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*APPLICATION NUMBER:*

**207931Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW**

<b>NDA: 207931</b>	Submission Date: February 25, 2015
<b>Brand Name</b>	TECHNIVIE™
<b>Generic Names</b>	Ombitasvir (ABT-267)/Paritaprevir (ABT-450)/ Ritonavir
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<b>OND Division</b>	Division of Antiviral Products (DAVP)
<b>Applicant</b>	Abbvie Inc.
<b>Formulation; strength(s) to-be-marketed</b>	Tablets; 12.5 mg/75 mg/50 mg ABT-267/ABT-450/ritonavir coformulated tablets
<b>Proposed Indication</b>	Treatment of HCV Genotype 4 Infection
<b>Review Type</b>	505 (b)(1) New Drug Application, Priority Review

<b>1</b>	<b>Background</b> .....	<b>2</b>
1.1	Recommendations .....	2
<b>2</b>	<b>Overview of Efficacy and Safety</b> .....	<b>3</b>
2.1	Exposure-Response (Efficacy and Safety) Relationships .....	4
<b>3</b>	<b>Formulation Development</b> .....	<b>4</b>
<b>4</b>	<b>Intrinsic Factors:</b> .....	<b>5</b>
4.1	Hepatic Impairment:.....	5
4.2	Renal Impairment:.....	6
<b>5</b>	<b>Extrinsic Factors</b> .....	<b>6</b>
5.1	Effect of Food.....	6
5.2	Drug-Drug Interactions (DDIs).....	7
<b>6.</b>	<b>Appendices</b> .....	<b>18</b>
6.1	Individual Study Reviews.....	18

## 1 Background

Abbvie Inc. is seeking approval of TECHNIVIE™, a co-formulated product containing Ombitasvir (ABT-267)/Paritaprevir (ABT-450)/ritonavir for the treatment of genotype 4 chronic hepatitis C infection. ABT-267 is a non-structural protein 5A [NS5A] inhibitor and ABT-450 is a NS3/4A protease inhibitor. The remainder of this review will refer to ombitasvir as ABT-267 and paritaprevir as ABT-450; the combination of ABT-267/ABT-450/ritonavir co-formulated tablet will be referred to as TECHNIVIE™ or the “2-DAA regimen”.

It should be noted that VIEKIRA PAK™, a combination of Ombitasvir (ABT-267)/Paritaprevir (ABT-450)/ritonavir co-formulated tablets and Dasabuvir (ABT-333) tablets is approved for the treatment of genotype 1 chronic hepatitis C infection (NDA # 206619). Because ABT-333 has no activity against HCV GT4, it was not included in the DAA combination regimen evaluated for the treatment of HCV GT4 under NDA 207931.

The applicant has proposed the use of TECHNIVIE™ + ribavirin (weight based; 1000 mg/day for patients < 75 kg and 1200 mg/day for patients ≥ 75 kg) for 12 weeks for the treatment of genotype 4 infection in patients without cirrhosis. The 2-DAA regimen (with or without ribavirin) was not evaluated in patients with genotype 4 infection with cirrhosis, hence an optimal treatment regimen and duration for this population has not been identified.

The proposed total daily dose of ABT-267/ABT-450/ritonavir co-formulated tablets is 25 mg/150 mg/100 mg (2 X 12.5/75/50 mg coformulated tablets given orally once daily with a meal).

The clinical development program for the 2-DAA regimen included one phase 2 randomized controlled trial, M13-393, “ A Randomized Open-Label Study to Evaluate the Safety and Efficacy of Co-administration of ABT-450 with ritonavir (ABT-450/r) and ABT-267 in Adults with Chronic Hepatitis C Virus Infection (PEARL-I)”. In addition, the applicant submitted the results from one absolute bioavailability trial (M14-229). As part of review of the current application, in addition to reviewing the results from M14-229, drug-drug interaction data obtained using the 2-DAA regimen (8 trials) was also reviewed. Further, information pertaining to the DDI trials conducted using the 2-DAA regimen that was previously reviewed as part of the VIEKIRA PAK™ NDA (NDA 206619) was incorporated in this review in the relevant sections.

### 1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information in this NDA and the information provided supports the approval of the application. The clinical pharmacology review team has the following recommendations which are different from the applicant’s proposed recommendations:

- 1) When TECHNIVIE™ is co-administered with buprenorphine/naloxone, clinical monitoring for sedation and cognitive effects is recommended.
- 2) TECHNIVIE™ can be co-administered with rosuvastatin without any “dose capping” of rosuvastatin (applicant had originally proposed to dose “cap” the rosuvastatin dose to 20 mg once daily).
- 3) Co-administration of TECHNIVIE™ with atazanavir is not recommended.
- 4) There is no pharmacokinetic data available to support co-administration of TECHNIVIE™ with darunavir/ritonavir 800/100 mg once daily (administered in the evening) and darunavir/ritonavir 600/100 mg twice daily regimen.

## 2 Overview of Efficacy and Safety

Trial M13-393 evaluated the 2-DAA regimen (ABT-450/r and ABT-267) in HCV GT4-infected treatment-naïve and treatment-experienced non-cirrhotic adult subjects. HCV GT4-infected patients received 2-DAA with and without RBV for 12 weeks. The study also evaluated 12 weeks of treatment with the 2-DAA regimen in HCV GT1b-infected treatment-naïve and treatment-experienced patients without cirrhosis and 24 weeks of treatment in HCV GT1b-infected patients with compensated cirrhosis. The primary efficacy end point was SVR<sub>12</sub> defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after the last dose. Table 1 shows the SVR<sub>12</sub> rates for treatment naïve and treatment experienced GT4 infected patients

**Table 1: SVR<sub>12</sub> rates for Treatment Naïve and Treatment Experienced GT4-infected Patients**

<b>Population</b>	<b>Regimen</b>	<b>SVR<sub>12</sub> rates</b>
<b>Treatment naïve, non-cirrhotic GT4</b>	<b>2-DAA for 12 weeks</b>	<b>90.9%</b>
<b>Treatment naïve, non-cirrhotic GT4</b>	<b>2-DAA+RBV for 12 weeks</b>	<b>100 %</b>
<b>Treatment experienced, non-cirrhotic GT4</b>	<b>2-DAA+RBV for 12 weeks</b>	<b>100 %</b>

In non-cirrhotic HCV GT4-infected treatment-naïve and treatment-experienced subjects, administration of the 2-DAA regimen for 12 weeks with or without RBV was generally well tolerated. Headache, asthenia, fatigue, nausea, and insomnia were the most common treatment-emergent adverse events and overall, the adverse event profile was consistent with that of VIEKIRA PAK™. In addition, per the applicant, bilirubin-related events, anemia-related, drug-induced rash, and hepatotoxicity-related events, including analyses of elevations in ALT in Study M13-393 were consistent with those observed with VIEKIRA PAK™. These data indicate that the safety profile of the 2-DAA regimen is similar to the safety profile of VIEKIRA PAK™.

## 2.1 Exposure-Response (Efficacy and Safety) Relationships

No exposure-response analysis for efficacy was conducted because there were only three virologic failures in trial M13-393.

Exposure-response analysis for safety was conducted as part of the clinical pharmacology review of VIEKIRA PAK™. As previously mentioned, the adverse event profile of the 2-DAA regimen was similar to VIEKIRA PAK™, in part because the majority of the adverse events are driven by increases in ABT-450 exposures (dose of ABT-450 is similar between VIEKIRA PAK™ and TECHNIVIE™).

## 3 Formulation Development

ABT-267/ABT-450/ritonavir is a film coated, co-formulated, immediate release tablet containing 12.5 mg ABT-267, 75 mg ABT-450, and 50 mg ritonavir.

In trial M13-393 (safety and efficacy trial in genotype 4 hepatitis C patients), the applicant used the ABT-450 (b)(4) tablet (ABT-450 150 mg dosed as three ABT-450 50 mg tablets) with ritonavir soft gelatin capsule ([SGC] dosed as one ritonavir 100 mg SGC) and ABT-267 (b)(4) tablet (dosed as one ABT-267 25 mg tablet) in combination with or without ribavirin (ribavirin 1000 mg to 1200 mg orally (PO) divided twice daily dosed as five to six 200 mg strength tablets). The applicant conducted trial M13-391 to compare the bioavailability of ABT-450, ritonavir, ABT-267 (administered as ABT-267/ABT-450/r co-formulated tablets) with reference to the ABT-450 (b)(4) tablet administered with ritonavir and ABT-267 and with reference to the ABT-450 and Ritonavir co-formulated tablets (ABT-450/r) administered with ABT-267. The summary of findings from trial M13-391 are shown in Table 2 below (please refer to the biopharmaceutics review of NDA 206619 for additional details):

**Table 2: Ratio of C<sub>max</sub> and AUC of ABT-450, ritonavir, and ABT-267 after single dose administration of ABT-450/ritonavir/ABT-267 coformulated tablet and ABT-450 (b)(4) tablet, RTV SGC tablet and ABT-267 (b)(4) tablet**

	ABT-450	RTV	ABT-267
	ABT-450/r/ABT-267 Co-formulated vs. ABT-450 (b)(4) Tablet + RTV SGC + ABT-267 (b)(4) Tablet		
C <sub>max</sub>	1.926	1.234	0.924
AUC	1.628	1.163	0.959
	ABT-450/r/ABT-267 Co-formulated vs. ABT-450/r Co-form + ABT-267 (b)(4)		
C <sub>max</sub>	0.917	0.989	0.845
AUC	0.886	0.988	0.890

Least Square Mean (LSM) Ratios.

Comparison shown for ABT-450 150 mg, RTV 100 mg and ABT-267 25 mg.

After single dose administration under non-fasting conditions, the mean  $C_{max}$  and AUC of ABT-450 administered as ABT-267/ABT-450/r co-formulated tablets was ~93 % and 63 % higher, respectively, compared with the mean AUC of ABT-450 (co-administered with ritonavir +ABT-267) administered as (b) (4) tablets. The mean systemic exposure of ritonavir and ABT-267 was similar between the co-formulated product and the individually administered products.

Because the to-be-marketed formulation will be the ABT-267/ABT-450/ritonavir coformulated product, the safety implications of higher ABT-450 exposures with the coformulated product was assessed. The differences in mean ABT-450 exposures between the ABT-267/ABT-450/r co-formulated tablets and ABT-450 (b) (4) tablets is not expected to be clinically relevant based on the following:

- 1) ABT-267/ABT-450/r co-formulated tablets were used in 6 Phase III trials of VIEKIRA PAK™ in which the coformulated product (in combination with ABT-333) was tolerated and safety was established.
- 2) The efficacy at the lower ABT-450 exposures with the (b) (4) tablet formulation was demonstrated in genotype 4 patients in trial M13-393.

