoxin



%Fe : fraction excreted in the urine

DAAs showed a minimal effect on the P-gp substrate, digoxin

Efflux (BCRP) and uptake transporters (OATP1B1/3): Effect of the 3-DAA Combination on Pravastatin & Rosuvastatin

	Period 1		14 Day Washout	Period 2	
N=12 Cohort 1	Day 1			Days 1 to 3	Days 4 to 17
	DAAs			Pravastatin 10 mg	DAAs + Pravastatin 10 mg

	Period 1		14 Day Washout	Period 2	
N=12 Cohort 2	Day 1			Days 1 to 7	Days 8 to 21
	DAAs			Rosuvastatin 5 mg	DAAs + Rosuvastatin 5 mg

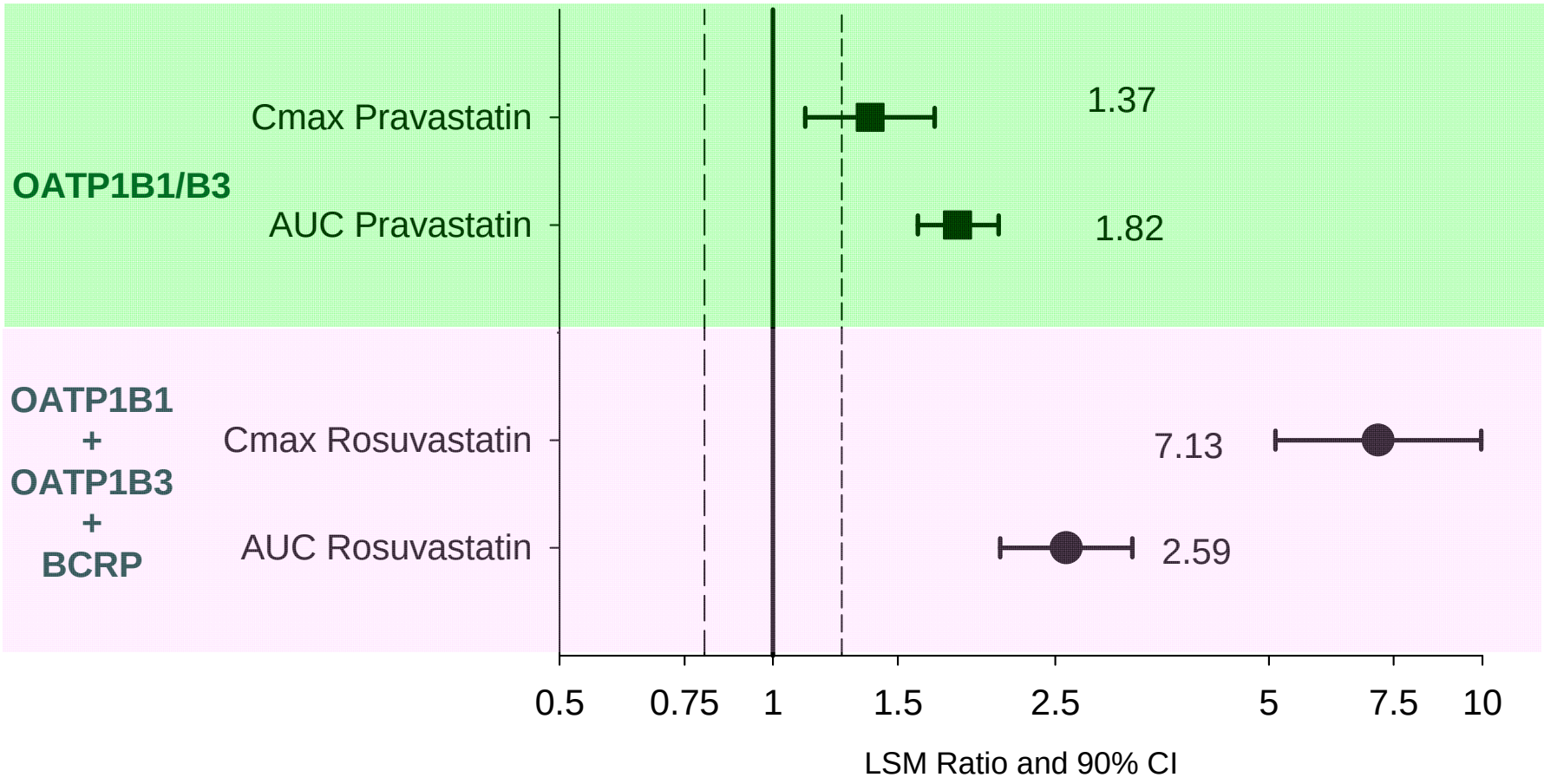
DAAs: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID

DAA plasma sampling: Period 1, Day 1 and Period 2, Days 4 and 17 (Cohort 1) and Period 2, Days 8 and 21 (Cohort 2)

Pravastatin plasma sampling: Days 3, 4 and 17

Rosuvastatin plasma sampling: Days 7, 8 and 21

Effect of the 3-DAA Combination on Pravastatin and Rosuvastatin



Dosing recommendations

Since exposures of OATP1B1/B3 and BCRP substrates are higher in the presence of the 3-DAA combination, dose reductions are recommended when dosing with the 3-DAA combination

- Pravastatin dose should be reduced by half
- Rosuvastatin dose should be limited to 10 mg

OAT1: Effect of the 3-DAA Combination on Tenofovir

N=18

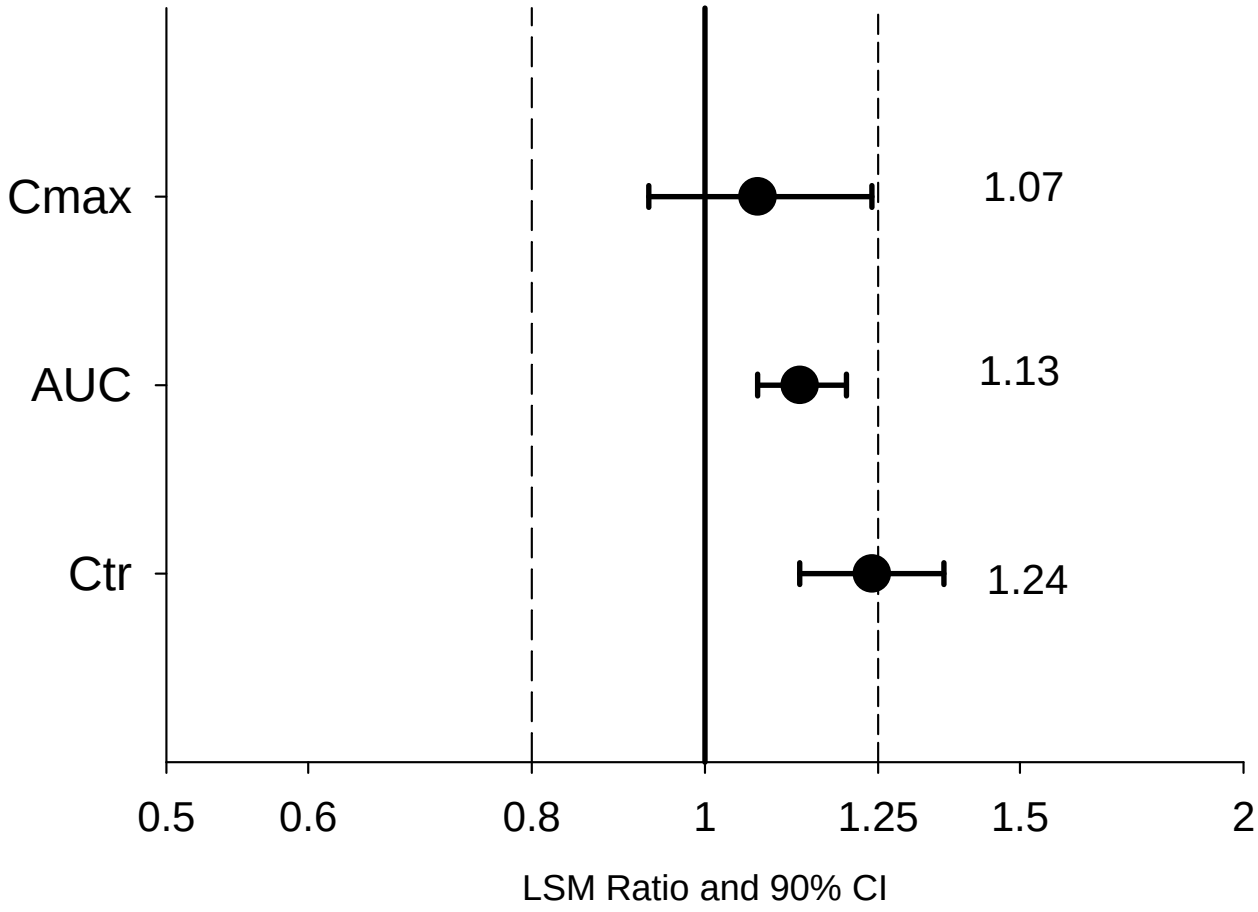
	Days 1-7	Days 8-14	Days 15-21
Cohort 1	DAAs		DAAs + Emtricitabine 200 mg QD + Tenofovir 300 mg QD
Cohort 2	Emtricitabine 200 mg QD + Tenofovir 300 mg QD	DAAs+ Emtricitabine 200 mg QD + Tenofovir 300 mg QD	

