The Pharmacokinetics and Safety of the Direct Acting Antiviral Regimen of ABT-450/r, Ombitasvir with/without Dasabuvir in Subjects with Mild, Moderate and Severe Renal Impairment Compared to Subjects with Normal Renal Function

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Disclosures

Amit Khatri, Sandeep Dutta, Lino Rodrigues-Jr, Haoyu Wang, Walid Awni and Rajeev Menon: Employees of AbbVie and may hold/ have filed **Patent** for AbbVie and hold **Stocks** of AbbVie

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This presentation contains information on the investigational products ABT-450/r, ombitasvir (ABT-267), and dasabuvir (ABT-333).

Background: Chronic Hepatitis C and Renal Insufficiency

- Epidemiologic studies suggest that chronic HCV infection is an independent risk factors for developing chronic renal insufficiency compared to patients without HCV [1, 2, 3]
- However, treatment with interferon (IFN)-based regimens have led to low sustained virologic response (SVR) rates in this patient population, particularly among those with advanced renal insufficiency [4]
- An IFN-free DAA regimen is not available for HCV genotype 1 infected patients with severe renal insufficiency

1: Tsui J 2007; 2 Butt A 2011; 3 Lucas 2013; 4. Fabrizi F 2013

The 3D Direct-Acting Antiviral Regimen

The 3 direct-acting antiviral (3D) regimen consists of:

- **ABT-450:** a potent HCV NS3/4A protease inhibitor (identified by AbbVie and Enanta)
  - Co-dosed with the pharmacokinetic enhancer **ritonavir*** (ABT-450/r) to increase peak and trough ABT-450 exposure, enabling once-daily dosing[1]
- **Ombitasvir** (formerly ABT-267): a potent NS5A inhibitor
- **Dasabuvir** (formerly ABT-333): a non-nucleoside NS5B RNA polymerase inhibitor

In Phase 3 trials, the 3D regimen with RBV achieved SVR_{12} rates of 96% in treatment-naïve and -experienced GT1 infected patients without cirrhosis and 92-96% in patients with cirrhosis; 3D without RBV achieved SVR_{12} rates of 100% in GT1b-infected treatment-naïve and -experienced patients [2, 3, 4, 5]

***Ritonavir does not have antiviral activity against HCV.**

1. Menon RM, et al. HEP DART. 2009 (Abstract 57). 2. Poordad F et al., N Engl J Med. 2014;370 (21):1973-82; 3. Feld JJ et al., N Engl J Med. 2014; 370 (17): 1594-03; 4. Ferenci P et al., N Engl J Med. 2014 ;370 (21):1983-92; 5. Zeuzem S et al., N Engl J Med 2014; 370:1604-1614

The 2D Direct-Acting Antiviral Regimen

The 2D regimen of ABT-450/r/ombitasvir is currently being investigated in HCV GT4 infected patients.

- Both DAAs have shown potent antiviral activity *in vitro* against HCV GT1a, 1b, 2a, 2b, 3a, 4a, and 6a
- In GT4-infected patients, the 2D regimen with RBV achieved SVR_{12} rates of 100% in treatment-naïve and treatment-experienced patients without cirrhosis[1]
  - 2D regimen without RBV achieved SVR_{12} rates of 91% in treatment-naïve GT4-infected patients[1]

1. Hezode C, et al. EASL. 2014

Objective

To evaluate the pharmacokinetics and safety of a single dose of the 3D and 2D regimens in HCV-negative subjects with various degrees of renal impairment.

3D regimen: ABT-450/r 150/100mg +ombitasvir 25mg +dasabuvir 400mg

2D regimen: ABT-450/r 150/100mg + ombitasvir 25mg

Methods: Study Design

Phase 1, multicenter, single dose, non-fasting, open-label, 2-period study

Renal Function Groups	Creatinine clearance* (ml/min)	N
Mild renal impairment	60 – 89	6
Moderate renal impairment	30 – 59	6
Severe renal impairment	15 – 29	6
Normal renal function	≥ 90	6

* Cockcroft-Gault equation; In addition eGFR was also estimated using the MDRD equation

- Subjects with normal renal function were matched to those with severe renal impairment based on age (± 10 yr), weight (± 10%), sex and race