#### *Determination of absolute bioavailability of ABT-450 and ABT-267*

The applicant also submitted the results of an absolute bioavailability study (M14-229). Following single dose administration of ABT-450 as an oral co-formulated product with ABT-267 and ritonavir under non-fasting conditions, the geometric mean absolute bioavailability of ABT-450 and ABT-267 is 52.6% and 48.1 %, respectively

## **4 Intrinsic Factors:**

### 4.1 Hepatic Impairment:

The pharmacokinetics of ABT-267/ABT-450/ritonavir co-formulated tablet was not evaluated in subjects with mild- (Child-Pugh Category A, score 5-6), moderate (Child-Pugh Category B, score 7-9). - or severe (Child Pugh Category C, score 10-15) hepatic impairment. In addition, there was no safety or efficacy data available from GT4 subjects with cirrhosis (trial M13-393 only included non-cirrhotic genotype 4 subjects). Based on the available pharmacokinetic data with VIEKIRA PAK™) in subjects with mild hepatic impairment, TECHNIVIE™ can be given to patients with mild hepatic impairment. TECHNIVIE™ will not be recommended for patients with moderate hepatic impairment because the safety and efficacy of TECHNIVIE™ has not been established in patients with decompensated cirrhosis. TECHNIVIE™ will be contraindicated in patients with severe hepatic impairment (Child Pugh Category C, score 10-15) due to an approximately 10-fold increase in the mean AUC of ABT-450 and increased risk of ALT elevation (based on results of trial M12-215 which was reviewed as part of Clinical Pharmacology Review of VIEKIRA PAK™).

## 4.2 Renal Impairment:

The pharmacokinetics of ABT-267/ABT-450/ritonavir co-formulated tablet was evaluated in subjects with mild ( $CL_{cr}$ : 60 to 89 mL/min), moderate ( $CL_{cr}$ : 30 to 59 mL/min), and severe ( $CL_{cr}$ : 15 to 29 mL/min) renal impairment. Table 3 shows the ratios (90 % CIs) of the DAA and ritonavir  $C_{max}$  and AUC for the various renal impairment groups versus control group (normal renal function)

**Table 3: Ratios (90 % CIs) of the DAA and ritonavir  $C_{max}$  and AUC for the various renal impairment groups versus control group (normal renal function)**

Pharmacokinetic Parameter (unit)	Ratio (90% CI): Renal-Impaired Group vs. Normal Renal Function Group		
	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
<b>ABT-450</b>			
$C_{max}$ (ng/mL)	0.892 (0.556 – 1.431)	0.827 (0.376 – 1.818)	0.781 (0.281 – 2.175)
$AUC_{\infty}$ (ng•h/mL)	1.107 (0.765 – 1.602)	1.185 (0.640 – 2.194)	1.247 (0.560 – 2.777)
<b>Ritonavir</b>			
$C_{max}$ (ng/mL)	1.282 (1.030 – 1.597)	1.514 (1.050 – 2.183)	1.714 (1.065 – 2.758)
$AUC_{\infty}$ (ng•h/mL)	1.404 (1.127 – 1.748)	1.759 (1.221 – 2.536)	2.084 (1.296 – 3.353)
<b>ABT-267</b>			
$C_{max}$ (ng/mL)	0.913 (0.818 – 1.019)	0.859 (0.715 – 1.032)	0.820 (0.646 – 1.041)
$AUC_{\infty}$ (ng•h/mL)	1.010 (0.891 – 1.145)	1.017 (0.825 – 1.254)	1.022 (0.779 – 1.342)

In addition, the percentages of unchanged drugs excreted in urine (%  $f_e$ ) for ABT-450 and ABT-267 in subjects with renal impairment and subjects with normal renal function were very low ( $\leq 2\%$ ) indicating minimal contribution of the renal route to the overall elimination of ABT-450 and ABT-267. Of note, pharmacokinetic data are not available on the use of the 2- DAA regimen in subjects with End Stage Renal Disease (ESRD).

## 5 Extrinsic Factors

### 5.1 Effect of Food

The food effect trial (M13-330) was reviewed as part of the clinical pharmacology review of VIEKIRA PAK™. Based on the review, the following recommendation (which is identical to the recommendation for VIEKIRA PAK™) is proposed: TECHNIVIE™ should always be taken with a meal. Differences in mean exposures of ABT-450, ritonavir, and ABT-267 observed after single dose administration of ABT-267/ABT-450/ritonavir coformulated tablets under moderate fat conditions and high fat conditions are not expected to be clinically relevant.

## 5.2 Drug-Drug Interactions (DDIs)

### 5.2.1 Summary of Results from In Vivo Drug-Drug Interactions (DDIs)

The anticipated- and observed DDIs with the 2-DAA regimen were “categorized” in the following 4 “categories” based on the similarity or differences in clinical recommendations between VIEKIRA PAK™ and the 2-DAA regimen:

#### *A) Contraindicated Medications*

The list of contraindicated drugs is similar between VIEKIRA PAK™ and the 2-DAA regimen with the exception of gemfibrozil (antihyperlipidemic agent). Gemfibrozil is contraindicated with VIEKIRA PAK™ due to the potential for increase in dasabuvir concentrations by 10-fold which may increase the risk of QT prolongation. Because dasabuvir is not part of the 2-DAA regimen, contraindication of gemfibrozil is not warranted in the prescribing information of TECHNIVIE™.

#### *B) Medications for which DDI data is NOT available from the 2-DAA regimen and the proposed clinical recommendation is the same between VIEKIRA PAK™ and the 2-DAA regimen*

For the following medications, the proposed clinical recommendation is based on the available DDI data with VIEKIRA PAK™:

- Alprazolam (CYP3A substrate)
- Amlodipine (CYP3A substrate)
- Furosemide (UGT substrate and excreted through the renal route)
- Progestin only contraceptives
- Rilpivirine (CYP3A substrate)
- Zolpidem (CYP3A substrate)

The majority of the drugs listed above are CYP3A substrates. Based on the available in vitro data, ABT-450 and ABT-267 have low potential for inhibiting CYP enzymes. Further, the dose of ritonavir, a potent CYP3A inhibitor, is similar between VIEKIRA PAK™ and the 2-DAA regimen; hence, the magnitude of increase in the exposures of the majority of drugs listed above is expected to be similar between VIEKIRA PAK™ and the 2-DAA regimen. Therefore, the clinical recommendations will be similar between VIEKIRA PAK™ and the 2-DAA regimen.

#### *C) Medications for which DDI data is available from the 2-DAA regimen*

Some DDI trials were conducted with VIEKIRA PAK™ and the 2-DAA regimen (same DDI trial evaluated VIEKIRA PAK™ and the 2-DAA regimen in two different arms). For the following medications, DDI data was available using the 2-DAA regimen:

- Cyclosporine
- Duloxetine
- Emtricitabine/Tenofovir
- Escitalopram
- Ketoconazole
- Methadone
- Omeprazole
- Pravastatin
- Tacrolimus
- Warfarin

The changes in the mean pharmacokinetic parameters of the medications listed above and the various components of the 2-DAA regimen were similar to the changes in the mean pharmacokinetic parameters of the medications listed above and the various components of VIEKIRA PAK™. Hence, the clinical recommendation will be similar between the 2-DAA regimen and VIEKIRA PAK™. Please refer to the individual study reviews for further details.

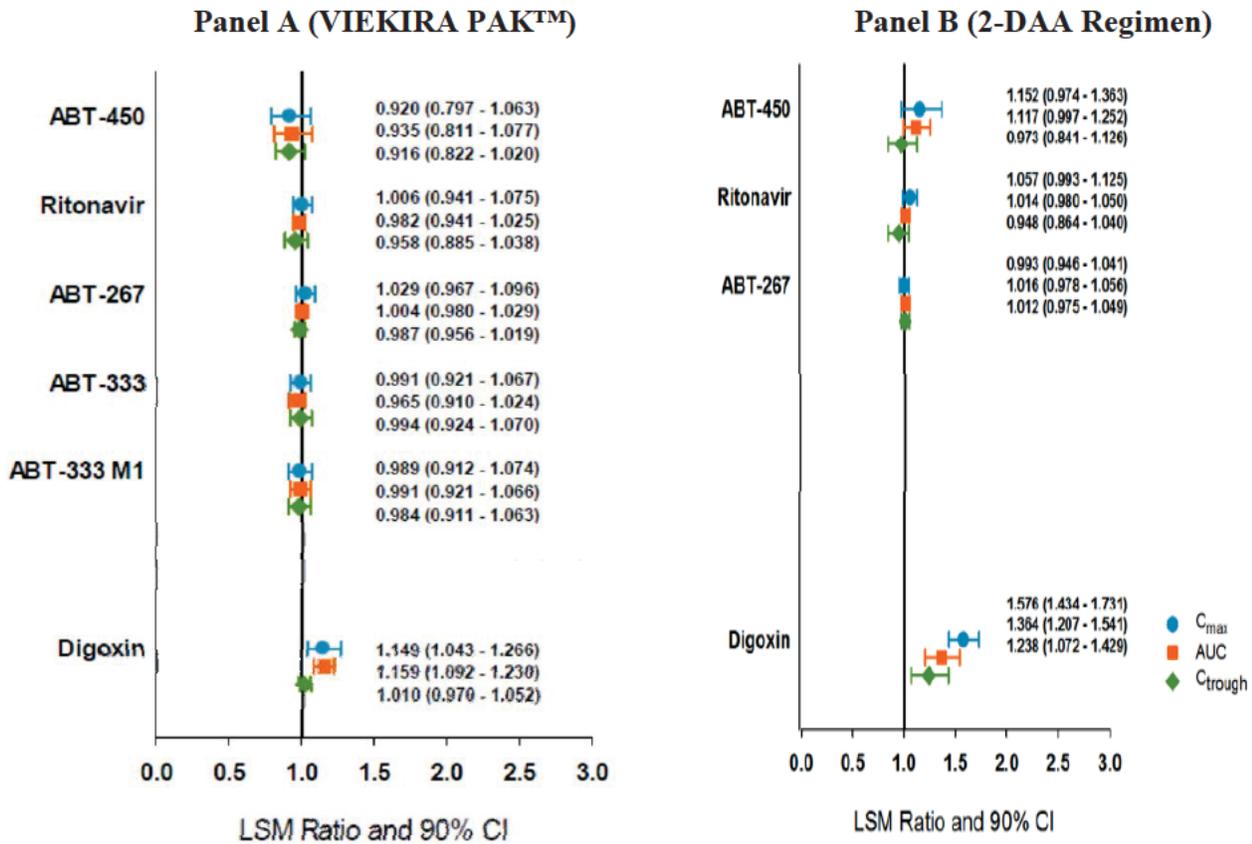
*D) Medications for which DDI data was available from the 2-DAA regimen and there are differences in clinical recommendation with VIEKIRA PAK™ and the 2-DAA regimen*

For the following medications, there were differences in the clinical recommendations with VIEKIRA PAK™ and the 2-DAA regimen (as proposed by the applicant):

**1) Digoxin:**

Figure 1 shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267 and digoxin after administration of digoxin with VIEKIRA PAK™ and 2-DAA regimen.

**Figure 1: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 and digoxin after administration of digoxin with VIEKIRA PAK™ (panel A) and 2-DAA regimen (panel B)**



Source: Clinical Pharmacology summaries of VIEKIRA PAK™ (Page 66) and TECHNIVIE™ (page 26)

In order to gain additional insight into whether the increase in digoxin exposures observed with the 2-DAA regimen are indeed higher than the increase in digoxin exposure with the 3-DAA regimen, the digoxin exposures in the “digoxin only” arms were compared. There was significant variability in digoxin exposures in both arms hence it is challenging to draw conclusions. It should be noted that the confidence intervals associated with  $C_{max}$  of digoxin, when co-administered with the 2-DAA regimen did not overlap with the confidence interval of  $C_{max}$  of digoxin, when co-administered with the 3-DAA regimen, thereby suggesting greater extent of p-gp inhibition with the 2-DAA regimen.