DAAs: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID

DAA plasma sampling:
Cohort 1: Days 14, 15 and 21
Cohort 2: Days 8 and 21

Emtricitabine and Tenofovir plasma sampling:
Cohort 1: Days 15 and 21
Cohort 2: Days 7, 8 and 21

Effect of the 3-DAA Combination on Tenofovir



DAAs showed a minimal effect on the OAT1 substrate, tenofovir

DAAs as Substrates of Transporters

The following inhibitors were used to evaluate the role of transporters on DAA disposition:

- Cyclosporine: OATP1B + P-gp + BCRP
- Atazanavir: OATP1B1/B3 (*also a CYP3A inhibitor)*
- Ketoconazole: P-gp (*also a CYP3A inhibitor)*

Ritonavir in the regimen is a CYP3A and P-gp inhibitor

For DAAs, data from Phase 2 studies indicate that a 50% decrease in exposure or a 100% increase in exposures did not meaningfully affect safety or efficacy. Thus no dose adjustments for DAAs are recommended for exposures 0.5x to 2.0x

OATP1B + P-gp + BCRP transporters: Effect of Cyclosporine A on DAAs

N=12

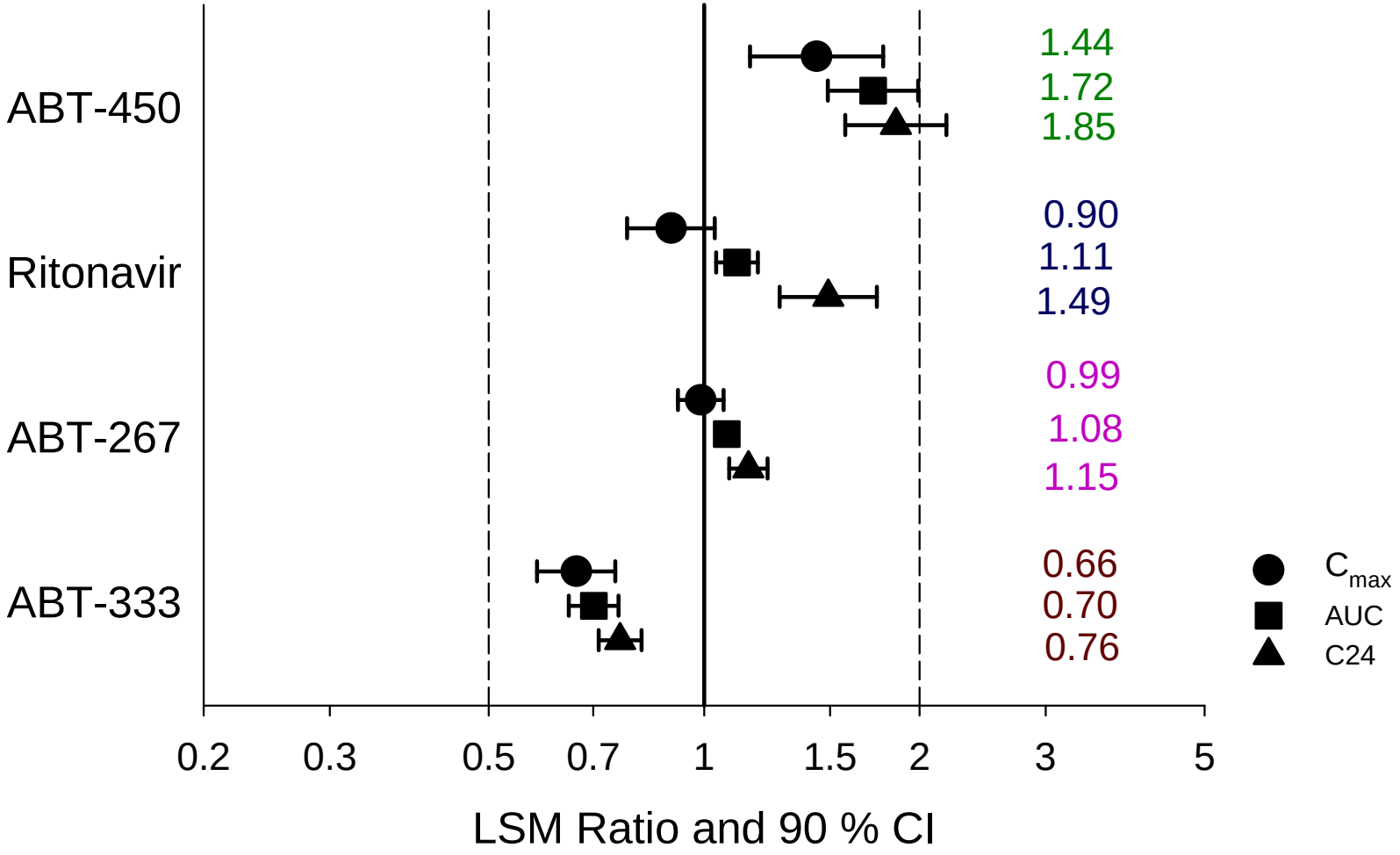
Period 1	7 Day Washout	Period 2			
Day 1		Day 1	Days 2-14	Day 15	Days 16-21
CsA 100 mg		DAAs + CsA 30 mg	DAAs	DAAs + CsA 30 mg	DAAs