Period 1 (7 days)	Washout 14 days	Period 2 (7 days)
3D regimen		2D regimen

- Intensive plasma and urine sampling up to 144 h post dose for PK assessment

Methods: Key Eligibility Criteria

- 18–70 years of age without HCV infection
- Body mass index ≥18 and <38 kg/m^2 and body weight > 50 kg
- Normal renal function: Judged to be in general good health based upon the results of a medical history, physical examination, laboratory profile, ECG and estimated CrCl ≥ 90 mL/min
- Renal impairment: Judged to be in stable condition based upon the results of a medical history, physical examination, laboratory profile and ECG with presence of clinically significant renal impairment based on estimated CrCl

Methods: Pharmacokinetic Analysis

- Pharmacokinetic parameters (C_{max}, AUC_{∞}, $t_{1/2}$) of DAAs and ritonavir were determined by non-compartmental analysis (Phoenix™ WinNonlin®, Version 6.3)
- Urinary excretion of DAAs and ritonavir was determined over 144 hours after dosing
- Plasma protein binding of DAAs and ritonavir was determined at concentrations comparable to their C_{max}
- Linear regression analyses (modeling) were conducted to evaluate the relationship between DAA and ritonavir exposure (C_{max} and AUC) and CrCl as a continuous variable
  - Regression analyses were also conducted using eGFR (estimated by the MDRD equation) as a measure of renal function

Results: Subject Demographics

	Mild Renal Impairment (N = 6)	Moderate Renal Impairment (N = 6)	Severe Renal Impairment (N = 6)	Normal Renal Function (N = 6)
Age	68 ± 3.3	62 ± 5.0	62 ± 9.5	59 ± 8.2
Weight	70 ± 7.7	83 ± 11.9	78 ± 12.1	91 ± 7.4
BMI	26.2 ± 3.1	28.7 ± 4.0	27.2 ± 3.2	30.1 ± 3.1
Gender	3 males	6 males	6 males	6 males
Race	6 Caucasians	4 Caucasians, 2 Blacks	5 Caucasians, 1 Black	5 Caucasians, 1 Black
Smokers	2 former, 4 never	3 former, 3 never	2 former, 4 never	1 former, 5 never
Alcohol	2 current, 4 never	2 former, 4 never	2 current, 4 never	1 current, 5 never

All renal function groups were comparable to each other, except for presence of females and lack of blacks in the mild renal impairment group.

Pharmacokinetic Results: 3D regimen (N = 24)

Compared to normal hosts the following changes were observed:

Mild renal impairment:

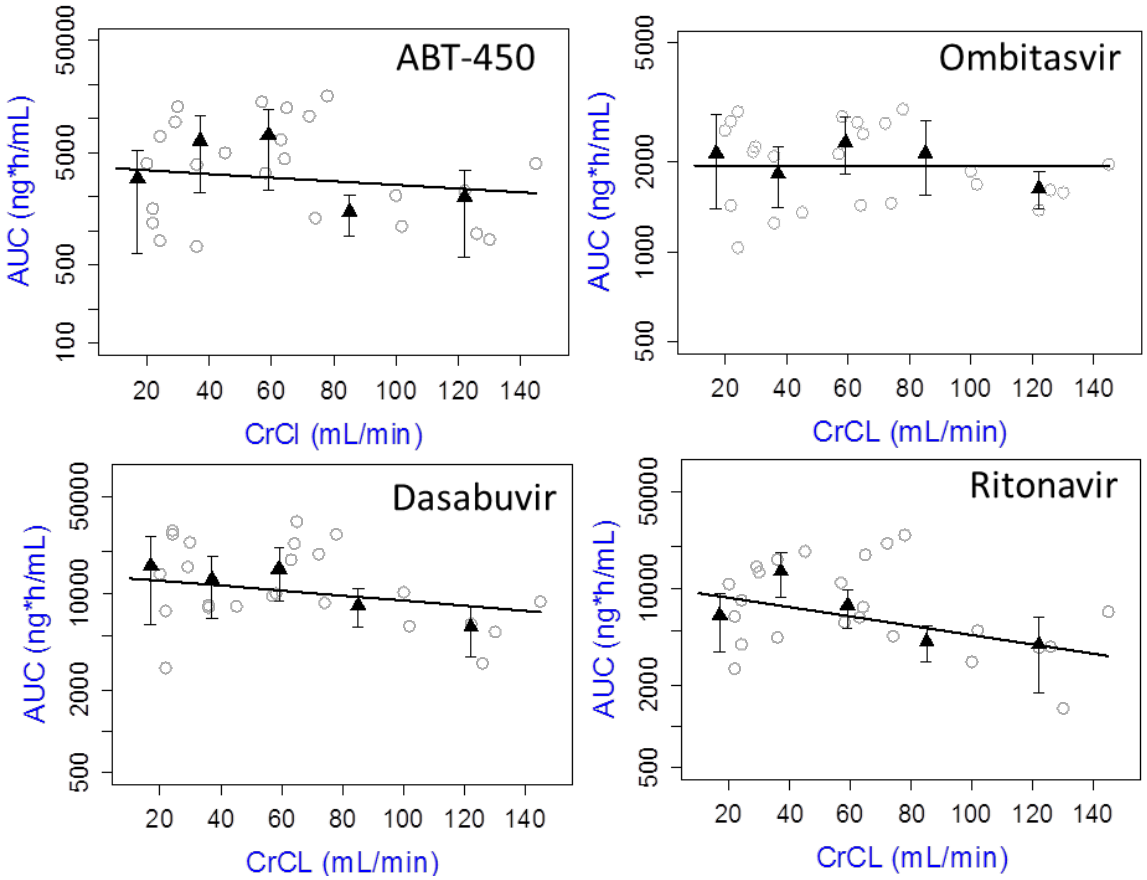
- Ombitasvir AUC was comparable
- ABT-450 and dasabuvir AUC were up to 20% higher
- RTV AUC was 42% higher

Moderate renal impairment:

- Ombitasvir AUC was comparable
- ABT-450 and dasabuvir AUC were up to 37% higher
- RTV AUC was 80% higher

Severe renal impairment:

- Ombitasvir AUC was comparable
- ABT-450 and dasabuvir AUC were up to 50% higher
- RTV AUC was 114% higher



▲ represents mean AUC in a bin of 4 to 5 subjects and error bars represents 95% CI .
Slope was statistically significant ($P < 0.05$) only for ritonavir.
Similar relationships were observed for C_{max} values and also with eGFR (instead of CrCL).

Pharmacokinetic Results: 2D regimen (N = 24)

Compared to normal hosts the following changes were observed:

Mild renal impairment:

- Ombitasvir AUC was comparable
- ABT-450 AUC was 11% higher
- RTV AUC was 40% higher