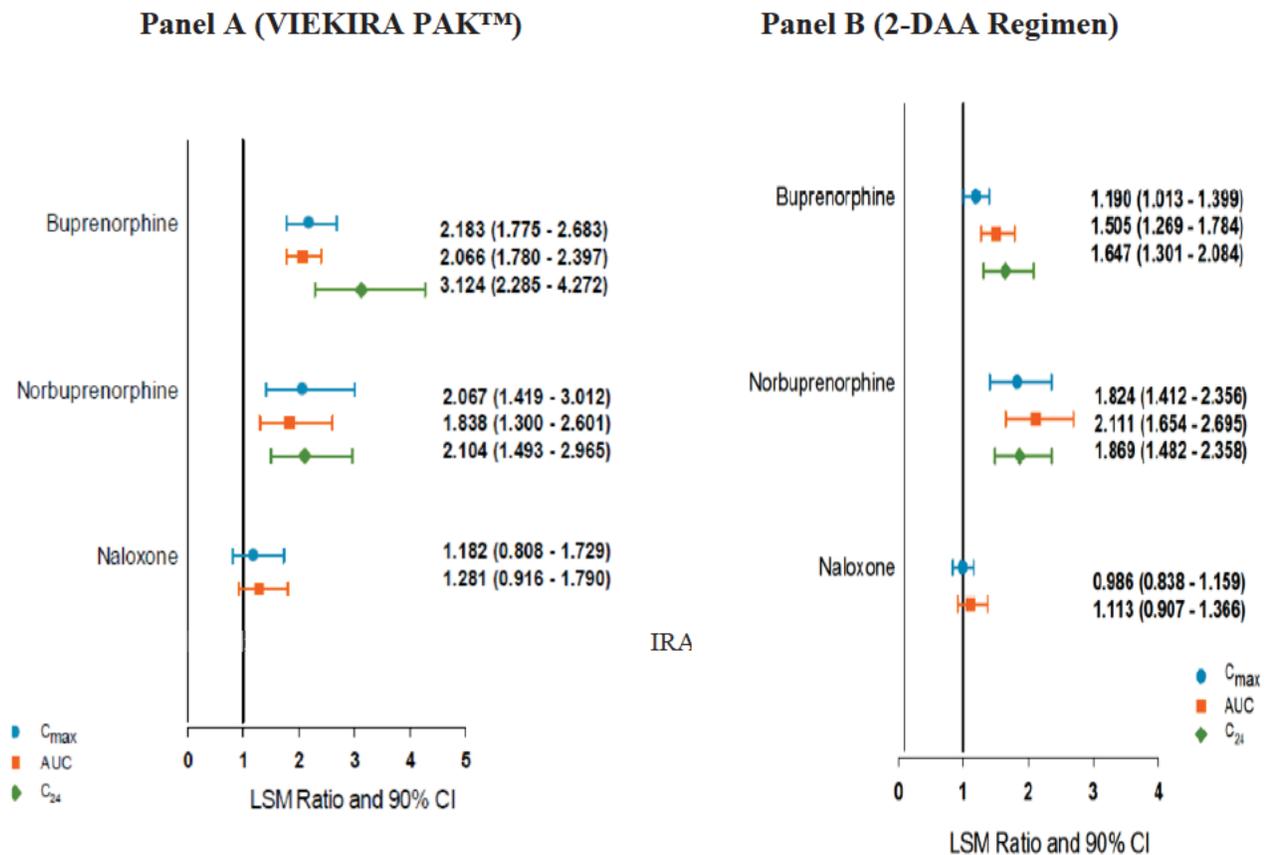
In the prescribing information of VIEKIRA PAK™, digoxin is listed in section 7.4,” Drugs without clinically significant interactions”. Because the magnitude of increase in digoxin mean AUC when co-administered with VIEKIRA PAK™ (~16 %) is less than than the magnitude of increase in mean AUC of digoxin with the 2-DAA regimen (~37 %), the applicant has proposed the following clinical recommendation with the 2-DAA regimen, “Decrease digoxin dose by 30-50 %. Appropriate monitoring of serum digoxin

levels is recommended". The clinical recommendation proposed by the applicant is acceptable. Per the approved digoxin prescribing information, the increase in mean digoxin  $C_{max}$  and AUC after co-administration with the 2-DAA regimen (58 % and 36%, respectively) is similar to the mean increase in digoxin exposures after co-administration with captopril (increase in  $C_{max}$  and AUC by 58 % and 39 %, respectively). When captopril is co-administered with digoxin, the following recommendation is included in the approved digoxin prescribing information: "measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin concentrations by decreasing dose by approximately 30-50 % or by modifying the dosing frequency and continue monitoring".

## 2) Buprenorphine/Naloxone:

Figure 2 shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267 and buprenorphine, norbuprenorphine, and naloxone after administration of VIEKIRA PAK™(panel A) and the 2-DAA regimen (panel B).

**Figure 2: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267 and buprenorphine, norbuprenorphine, and naloxone after administration of VIEKIRA PAK™(panel A) and the 2-DAA regimen (panel B)**



Source: Clinical Pharmacology summaries of VIEKIRA PAK™ (Page 107) and TECHNIVIE™ (page 56)

In the prescribing information of VIEKIRA PAK™, the following clinical recommendation is included for buprenorphine/naloxone, “No dose adjustment of BUP/NAL is required upon co-administration with VIEKIRA PAK™. Patients should be closely monitored for sedation and cognitive effects”. Because the magnitude of change in buprenorphine mean AUC when co-administered with the 2-DAA regimen (~50 %) is lower than the magnitude of change in the mean AUC of buprenorphine when co-administered with VIEKIRA PAK™ (~106 %), the applicant has (b) (4)

The applicant’s proposal (b) (4) is not acceptable. Instead the following clinical recommendation is proposed:

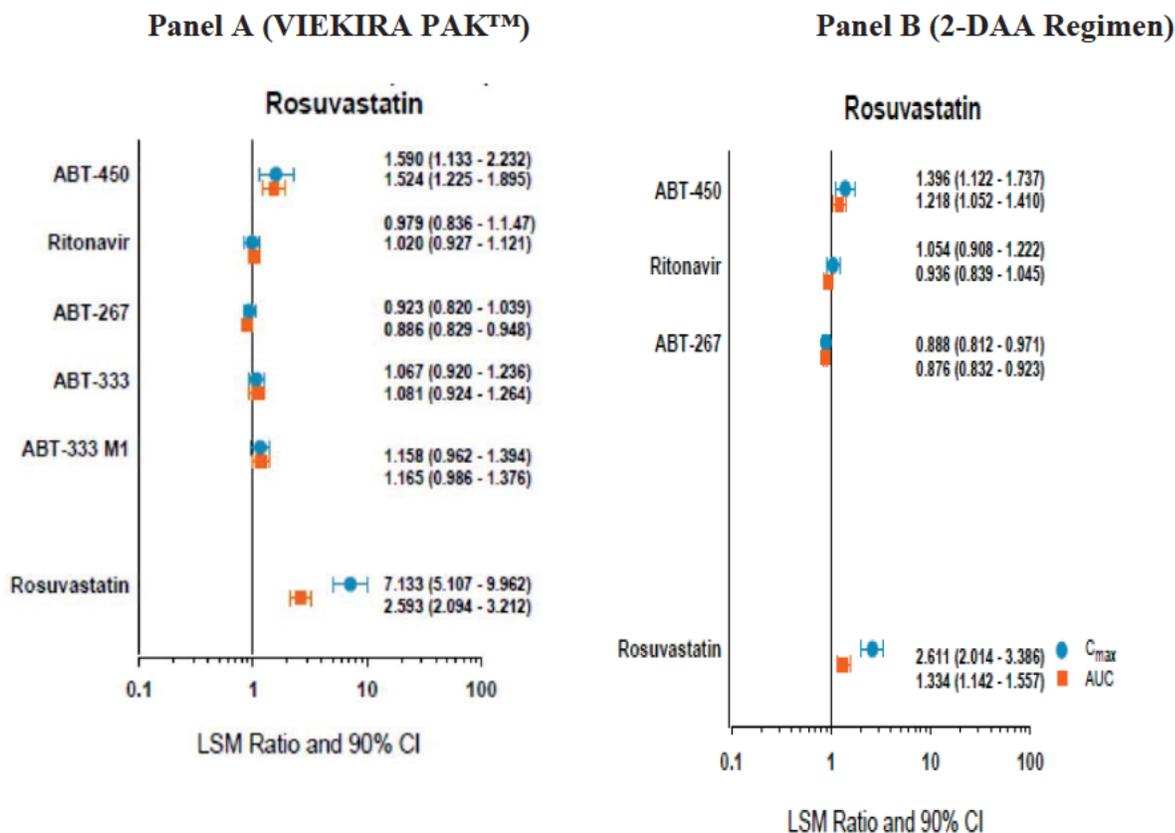
“No dose adjustment of BUP/NAL is required upon co-administration with the 2-DAA regimen. Patients should be closely monitored for sedation and cognitive effects”.

The recommendation outlined above is identical to the approved clinical recommendation related to co-administration of VIEKIRA PAK™ (3-DAA regimen) with buprenorphine/naloxone. Although the magnitude of increase in buprenorphine exposures, when buprenorphine/naloxone is co-administered with the 2-DAA regimen (~50 %) is smaller than the increase in buprenorphine exposures when buprenorphine/naloxone is co-administered with the 3-DAA regimen (~106 %), the magnitude of increase in norbuprenorphine exposures with the 2-DAA regimen (111 %) is higher as compared to the 3-DAA regimen (83 %). In addition, the approved prescribing information of Stribild™ provides a similar recommendation with buprenorphine/naloxone, despite a lower magnitude of increase in buprenorphine exposures. Hence, to be conservative and consistent across antiviral labels, the recommendation outlined above is proposed.

### 3) Rosuvastatin:

Figure 3 shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 and rosuvastatin after administration of rosuvastatin with VIEKIRA PAK™ (panel A) and the 2-DAA regimen (panel B).

**Figure 3: Least squares mean ratio and 90 % CI of the pharmacokinetic parameters of ABT-450,ritonavir, ABT-267, ABT-333, ABT-333 M1 and rosuvastatin after administration of rosuvastatin with VIEKIRA PAK™ (panel A) and the 2-DAA regimen (panel B).**



Source: Clinical Pharmacology summaries of VIEKIRA PAK™ (Page 69) and TECHNIVIE™ (page 29)

The higher increase in the mean rosuvastatin  $C_{max}$  and AUC with the 3-DAA regimen as compared with the 2-DAA regimen could likely be due to inhibition of BCRP transporters by dasabuvir (rosuvastatin is a substrate of OATP and BCRP transporters).