DAAs: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID

Cyclosporine blood sampling: Period 1, Day 1 and Period 2, Days 1 and 15

DAA plasma sampling: Day 14 and 15

Effect of Cyclosporine on DAAs



Dose Recommendation

- Inhibition of P-gp, BCRP and OATP1B showed a modest increase in ABT-450 exposures and a modest decrease in ABT-333 exposures.
- No dose adjustment for DAAs is recommended when dosed with cyclosporine.

OATP1B1/B3: Effect of Atazanavir on DAAs

N=24

	Days 1-14	Days 15-28
Cohort 1	DAAs	DAAs + Atazanavir 300 mg QD
Cohort 2	Atazanavir 300 mg QD + ritonavir 100 mg	DAAs + Atazanavir 300 mg QD

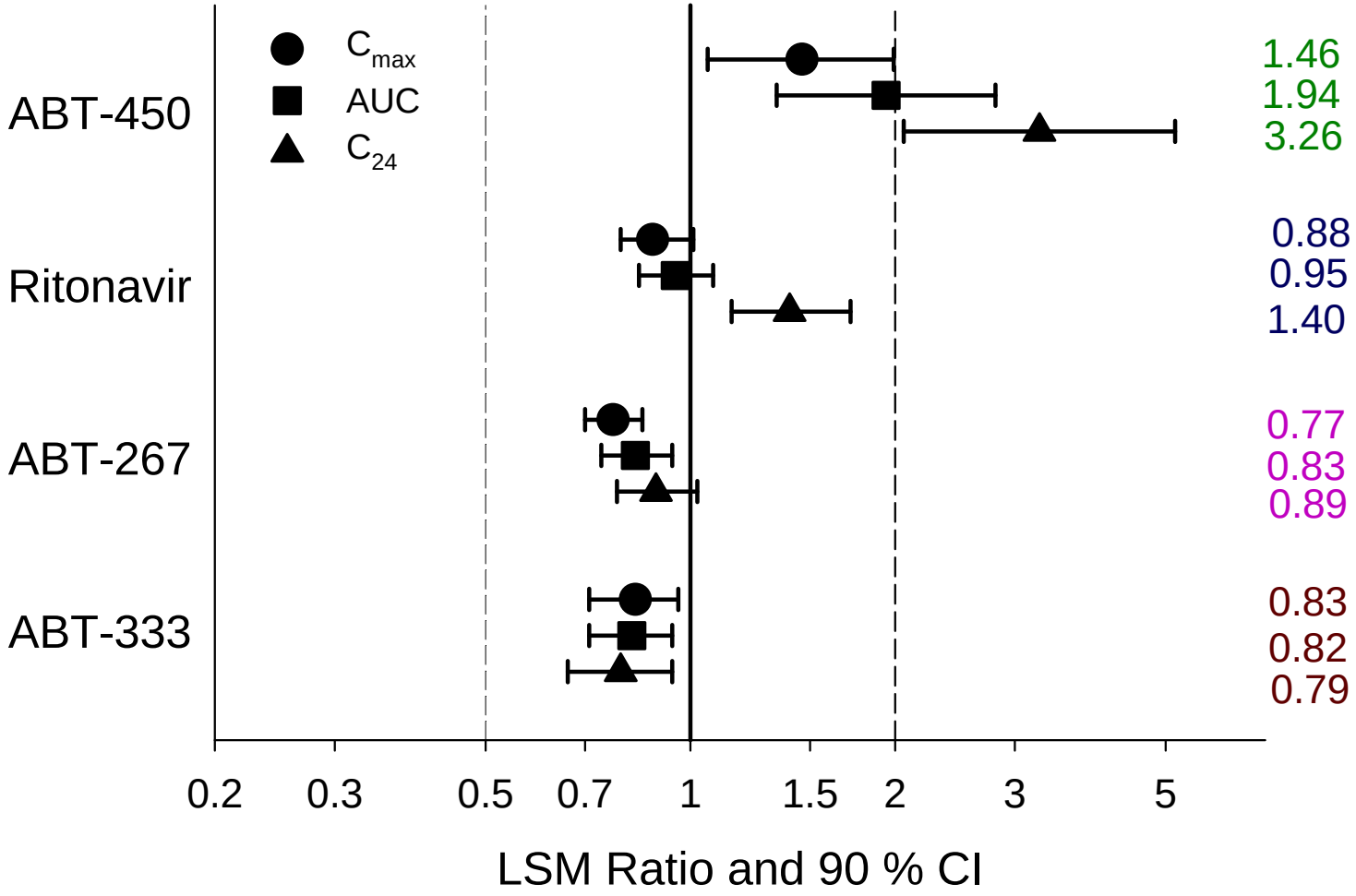
DAAs: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID

DAA plasma sampling:
Cohort 1: Days 14, 15 and 28
Cohort 2: Days 15 and 28

Atazanavir sampling:
Cohort 1: Days 15 and 28
Cohort 2: Days 14, 15 and 28

Atazanavir is also a moderate inhibitor of CYP3A.

Effect of Atazanavir on DAAs



Atazanavir is also a moderate inhibitor of CYP3A.

Dosing recommendations

Inhibition of OATP1B1/B3 increases ABT-450 exposures by up to 2-fold. Exposures >2-fold have been found to be safe and well tolerated in Phase 2 studies.

- No dose adjustment for DAAs is required when dosed with atazanavir.

Efflux transporter P-gp: Effect of Ketoconazole on DAAs

N=12

Period 1	7 Day Washout	Period 2		
Day 1		Days 1 and 2	Day 3	Days 4 to 6
DAAs		Ketoconazole 400 mg QD	DAAs + Ketoconazole 400 mg QD	Ketoconazole 400 mg QD

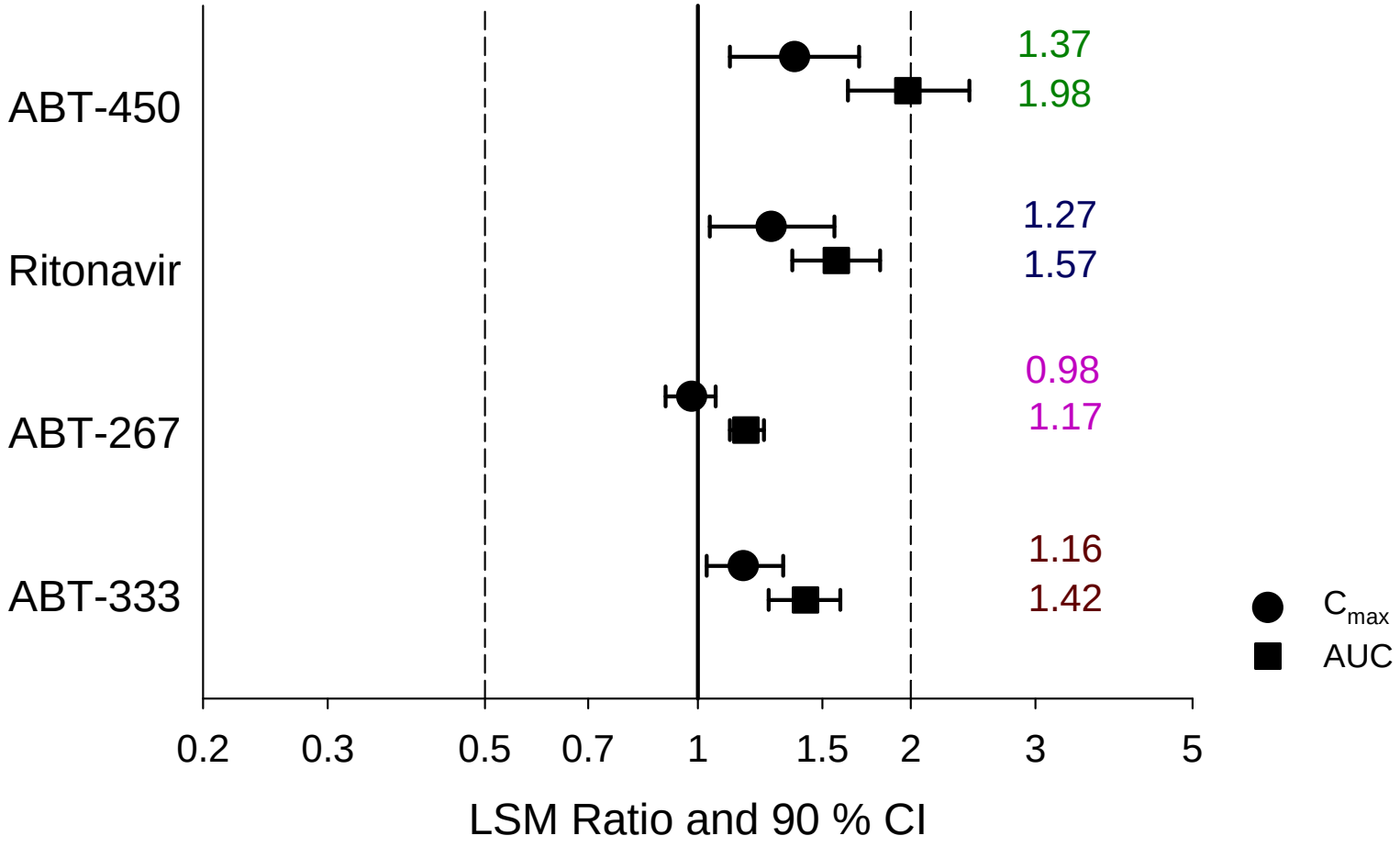
DAAs: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 400 mg BID

DAA plasma sampling: Period 1, Day 1 and Period 2, Day 3

Ketoconazole plasma sampling: Period 2, Day 2 and Day 3

Ketoconazole is also a strong inhibitor of CYP3A.

Effect of Ketoconazole on the 3-DAA combination



Ketoconazole is also a strong inhibitor of CYP3A.

Dose Recommendations

Inhibition of P-gp + CYP3A by ketoconazole (*in addition to that due to ritonavir in the regimen*) increases ABT-450 exposures by up to 2-fold. Exposures >2-fold have been found to be safe and well tolerated in Phase 2 studies.

- No dose adjustment of DAAs is recommended when dosed with ketoconazole

List of Substrates and Inhibitors Co-administered in Phase 3 Studies

Substrate	Number of Subjects