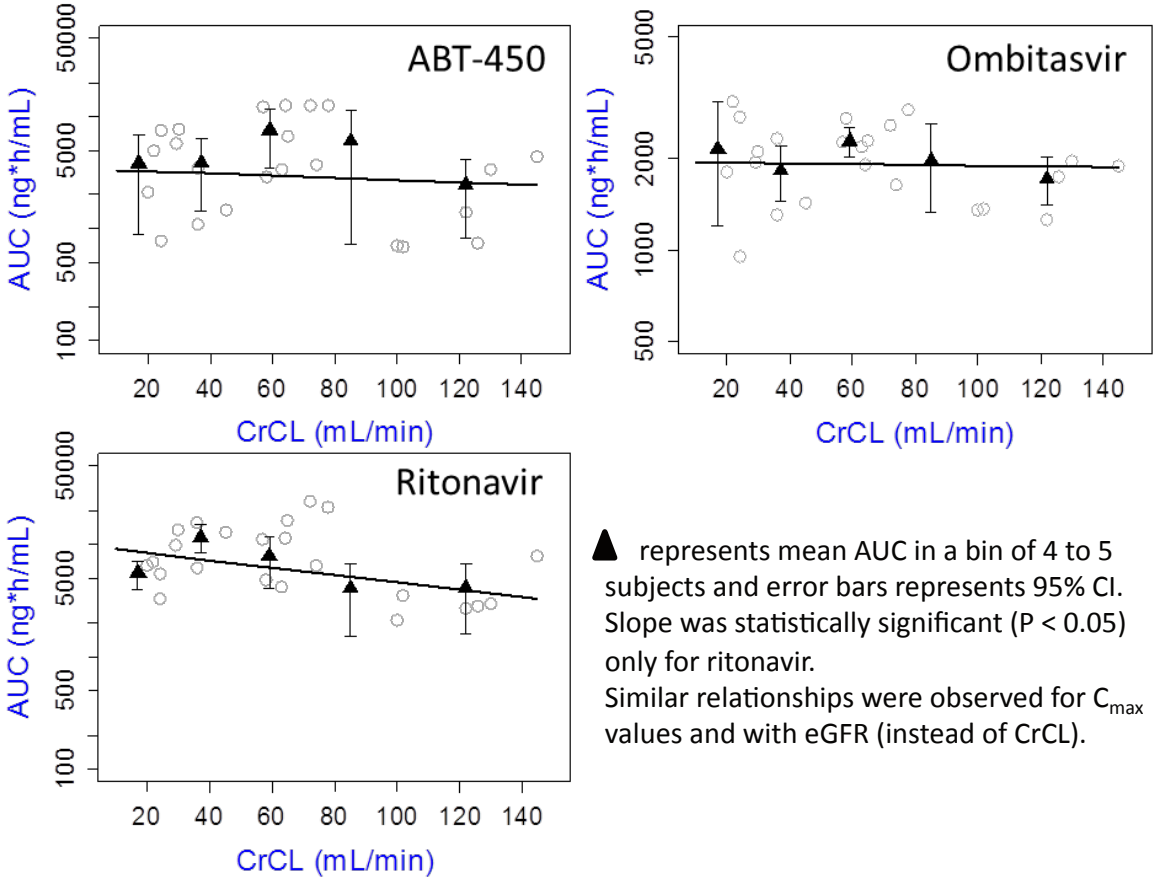
Moderate renal impairment:

- Ombitasvir AUC was comparable
- ABT-450 AUC was 20% higher
- RTV AUC was 76% higher

Severe renal impairment:

- Ombitasvir AUC was comparable
- ABT-450 AUC was 25% higher
- RTV AUC was 108% higher

2D regimen results are consistent with 3D regimen



▲ represents mean AUC in a bin of 4 to 5 subjects and error bars represents 95% CI. Slope was statistically significant ($P < 0.05$) only for ritonavir.
Similar relationships were observed for C_{max} values and with eGFR (instead of CrCL).

Pharmacokinetic Results: 3D and 2D regimen

- None of the changes in drug exposures were clinically relevant
  - Based on Phase 2 studies, these changes in DAA exposures are not clinically relevant for safety
  - 2-fold higher ritonavir doses (200 mg/day) compared to those included as part of the 3D or 2D regimens (100 mg/day) are used for boosting of HIV-1 protease inhibitors (darunavir, lopinavir, saquinavir and tipranavir)
- The half-lives of the DAAs and ritonavir in renal impaired subjects was comparable to healthy subjects
- The urinary fraction of unchanged excreted drugs was ≤1.5%
- The fraction of drugs unbound to plasma proteins was unaffected by renal impairment

Safety Results: 3D and 2D regimen

- No new or unexpected safety findings were observed (N = 24)
- No treatment emergent adverse events (TEAEs) occurred in more than 1 subject in any group
- No serious TEAEs were reported

Regimen	TEAE	Normal	Mild RI	Mod. RI	Severe RI
3D	Nausea			1/6	
	Myalgia			1/6	
	catheter site erythema/ swelling			1/6	
2D	Nausea/vomiting			1/6	1/6
	Diarrhea		1/6		
	catheter site phlebitis				1/6
	Concussion*		1/6		

RI = Renal Impairment

*subject accidentally closed the car door on the head

Conclusions

- Pharmacokinetic results were consistent across the 3D and 2D regimens
- The exposure of DAAs were ≤ 20%, 37% and 50% higher and of ritonavir were ≤ 42%, 80% and 114% higher in subjects with mild, moderate and severe renal impairment, respectively, compared to subjects with normal renal function
- None of the changes in drug exposures were clinically relevant and they do not require dose adjustment
- Clinical studies in HCV-infected patients with renal insufficiency are planned in light of these pharmacokinetic results

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