In the prescribing information of VIEKIRA PAK™, the following clinical recommendation is included for rosuvastatin, “When VIEKIRA PAK™ is co-administered with rosuvastatin, the dose of rosuvastatin should not exceed 10 mg per day”. Because the magnitude of change in rosuvastatin mean AUC (~160 %) when co-administered with VIEKIRA PAK™ is greater than the change in rosuvastatin mean AUC when co-administered with the 2-DAA regimen (~33 %), the applicant has proposed the following clinical recommendation when rosuvastatin is co-administered with the 2-DAA regimen. (b) (4)

The applicant's proposed recommendation to [REDACTED] (b) (4) is not acceptable. Per the approved prescribing information of Crestor™ (rosuvastatin), increase in AUC of rosuvastatin by 40-60 % with some protease inhibitors (for example with darunavir/ritonavir (50 % increase in mean rosuvastatin AUC) and tipranavir/ritonavir (40 % increase in mean rosuvastatin AUC) is not considered to be clinically significant and the prescribing information of rosuvastatin does not provide any clinical recommendation related to [REDACTED] (b) (4)

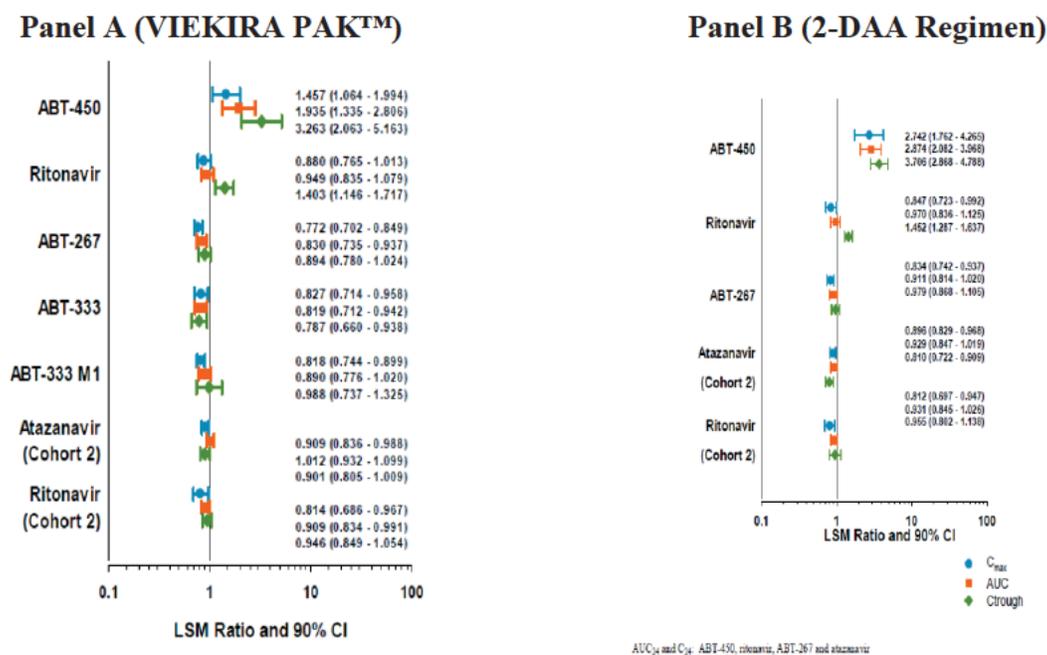
[REDACTED] In addition, based on discussion with the metabolic and endocrine clinical pharmacology review team, the magnitude of increase in rosuvastatin  $C_{max}$  and AUC observed with the 2-DAA regimen does not warrant any [REDACTED] (b) (4)

[REDACTED] Hence, rosuvastatin will be moved [REDACTED] (b) (4) to section 7.4 (Drugs without clinically significant interactions with TECHNIVIE™).

#### 4) Atazanavir (given in the morning):

Figure 4 shows the least squares mean ratio and 90 % CI of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, atazanavir (cohort 2), and ritonavir (cohort 2) after administration of atazanavir with VIEKIRA PAK™ (panel A) and the 2-DAA regimen (panel B).

**Figure 4: Least squares mean ratio and 90 % CI of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, atazanavir (cohort 2), and ritonavir (cohort 2) after administration of atazanavir with VIEKIRA PAK™ (panel A) and the 2-DAA regimen (panel B).**



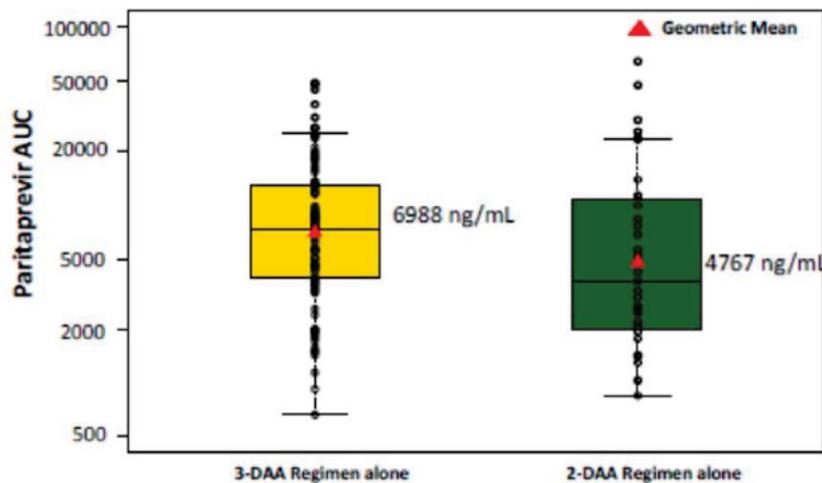
Source: Clinical Pharmacology summaries of VIEKIRA PAK™ (Page 84) and TECHNIVIE™ (page 40)

In the prescribing information of VIEKIRA PAK™, the following clinical recommendation is included for atazanavir (administered in the morning without ritonavir) “When co-administered with VIEKIRA PAK™, atazanavir should only be given in the morning”. The applicant has proposed [REDACTED] (b) (4)

[REDACTED] (b) (4)

The mean exposures (AUC) of paritaprevir are lower after administration of the 2-DAA regimen as compared with VIEKIRA PAK™ as shown in Figure 5 below.

**Figure 5: Paritaprevir exposures (AUC) following administration of the 3-DAA regimen and the 2-DAA regimen**



Source: eCTD sequence number 701, letter date 05/27/2015

Hence, if the lower mean exposures of paritaprevir after the 2-DAA regimen are taken into account, the mean paritaprevir exposures when 2-DAA regimen is co-administered with atazanavir are expected to be approximately 58 % higher as compared with mean paritaprevir exposures after administration of VIEKIRA PAK™ alone as shown in 4 below.

**Table 4: Changes in paritaprevir exposures with various regimens relative to paritaprevir exposures after administration of VIEKIRA PAK™ alone**

Paritaprevir AUC with 3D Regimen Alone	Change in Paritaprevir AUC Relative to the Values Achieved with the 3D Regimen Alone (1×)		
	Paritaprevir AUC with 3D Regimen + Atazanavir	Paritaprevir AUC with 2D Regimen Alone	Paritaprevir AUC with 2D Regimen + Atazanavir
1×	1 × 1.94-fold (or 94% ↑) = 1.94×	1 × 0.55-fold (or 45% ↓) = 0.55×	1 × 0.55-fold × 2.87-fold (or 187% ↑) = 1.58×

Source: Page 23 of White Paper on DDIs, IND 103526 SDN 679, Date of Submission March 13, 2015

The expected 58 % higher mean paritaprevir exposures (after administration of 2-DAA +atazanavir) are lower than the 94 % higher mean paritaprevir exposures observed after administration of atazanavir with VIEKIRA PAK™. It should be noted that atazanavir can be co-administered with VIEKIRA PAK™ without any need for dose adjustments. Hence, per the applicant, atazanavir can be co-administered with the 2-DAA regimen without any need for dose adjustments. Further, per the applicant, dasabuvir is an inhibitor of BCRP and P-gp in vitro; therefore, the higher paritaprevir exposures for the 3-DAA regimen (presence of dasabuvir) compared to the 2-DAA regimen (absence of dasabuvir) could likely be due to the inhibition of these efflux transporters.

The applicant's proposed recommendation is not acceptable

(b) (4)

Overall, the applicant's proposed recommendation is not acceptable and the following recommendation is proposed:

Co-administration of the 2-DAA regimen with atazanavir is not recommended.

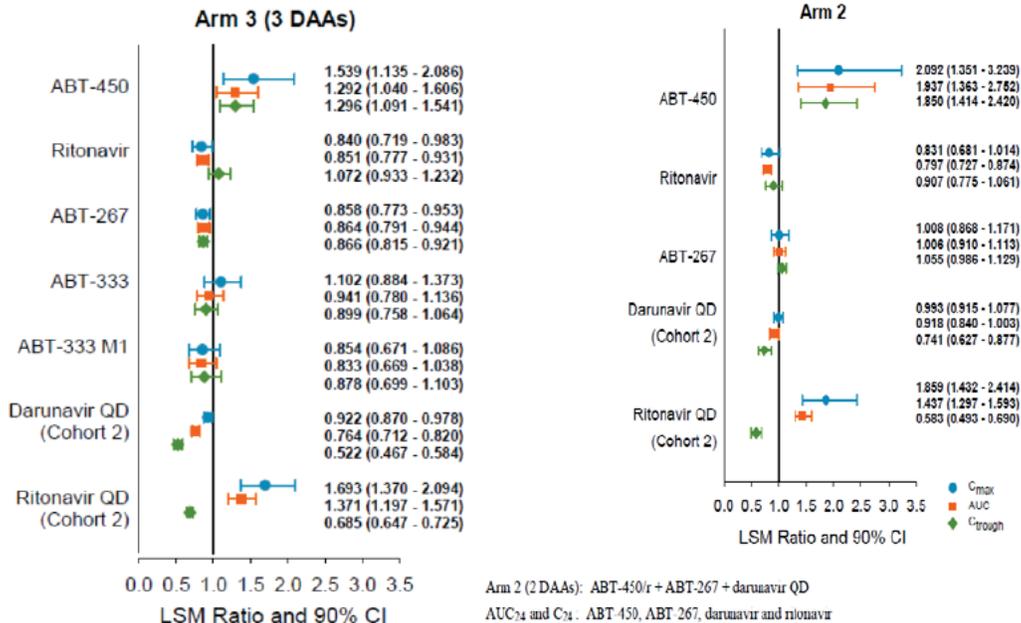
## 5) Darunavir/ritonavir

Figure 6 shows the least squares mean ratio and 90 % CI of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, darunavir once daily (administered in the morning) and ritonavir (cohort 2) after administration of darunavir with VIEKIRA PAK™ (panel A) and the 2-DAA regimen (panel B).

Figure 6: Least squares mean ratio and 90 % CI of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, darunavir once daily (administered in the morning) and ritonavir (cohort 2) after administration of darunavir with VIEKIRA PAK™ (panel A) and the 2-DAA regimen (panel B).

Panel A (VIEKIRA PAK™)

Panel B (2-DAA Regimen)



Source: Clinical Pharmacology summaries of VIEKIRA PAK™ (Page 78) and TECHNIVIE™ (page 37)

Of note, co-administration of darunavir/ritonavir with VIEKIRA PAK™ is not recommended because of the decrease in mean darunavir C<sub>trough</sub> by 45 % (darunavir administered once daily in the evening with ritonavir), 43 % (darunavir administered twice daily [darunavir administered in the evening with ritonavir; darunavir administered in the morning with VIEKIRA PAK™ regimen] and 48 % [darunavir administered once daily in the morning with VIEKIRA PAK™].