OATP1B	374
P-gp	739
BCRP	473
MRP2	336
Inhibitors	**Number of Subjects**
OATP1B	969
P-gp	52
BCRP	461
MRP2	553

> 6 weeks of co-administration

- The effect of inhibitors on DAA AUC was evaluated based on post-hoc values from the population pharmacokinetic models. Results were consistent with data from Phase 1 studies described earlier.
- Substrates were successfully managed in the clinical trials using clinical monitoring and/or dose adjustment of the substrates (e.g. statins).

Conclusions

The 3-DAA combination did not show clinically meaningful inhibition of the **P-glycoprotein** substrate, digoxin.

The 3-DAA combination showed a modest inhibitory effect on **OATP1B**. Dose reductions up to 50% for OATP1B substrates might be required.

Substrates of all three transporters (**OATP1B1 + OATP1B3 + BCRP**) showed a greater increase in exposure requiring > 2-fold reduction in dose when dosed with the 3-DAA combination.

Inhibitors of **OATP1B1/B3, P-glycoprotein, and BCRP** showed minimal effect on ABT-333 and ABT-267 and increased exposures of ABT-450 by up to 2-fold. No dose modification of the DAAs is recommended based on this interaction.

Based on in vitro data and clinical exposures, DAAs (or ritonavir) are not expected to interact with substrates of renal transporters

The effect of transporter inhibitors in Phase 3 studies was consistent with data from Phase 1 studies. Transporter substrates were successfully managed in the clinical trials using clinical monitoring and/or dose adjustment of the substrates.