The applicant has proposed the following recommendation,"

(b) (4)

The following wording proposed by the applicant is acceptable,”

(b) (4)

The following wording proposed by the applicant is not acceptable,”

(b) (4)

Darunavir twice daily or darunavir once daily (darunavir administered in the evening with ritonavir) was not evaluated with the 2-DAA regimen in DDI trial(s), hence there is no pharmacokinetic data to provide a clinical recommendation regarding the aforementioned darunavir regimens in the prescribing information of TECHNIVIE™.

## **6. Appendices**

### 6.1 Individual Study Reviews

## **Drug-Drug Interaction Trial with Ketoconazole**

### **M12-189**

#### **Title**

**A Phase 1, Open Label Study to Evaluate the Effect of Ketoconazole (KTZ) on the Pharmacokinetics, Safety, and Tolerability of a Single dose of ABT-450 Plus Ritonavir Plus ABT-267 (ABT-450/r/ABT-267), With and Without ABT-333 in Healthy Adult Subjects.**

#### **Trial Period**

January 15, 2013 February 22, 2013

Final report date: July 29, 2013

*Reviewer's Note: As the proposed labeling recommendations in NDA 207931 are based on 2 DAAs (ABT-450/ritonavir/ABT-267), the results section in this review focuses only on the results observed with the 2-DAAs. For results with the 3-DAAs, please refer to the review of NDA 206619.*

#### **Trial Objectives**

The objective of the trial was to determine the effect of steady state KTZ on the pharmacokinetics, safety and tolerability of a single dose of ABT-450/r/ABT-267 with and without ABT-333 in healthy subjects. The trial also evaluated the effect of single-dose DAAs on the pharmacokinetics, safety and tolerability of steady-state KTZ.

#### **Trial Design**

Phase 1, single-center, randomized, multiple dose, non-fasting, open-label study to evaluate the pharmacokinetics, safety, tolerability of KTZ and 2-or 3-DAAs when given alone or in combination. Adult male and female subjects (N = 24) were selected to participate in the study and were randomly assigned in equal numbers to one of two sequence groups as shown in table 1 below:

Sequence Group	Subject Numbers	N	Regimens	
			Period 1	Period 2
Arm 1	101, 104, 105, 107, 109, 112, 114, 117, 118, 120, 123, 124	12	A	B
Arm 2	102, 103, 106, 108, 110, 111, 113, 115, 116, 119, 121, 122	12	C	D

Regimen A = ABT-450/r/ABT-267 150/100/25 mg and ABT-333 250 mg administered under non-fasting conditions as a single dose on Study Day 1 followed by a washout period of 7 days.

Regimen B = KTZ 400 mg QD administered under non-fasting conditions in the morning for 6 days (Study Days 8 through 13). On Study Day 10, ABT-450/r/ABT-267 150/100/25 mg and ABT-333 250 mg administered as a single dose under non-fasting conditions.

Regimen C = ABT-450/r/ABT-267 150/100/25 mg administered under non-fasting conditions as a single dose on Study Day 1 followed by a washout period of 7 days.

Regimen D = KTZ 400 mg QD administered under non-fasting conditions in the morning for 6 days (Study Days 8 through 13). On Study Day 10, ABT-450/r/ABT-267 150/100/25 mg administered as a single dose under non-fasting conditions.

Each dose of the study drug was taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast. A washout interval of 7 days separated the dose of Period 1 from the first dose of Period 2. Subjects received a standardized diet, providing approximately 40% of the daily calories from fat and up to 45% of daily calories from carbohydrates, for each meal during confinement. The total daily calories were approximately 2200 calories/day. Starting with lunch on Study Day – 1 until after the 96-hour blood collection on Study Day 14, the subjects consumed only the scheduled meals provided

*Reviewer's Note:*

*The label of KTZ (Nizoral<sup>®</sup>) label indicates that the oral bioavailability of ketoconazole is maximal when taken with a meal.*

### **Rationale for Conducting the Trial**

ABT-450 and ABT-267 have been shown to be *in vitro* substrates of CYP3A and ritonavir is a CYP3A4 substrate and inhibitor. KTZ, an azole antifungal agent, is a reversible inhibitor of CYP3A. Hence, this trial was designed to evaluate the effect of ketoconazole on the disposition of the DAAs.

### **Rationale for Dose Selection**

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), and ABT-267 (25 mg) were the doses evaluated in Phase 3 trials. The dose of KTZ (400 mg once daily) is the dose used in CYP3A inhibition studies.

### **Identity of Investigational Products**

Table 2 shows the identity of the investigational products used in the trial.

	ABT-450/Ritonavir/ABT-267	ABT-333	Ketoconazole
Dosage Form	Tablet	Tablet	Tablet
Strength	75/50/12.5 mg	250 mg	200 mg
Bulk Product Lot Number	12-006414	12-004533	12-007641
Manufacturing Site	AbbVie, Inc. North Chicago, IL	AbbVie, Inc. North Chicago, IL	(b) (4)
Finishing Lot Number	12-008101	12-008102	12-008103
Retest Date	(b) (4)	(b) (4)	(b) (4)

Ketoconazole, 200 mg tablets were manufactured by (b) (4) as Lot 3036319, NDC 0378-0261-01.

## Sample Collection

Blood samples for measurement of the concentrations of ABT-450, ritonavir, and ABT-267 were collected by venipuncture on the following days:

- Prior to dosing (0 hour) and up to 72 hours after dosing on day 1.
- Prior to dosing (0 hour) and up to 96 hours after dosing on day 10.

Blood samples for measurement of KTZ were collected on the following days:

- Prior to dosing (0 hour) and up to 16 hours after dosing on day 9.
- Prior to dosing (0 hour) and up to 24 hours after dosing on study day 10 or upon subject discontinuation due to an adverse event.

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ABT-267 and KTZ were computed using non-compartmental methods.

## Results

### *Bioanalytical methods*

Table 3 provides the summary of the bioanalytical assay parameters.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.6-431	0.6	1.58, 26.4, 330	5.4 % to 9.3 %	6.4 % to 12.7 %
Ritonavir	4.71-3380	4.71	12.7, 211, 2640	11.5 % to 14.6 %	2.7 % to 9.5 %
ABT-267	0.417-299	0.417	1.09, 18.1, and 227	4.8 % to 8.1 %	0.9 % to 5.3 %
Ketoconazole*	0.1-20	0.1	0.2, 0.5, 1.5, 4, and 15	1.64 % to 7.21 %	-0.5 % to 4.21 %

\*: Concentrations are in µg/mL

### *Subject Disposition and Demographics*

Adult male and female subjects (N = 24) were enrolled in the study and all subjects completed the study.

Table 4 below shows the demographic summary of all subjects enrolled in the trial.

	Mean ± SD (N = 24)	Min – Max
Age (years)	33.2 ± 10.0	20 – 54
Weight (kg)	74.3 ± 9.6	55 – 100
Height (cm)	170 ± 8.9	153 – 186
Sex	15 Males (62.5%), 9 Females (37.5%)	
Race	15 White (62.5%), 6 Black (25.0%), 2 Native Hawaiian or Other Pacific Islander (8.3%), 1 Multi-race (4.2%)	

### *Concomitant Medications and Supplements*

Four subjects reported taking concurrent medication during the study; three subjects used topical vaseline on day 9 for either dry lips or for irritation at the ECG site and one subject took prune juice on day 11. None of the concurrent medications or supplements is expected to alter the results of the trial.

### *Pharmacokinetics*

#### ABT-450 (Arm 2)

Table 5 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 2.

ABT-450 Pharmacokinetic Parameters	(Units)	Regimen C Study Day 1 (N = 12)	Regimen D Study Day 10 (N = 12)
C <sub>max</sub>	(ng/mL)	1320 ± 925	2030 ± 1260
T <sub>max</sub>	(h)	4.6 ± 1.7	4.6 ± 1.1
t <sub>1/2</sub> <sup>a</sup>	(h)	6.2 ± 1.0	14.4 ± 3.1
AUC <sub>t</sub>	(ng•h/mL)	7510 ± 4560	14700 ± 7560
AUC <sub>∞</sub>	(ng•h/mL)	7530 ± 4570	14800 ± 7570

Regimen C = ABT-450/r/ABT-267 150/100/25 mg administered under non-fasting conditions as a single dose on Study Day 1 followed by a washout period of 7 days.

Regimen D = KTZ 400 mg QD administered under non-fasting conditions in the morning for 6 days (Study Days 8 through 13). On Study Day 10, ABT-450/r/ABT-267 150/100/25 mg administered as a single dose under non-fasting conditions.

a. Harmonic mean ± pseudo-standard deviation.

Table 6 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 2.

<b>Ritonavir Pharmacokinetic Parameters</b>	<b>(Units)</b>	<b>Regimen C Study Day 1 (N = 12)</b>	<b>Regimen D Study Day 10 (N = 12)</b>
$C_{max}$	(ng/mL)	1610 $\pm$ 666	1930 $\pm$ 559
$T_{max}$	(h)	3.8 $\pm$ 1.1	3.9 $\pm$ 0.8
$t_{1/2}$ <sup>a</sup>	(h)	4.2 $\pm$ 1.0	6.0 $\pm$ 1.2
$AUC_t$	(ng•h/mL)	10700 $\pm$ 5870	15300 $\pm$ 5850
$AUC_{\infty}$	(ng•h/mL)	10800 $\pm$ 5880	15400 $\pm$ 5870

Regimen C = ABT-450/r/ABT-267 150/100/25 mg administered under non-fasting conditions as a single dose on Study Day 1 followed by a washout period of 7 days.

Regimen D = KTZ 400 mg QD administered under non-fasting conditions in the morning for 6 days (Study Days 8 through 13). On Study Day 10, ABT-450/r/ABT-267 150/100/25 mg administered as a single dose under non-fasting conditions.

a. Harmonic mean  $\pm$  pseudo-standard deviation.

### ABT-267 (Arm 2)

Table 7 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 in Arm 2.

<b>ABT-267 Pharmacokinetic Parameters</b>	<b>(Units)</b>	<b>Regimen C Study Day 1 (N = 12)</b>	<b>Regimen D Study Day 10 (N = 12)</b>
$C_{max}$	(ng/mL)	114 $\pm$ 16.7	111 $\pm$ 17.8
$T_{max}$	(h)	5.6 $\pm$ 1.7	5.8 $\pm$ 0.9
$t_{1/2}$ <sup>a</sup>	(h)	24.9 $\pm$ 5.0	39.5 $\pm$ 8.6
$AUC_t$	(ng•h/mL)	1570 $\pm$ 251	1910 $\pm$ 285
$AUC_{\infty}$	(ng•h/mL)	1720 $\pm$ 320	2160 $\pm$ 373

Regimen C = ABT-450/r/ABT-267 150/100/25 mg administered under non-fasting conditions as a single dose on Study Day 1 followed by a washout period of 7 days.

Regimen D = KTZ 400 mg QD administered under non-fasting conditions in the morning for 6 days (Study Days 8 through 13). On Study Day 10, ABT-450/r/ABT-267 150/100/25 mg administered as a single dose under non-fasting conditions.

a. Harmonic mean  $\pm$  pseudo-standard deviation.

### Ketoconazole (Arm 2)

Table 8 shows the mean pharmacokinetic parameters of ketoconazole in Arm 2.

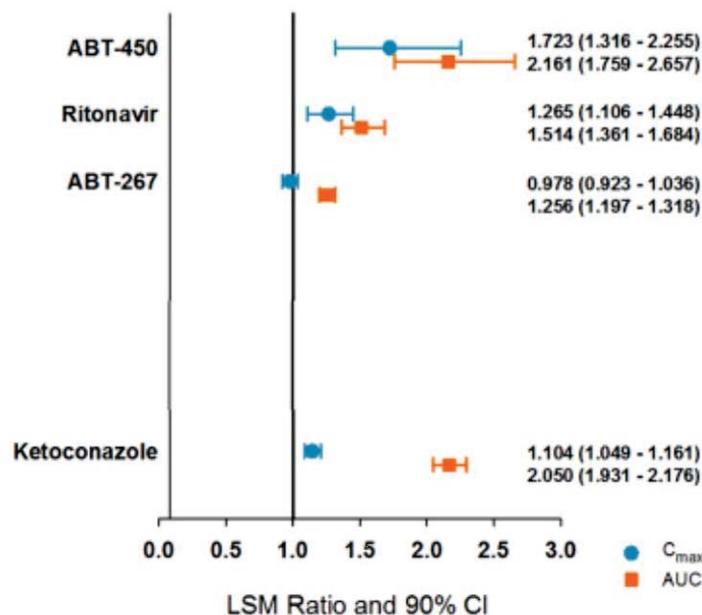
Ketoconazole Pharmacokinetic Parameters	(Units)	Regimen D	Regimen D
		Study Day 9 (N = 12)	Study Day 10 (N = 12)
$C_{max}$	( $\mu\text{g/mL}$ )	$11.3 \pm 2.3$	$12.4 \pm 2.4$
$T_{max}$	(h)	$3.2 \pm 0.8$	$3.8 \pm 0.4$
$t_{1/2}^a$	(h)	$4.3 \pm 0.9$	$16.0 \pm 4.4$
$AUC_{24}$	( $\mu\text{g}\cdot\text{h/mL}$ )	$88.7 \pm 19.8$	$181 \pm 37.8$

Regimen D = KTZ 400 mg QD administered under non-fasting conditions in the morning for 6 days (Study Days 8 through 13). On Study Day 10, ABT-450/r/ABT-267 150/100/25 mg administered as a single dose under non-fasting conditions.

a. Harmonic mean  $\pm$  pseudo-standard deviation.

### Statistical Evaluation of the Pharmacokinetic Parameters

Fig 1 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, and ketoconazole.



$AUC_{24}$ : ABT-450, ritonavir and ABT-267;  $AUC_{24}$ : ketoconazole

### Reviewer's Interpretation of the Increase in Exposures of the Various Medications Evaluated in Trial M12-189

- Ketoconazole is a potent CYP3A/Pgp inhibitor and ABT-450 is a substrate of CYP3A and P-gp. Although ABT-450 was co-administered with ritonavir in trial M12-189, the additional effect of ketoconazole on ABT-450 exposures over that of ritonavir 100 mg was comparable to the effect of ritonavir 200 mg on 100 ABT-450 exposures (trial M10-749); results from trial M10-749 showed that by increasing the ritonavir dose from 100 mg to 200 mg, ABT-450 (100 mg dose)

mean  $C_{max}$  and AUC increased by 1.6- to 2-fold, respectively, but the ABT-450 mean  $t_{1/2}$  did not appear to change with ritonavir dose..

- Ritonavir and ABT-267 are substrates of P-gp (ABT-267 is also a substrate of BCRP); hence, the increase in exposures of ABT-267 and ritonavir may be due to P-gp inhibition.
- Ketoconazole is a CYP3A substrate; hence increase in ketoconazole exposures may be due to the CYP3A inhibitory effect of ritonavir. However, the increase in ketoconazole exposures observed in this trial appear to be lower than the increase in ketoconazole exposures observed in other trials conducted with antiretroviral protease inhibitor combinations as shown the following table:

<i>Co-Administered Protease Inhibitor[Dosing Regimen]</i>	<i>Fold Increase in Ketoconazole Exposures (AUC)</i>	<i>Clinical Recommendation in the Prescribing Information</i>
<i>Darunavir/ritonavir (400/100 mg BID)</i>	3.12	<i>When co-administration is required, the daily dose of ketoconazole (or itraconazole) should not exceed 200 mg</i>
<i>Lopinavir/ritonavir (400/100 mg BID)</i>	3.04	<i>Higher doses of ketoconazole (greater than 200 mg per day) are not recommended</i>
<i>Saquinavir/ritonavir (1000/100 mg BID)</i>	2.68 (168 % higher)	<i>When INVIRASE/ritonavir and ketoconazole are co-administered, the plasma concentrations of ketoconazole are increased. Hence, doses of ketoconazole or itraconazole &gt; 200 mg/day are not recommended.</i>
<i>Fosamprenavir/ritonavir (700/100 mg BID)</i>	2.69 (169 % higher)	<i>High doses of ketoconazole or itraconazole (greater than 200 mg/day) are not recommended.</i>

## Results

Co-administration of ABT-450/r/ABT-267 with ketoconazole:

- Increased the mean  $C_{max}$  and AUC of ABT-450 by 72 % and 116 % , respectively.
- Increased the mean  $C_{max}$  and AUC of ritonavir by 26% and 51 % , respectively.
- Decreased the mean  $C_{max}$  of ABT-267 by 2 % and increased ABT-267 AUC by 25 %.
- Increased the mean  $C_{max}$  and AUC of ketoconazole by 10 % and 105 % , respectively.

## **Conclusion**

When ABT-450/ritonavir/ABT-267 is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg/day.

## Drug-Drug Interaction Trial with Digoxin

### M12-201

#### Title

**A Phase 1, Open Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-Administration of Digoxin with Combination of ABT-450 with Ritonavir (ABT-450/r), with ABT-267 and/or ABT-333 in Healthy Adult Subjects.**

#### Trial Period

September 7, 2012 to March 25, 2013

Final report date: October 14, 2013

*Reviewer's Note: As the proposed labeling recommendations in NDA 207931 are based on 2 DAAs (ABT-450/ritonavir/ABT-267), the results section in this review focuses only on the results observed with the 2-DAAs. For results with the 3-DAAs, please refer to the review of NDA 206619.*

#### Trial Objectives

To evaluate the pharmacokinetics, safety and tolerability of a single dose of digoxin when co-administered with a combination of ABT-450 with ritonavir (ABT-450/r), and ABT-267 with or without ABT-333 in healthy subjects at steady state and to evaluate the pharmacokinetics, safety and tolerability of the combination of ABT-450/r, and ABT-267 with or without ABT-333 at steady state when co administered with a single dose of digoxin in healthy subjects.

#### Trial Design

Phase 1, single-center, multiple-dose, sequential, open-label study designed to evaluate the co-administration of digoxin with two and three DAAs: Arm 1: ABT-450/r, ABT-267 and ABT-333 with digoxin; Arm 2: ABT 450/r and ABT-267 with digoxin. Based on the results from Arm 1 and Arm 2, the sponsor made a decision regarding whether to conduct the next sequential Arm 3. Doses in Arm 3 (Regimen E and Regimen F) could have been modified based on safety, tolerability and pharmacokinetic results from the preceding arm(s). Doses in Arm 3 would not have exceeded ABT-450/r 250/100 mg QD, ABT 333 800 mg BID, ABT-267 100 mg QD and digoxin 0.5 mg single dose. **Arm 3 was not conducted.**

Fig 1 shows the study schematic of the trial:

Fig 1: Schematic of the Trial

Period 1			Period 2		
Arms 1, 2 and 3 <sup>a</sup>	Day 1	10-day washout	Days 1 – 14	Day 15	Days 16 – 19
	Digoxin Single Dose		DAAAs	Digoxin Single Dose + DAAAs	DAAAs

a Optional Arm 3 was not conducted.

Subjects randomized to Arm 1 received regimen A in period 1 and regimen B in period 2. Subjects randomized to Arm 2 received regimen C in period 1 and regimen D in period 2.

*Reviewer’s Note: The “DAAAs” in the schematic above refer to the 3-DAAAs (ABT-450/r, ABT-267, and ABT-333) and the 2-DAAAs (ABT-450/r and ABT-267). Subjects randomized to Arm 1 received 3-DAAAs in Period 2 (treatment B) whereas subjects randomized to Arm 2 received 2-DAAAs in Period 2.*

Table 1 shows the various dosing regimens in the trial.

<b>Regimen A</b>	Single dose of digoxin 0.5 mg on Period 1, Day 1 followed by a washout interval of at least 10 days
<b>Regimen B</b>	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID on Days 1 through 19 in Period 2; single dose of digoxin 0.5 mg on Day 15 in Period 2
<b>Regimen C</b>	Single dose of digoxin 0.5 mg on Period 1, Day 1 followed by a washout interval of at least 10 days
<b>Regimen D</b>	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD on Days 1 through 19 in Period 2; single dose of digoxin 0.5 mg on Day 15 in Period 2
<b>Regimen E<sup>a,b</sup></b>	Single dose of digoxin 0.5 mg on Period 1, Day 1 followed by a washout interval of at least 10 days
<b>Regimen F<sup>a,b</sup></b>	ABT-450/r 150/100 mg QD ± ABT-333 400 mg BID ± ABT-267 25 mg QD on Days 1 through 19 in Period 2; single dose of digoxin 0.5 mg on Day 15 in Period 2

a. Arms were conducted sequentially. Based on a review of the tolerability, safety and pharmacokinetic results of the previous arm(s), a decision was made whether to conduct the next sequential Arm 3. Doses in Arm 3 (Regimen E and Regimen F) could have been modified based on safety, tolerability and pharmacokinetic results from the preceding arm(s). Doses in Arm 3 could have been as low as 0 mg and would not have exceeded ABT-450/r 250/100 mg QD, ABT-333 800 mg BID, ABT-267 100 mg QD and digoxin 0.5 mg single dose.

b. Optional Arm 3 was not conducted; Regimens E and F were not administered.

Subjects received a standardized diet, providing approximately 40% of the daily calories from fat and up to 45% of daily calories from carbohydrates (approximately 1900 calories/day). During period 1, study drug was administered approximately 30 minutes after the start of a standardized breakfast. During period 2, for morning dosing, the study drug was administered approximately 30 minutes after the start of a standardized breakfast. The meal content was identical on pharmacokinetic sampling days.

Each dose of the study drug was taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast. A washout interval of 7 days separated the dose of Period 1 from the first dose of Period 2.

### Rationale for Conducting the Trial

The transmembrane transporter P-gp is an efflux transporter present in the gut, liver and

kidneys and can affect drug disposition. Ritonavir is a P-gp inhibitor. ABT-450, ABT-333 and ABT-267 have a potential to inhibit P-gp. Digoxin is a substrate of p-gp transporters, hence, this trial was designed to evaluate the effect of DAAs on the pharmacokinetics of digoxin, a substrate of P-gp.

### Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), and ABT-267 (25 mg) were the doses (or doses that provided comparable systemic exposures) that were determined to be safe and efficacious in the Phase 2 trials. Further, these doses were also evaluated in the Phase 3 trials. The dose of digoxin (0.5 mg) is a commonly used dose in DDI studies.

### Identity of Investigational Products

Table 2 shows the identity of the investigational products used in the trial.

	<b>ABT-450</b>	<b>Ritonavir</b>	<b>ABT-267</b>
Dosage Form	Tablet	Soft Gelatin Capsule	Tablet
Strength (mg)	50 mg	100 mg	25 mg
Bulk Product Lot Number	11-000781	11-005635	11-002033
Manufacturing Site	AbbVie North Chicago, IL	AbbVie North Chicago, IL	AbbVie North Chicago, IL
Finishing Lot Number	12-005624	12-005625	12-005620
Expiration Date	30 June 2013	30 September 2013	30 June 2013
		<b>Lanoxin<sup>®</sup> (Digoxin)</b>	--
	<b>ABT-333</b>		
Dosage Form	Tablet	Tablet	--
Strength (mg)	400 mg	0.25 mg	--
Bulk Product Lot Number	12-005348	12-000171	--
Manufacturing Site	AbbVie North Chicago, IL	(b) (4)	--
Finishing Lot Number	12-005622	12-005626	--
Expiration Date	31 January 2015	31 July 2015	--

### Sample Collection

#### Digoxin:

Arms 1 and 2, Period 1, Day 1: Prior to dosing (0 hours) and up to 120 hours after the morning dose on day 1.

Arms 1 and 2, Period 2, Day 15: Prior to dosing (0 hours) and up to 120 hours after the morning dose on day 15.

#### DAAs:

Arms 1 and 2, Period 2:

Day 14 : prior to dosing (0 hours) and up to 16 hours after the morning dose on day 14.  
 Day 15 : prior to dosing (0 hours) and up to 16 hours after the morning dose on day 15.  
 Trough Samples: Prior to morning dosing on days 9, 13, 16, 18, and 20.

Urine samples for digoxin analysis were collected in containers without preservatives over the following time intervals: 0-24, 24-48, 48-72, 72-96, 96-120 hours after dosing on day1 period 1 and day 15, period 2.

### Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, and ABT-267 were estimated using non-compartmental methods.

### Results

#### *Bioanalytical methods*

The concentrations of ABT-450, ritonavir, ABT-267 and digoxin were determined using HPLC with MS/MS detection. All samples were analyzed within the maximum validated storage stability.

Table 3 shows the bioanalytical assay parameters.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.6-431	0.6	1.58, 26.4, 330	1.8 % to 6.7 %	5.7 % to 10.1 %
Ritonavir	4.71-3380	4.71	12.7, 211, 2640	3.2 % to 3.6 %	2.7 % to 3.9 %.
ABT-267	0.417-299	0.417	1.09, 18.1, and 227	2.2 % to 3.9 %	5.5 % to 6.6 %
Digoxin*	10-10,000	10	25,75, 300, 1250, and 7500	2.69 % to 4.6 %	-1.15 % to 3.54 %

\*: Concentrations are in pg/mL

#### *Subject Disposition and Demographics*

Out of the 24 subjects enrolled in the trial, 23 subjects (16 males and 7 females) completed the trial. One subject in Arm 2 was prematurely discontinued due to elevated ALT and the data from this subject was not included in the statistical analysis of the DAAs and digoxin pharmacokinetic parameters for period 2.

Table 4 below shows the shows the demographic summary of all subjects enrolled in the trial.

	Arm 1		Arm 2		Overall	
	Mean ± SD (N = 12)	Min – Max	Mean ± SD (N = 12)	Min – Max	Mean ± SD (N = 24)	Min – Max
Age (years)	35.3 ± 11.2	21 – 55	30.3 ± 7.41	21 – 45	32.8 ± 9.61	21 – 55
Weight (kg)	76.8 ± 12.7	60 – 100	74.8 ± 10.5	60 – 100	75.8 ± 11.4	60 – 100
Height (cm)	171 ± 12.4	154 – 188	172 ± 10.1	163 – 195	172 ± 11.1	154 – 195
Sex	9 Males (75.0%), 3 Females (25.0%)		8 Males (66.7%), 4 Female (33.3%)		17 Males (70.8%), 7 Female (29.2%)	
Race	9 White (75.0%), 2 Black (16.7%), 1 Asian (8.3%)		6 White (50.0%), 6 Black (50.0%)		15 White (62.5%), 8 Black (33.3%), 1 Asian (4.2%)	

SD = standard deviation, Min = minimum, Max = maximum

### *Pharmacokinetics*

*Note: Only the results from Arm 2 are presented in this review.*

#### ABT-450 (Arm 2)

Table 5 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 2.

Parameter (Unit)	Day 14, Period 2 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD	Day 15, Period 2 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + digoxin 0.5 mg
N	11	11
C <sub>max</sub> (ng/mL)	2090 ± 2100	2730 ± 2950
T <sub>max</sub> (h)	4.0 ± 0.8	3.7 ± 0.5
AUC <sub>24</sub> (ng•h/mL)	9320 ± 8840	11600 ± 12300
C <sub>24</sub> (ng/mL)	27.8 ± 29.8	30.6 ± 37.3

#### Ritonavir (Arm 2)

Table 6 shows the mean ± SD pharmacokinetic parameters of ritonavir in Arm 2.

Parameter (Unit)	Day 14, Period 2 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD	Day 15, Period 2 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + digoxin 0.5 mg
N	11	11
C <sub>max</sub> (ng/mL)	2420 ± 1130	2540 ± 1190
T <sub>max</sub> (h)	4.1 ± 0.7	4.1 ± 0.8
AUC <sub>24</sub> (ng•h/mL)	14200 ± 6960	14300 ± 6760
C <sub>24</sub> (ng/mL)	58.0 ± 42.9	55.1 ± 44.0

## ABT-267 (Arm 2)

Table 7 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 in Arm 2.

Parameter (Unit)	Day 14, Period 2 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD	Day 15, Period 2 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + digoxin 0.5 mg
N	11	11
$C_{max}$ (ng/mL)	154 $\pm$ 42.2	152 $\pm$ 39.0
$T_{max}$ (h)	4.8 $\pm$ 0.6	4.8 $\pm$ 0.6
AUC <sub>24</sub> (ng·h/mL)	1500 $\pm$ 410	1520 $\pm$ 417
$C_{24}$ (ng/mL)	29.7 $\pm$ 11.9	30.4 $\pm$ 13.0

## Digoxin (Arm 2)

Fig 2 shows the mean digoxin plasma concentration-time profiles in Arm 1.

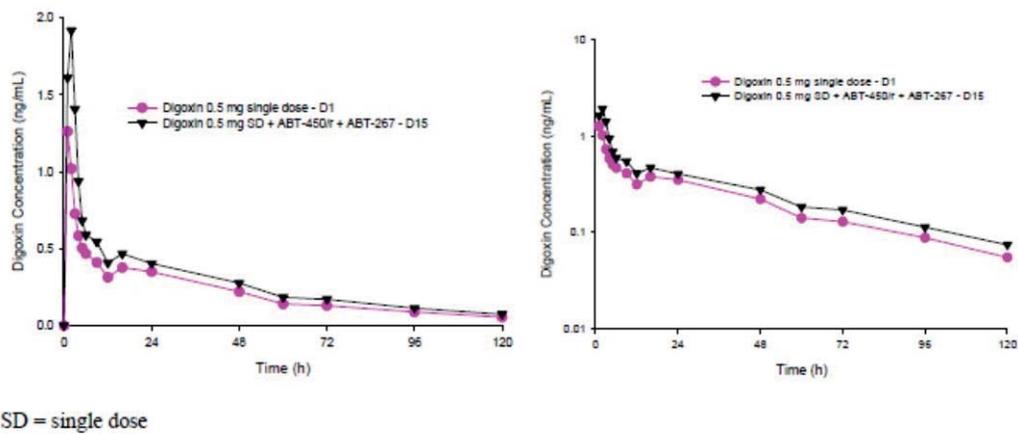


Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of digoxin in Arm 2.

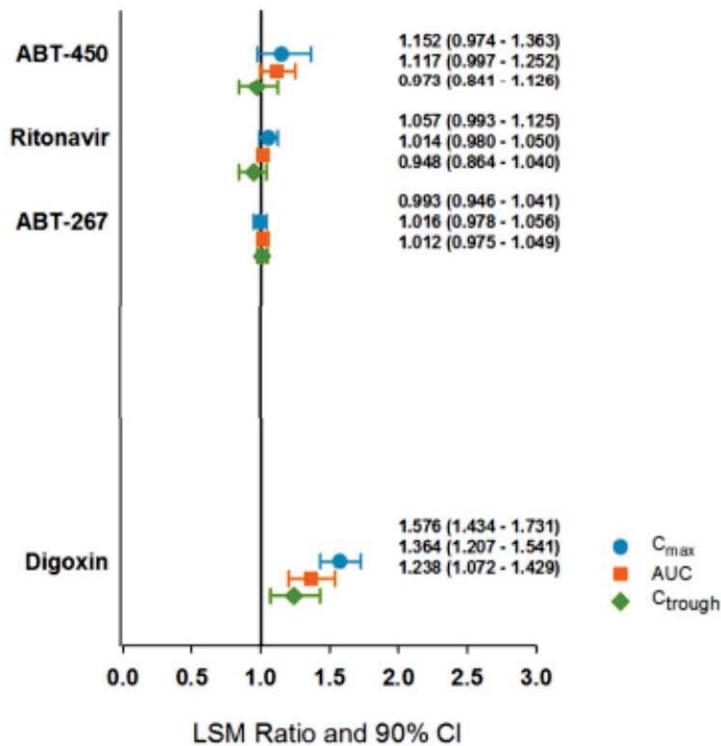
Parameter (Unit)	Day 1, Period 1	Day 15, Period 2
	digoxin 0.5 mg	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + digoxin 0.5 mg
N	12	11
C <sub>max</sub> (ng/mL)	1.38 ± 0.37	2.20 ± 0.42
T <sub>max</sub> (h)	1.6 ± 1.2	1.7 ± 0.7
AUC <sub>t</sub> (ng•h/mL)	26.0 ± 7.95	33.9 ± 6.04
AUC <sub>inf</sub> (ng•h/mL)	29.1 ± 8.99	38.1 ± 6.64
t <sub>1/2</sub> <sup>a</sup> (h)	37.5 ± 5.85	38.4 ± 4.78
C <sub>24</sub> (ng/mL)	0.35 ± 0.13	0.40 ± 0.08
f <sub>e</sub> (%)	31.6 ± 8.47 <sup>b</sup>	34.7 ± 9.24
CL <sub>ren</sub> (L/h)	6.32 ± 1.14 <sup>b</sup>	5.20 ± 1.33

a. Harmonic mean ± pseudo-standard deviation.

b. N = 11 subjects for urine parameters for Day 1 Period 1.

### Statistical Evaluation of the Pharmacokinetic Parameters

Fig 3 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267 and digoxin in Arm 2.



AUC<sub>24</sub> and C<sub>24</sub>: ABT-450, ritonavir and ABT-267; AUC<sub>∞</sub> and C<sub>24</sub>: digoxin

## **Safety**

No deaths or serious adverse events were reported in the trial.

## **Results**

Co-administration of ABT-450/r, ABT-267 with digoxin:

- Increased the mean  $C_{\max}$  and AUC of digoxin by 58 % and 36 %, respectively.
- Did not significantly alter the mean  $C_{\max}$  and AUC of ABT-450, ritonavir, and ABT-267.

## **Conclusion**

Per the approved digoxin prescribing information, the increase in mean digoxin  $C_{\max}$  and AUC after co-administration with the 2-DAA regimen (58 % and 36%, respectively) is similar to the mean increase in digoxin exposures after co-administration with captopril (increase in  $C_{\max}$  and AUC by 58 % and 39 %, respectively). When captopril is co-administered with digoxin, the following recommendation is included in the approved digoxin prescribing information: “measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin concentrations by decreasing dose by approximately 30-50 % or by modifying the dosing frequency and continue monitoring”. Hence, a similar recommendation will be included in the 2-DAA prescribing information.

## **Clinical Recommendation**

Decrease digoxin dose by 30-50 %. Appropriate monitoring of serum digoxin levels is recommended.

## **Drug-Drug Interaction Trial with Methadone**

### **M12-997**

#### **Title**

**An Open Label, Phase 1 Study to Assess the Effect of the Combination of ABT-450 plus ritonavir (ABT-450/r) with ABT-333 and/or ABT-267 on the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Methadone in Subjects on Stable Maintenance Therapy.**

#### **Trial Period**

July 17, 2012 to March 12, 2013

Final report date: October 23, 2013.

*Reviewer's Note: As the proposed labeling recommendations in NDA 207931 are based on 2 DAAs (ABT-450/ritonavir/ABT-267), the results section in this review focuses only on the results observed with the 2-DAA (Arm 2). For results with the 3-DAAs, please refer to the review of NDA 206619.*

#### **Trial Objectives**

The objective of the trial were:

- To evaluate the effect of steady-state DAA dosing on the steady-state pharmacokinetics of methadone (R-methadone and S-methadone).
- To evaluate the effect of steady-state DAA dosing on the pharmacodynamic effects of stable methadone maintenance therapy.
- To evaluate the safety and tolerability during coadministration of DAAs and methadone during stable methadone maintenance therapy.
- To characterize the pharmacokinetics of DAAs and metabolites when dosed with methadone.
- To characterize the effect of different dosing schemes on DAA and methadone pharmacokinetics.

#### **Trial Design**

Phase 1, multiple-center, open-label, sequential, multiple-dose study to evaluate the co-administration of methadone with DAAs. Arm 2 included a 2-DAA regimen of ABT-450/r with ABT-267.

Methadone Dosing:

The dose of methadone did not differ throughout the study for a given subject. For Arm 2, methadone dosing was approximately 30 minutes after the start of a standardized breakfast.

DAA Dosing:

DAAs were administered approximately 30 minutes after the start of a standardized breakfast.

Two different ABT-450, ritonavir, and ABT-267 formulations were used in the study. Arms 1 and 2 used the (b) (4) tablet of ABT-450, ritonavir capsules, and the (b) (4) tablet of ABT-267. Arm 3 used the ABT-450/r/ABT-267 co-formulated tablet.

Table 1 shows the various sequence groups in the trial:

	Subject Numbers	Regimens	
		Study Days 1 through 8 and 23 through 25	Study Days 9 through 22
Arm 1	1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, and 1012	A	B
Arm 2	2001, 2002, 2003, 2004, 2005, 2006, 2008, 2009, 2010, 2011, 2012, and 2013	A	C
Arm 3	3001, 3002, 3003, 3004, 3005, 3006, 3007, 3008 <sup>a</sup> , 3009, 3010, 3013, and 3014	A	D

a. Subject 3008 withdrew consent and was discontinued from study drugs and the study on Study Day 10.

In all the arms, the study drug was administered on study day 1 as shown in table 2 below.

<b>Regimen A<sup>a</sup></b>	Methadone QD was administered (as per prescribing physician's instructions) on Study Days 1 through 8, and 23 through 25 under non-fasting conditions.
<b>Regimen B</b>	On Study Days 9 through 22, methadone QD (as per prescribing physician's instructions) + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID were administered under non-fasting conditions.
<b>Regimen C<sup>b</sup></b>	On Study Days 9 through 22, methadone QD (as per prescribing physician's instructions) + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD were administered under non-fasting conditions.
<b>Regimen D<sup>b</sup></b>	On Study Days 9 through 22, ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 400 mg BID were administered under non-fasting conditions in the morning, 30 minutes after the start of a standardized breakfast (AM dose) and 30 minutes after the evening snack (PM dose). Methadone QD was administered under non-fasting conditions 30 minutes after the start of a standardized lunch, 4 hours after DAA administration.

- a. In Arms 1 and 2, methadone was administered 30 minutes after the start of a standardized breakfast. In Arm 3, methadone was administered 30 minutes after the start of a standardized lunch. At the investigator's discretion, in Arm 3, the subject's time of methadone dose could have been gradually incremented such that the subject took methadone approximately 30 minutes after the start of lunch by Study Day 6. In these cases, subjects could have taken methadone without regard to meals from Study Days 1 to 5.
- b. Doses in Arm 2 (Regimen C) could have been modified based on safety, tolerability, and pharmacokinetic results from the preceding arm. Doses in Arm 3 (Regimen D) could have been modified based on safety, tolerability, and pharmacokinetic results from Arm 1 with all 3 DAAs and available data from Arm 2 with 2 DAAs. Doses in Arm 2 (Regimen C) could have been as low as 0 mg and were not to exceed ABT-450/r 250/100 mg QD, ABT-333 800 mg BID, and ABT-267 100 mg QD. Doses in Arm 3 (Regimen D) could have been as low as 0 mg and were not to exceed ABT-450/r/ABT-267 225/150/37.5 mg QD and ABT-333 800 mg BID. The dose of methadone did not differ throughout the study for a given subject.

## Rationale for Conducting the Trial

Methadone is a substrate for CYP3A4, CYP2B6, CYP2C8, CYP2C19, and CYP2D6. CYP3A4 is involved in ABT-450 and ritonavir metabolism. Ritonavir inhibits CYP3A4 and to a lesser extent, CYP2D6. The overlapping enzymes involved in the metabolism can lead to the possibility of drug-drug interactions of methadone with ABT-450, ritonavir, and ABT-267.

## Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), and ABT-267 (25 mg) were the doses that were determined to be safe and efficacious in Phase 3 trials. The dose of methadone was individualized for each subject who enrolled in the trial and ranged from 20 mg to 120 mg. The subjects were receiving the individualized dose for at least 14 days prior to screening.

## Identity of Investigational Products

Table 3 shows the identity of the investigational products used in the trial.

	ABT-267	ABT-450	Ritonavir	ABT-333	ABT-450/r/ABT-267 Co-formulation
Dosage Form	Film Coated (b) (4) (b) (4) Tablet	(b) (4) (b) (4) Tablet	Soft Gelatin Capsule	Tablet	Tablet
Mode of Administration	Oral	Oral	Oral	Oral	Oral
Strength (mg)	25	50	100 mg	400	75/50/12.5
Bulk Product Lot Number	11-002033	11-000781	11-005635	11-005348	12-006414
Potency (% of Label Claim)	101.3	100.5	100.8	100.7	101.6/100.3/102.3
Manufacturing Site	AbbVie, Ludwigshafen	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL
Manufacturing Date	10 June 2011	09 December 2010	07 October 2011	06 January 2012	10 May 2012
Finishing Lot Number	12-003264	12-003267	12-003270 and 12-006467	12-003268	12-007522
Expiration/Retest Date	(b) (4)				

## Sample Collection

### Pharmacokinetics

#### *Arm 1, 2, 3, Study Days 9 through 25-DAA/ritonavir Sampling*

Prior to dosing (0 hour) and up to at 24 hours after dosing on study day 9. On day 22, in addition to the 24 hour sampling, additional samples were collected on days 23, 24, and 25. Trough samples were also collected before the morning dosing on study days 11, 13, 15, 17, and 21.

#### *Arms 1 and 2, Methadone Sampling*

Study days 1 through 8: Prior to dosing (0 hour) and up to 16 hours after dosing on day 8. Trough samples were collected prior to methadone dosing on study day 7.

Study days 9 through 25: Prior to dosing (0 hour) and up to 24 hours after dosing on days 9 and 22. Trough samples were collected prior to the morning dose on study days 11, 13, 15, 17, 21, 24, and 25.

### **Pharmacodynamic Assessments**

Pharmacodynamic (PD) measurements were assessed 2 hours prior to dosing and at 1, 2, and 4 hours after methadone dosing on Study Days 8 through 11, 13, 15, 17, and Study Days 21 through 25 (or upon early discontinuation). The PD measurements taken on Study Day 8 served as baseline and were assessed on subjective (Short Opiate Withdrawal Scale [SOWS] and Desires for Drug Questionnaires [DDQ]) and physiologic (pupillometry) indexes.

### **Pharmacokinetic Analysis**

The pharmacokinetic parameters of ABT-450, ritonavir, and ABT-267 were determined using non-compartmental methods.

## Results

### *Bioanalytical methods*

Table 4 provides the summary of the bioanalytical assay parameters.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.595-406	0.595	1.58, 26.4, 330	3.9 % to 8.2 %	0.3 % to 3.3 %
Ritonavir	4.91-3340	4.91	12.7, 211, 2640	4.5 % to 4.9 %	0 % to 3 %.
ABT-267	0.46-314	0.46	1.18, 20.1, and 251	3.1% to 9.9 %	2.8 % to 4.2 %
R-Methadone	1-1000	1	3,75, 750	2.2 % to 8 %	-1.3 % to -0.3 %
S-Methadone	1-1000	1	3,75, 750	2.1 % to 11.2 %	-1.5 % to -1.3 %

### *Subject Disposition and Demographics*

36 subjects (21 male and 15 female) were enrolled in the study and 30 subjects (19 males and 11 females) completed the study. 1 subject withdrew consent (data from this subject was not included in the pharmacokinetic and statistical analysis) and 5 subjects were lost to follow up and did not complete the trial. The available data from subjects who were lost to follow up were included in the statistical analysis.

Table 5 below shows the shows the demographic summary of all subjects enrolled in the trial.

	Mean ± SD (N = 36)	Min – Max
Age (years)	34.7 ± 8.1	21 – 51
Weight (kg)	74.1 ± 10.5	48.5 – 96.4
Height (cm)	170.1 ± 8.1	157.6 – 188.8
Sex	21 Males (58.3%) and 15 Females (41.7%)	
Race	4 Black or African American (11.1%), 30 White (83.3%), and 2 Asian (5.6%)	

### *Pharmacokinetics*

*Note: Only the results from Arm 2 are presented in this review.*

## Arm 2:

### ABT-450

Table 6 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 in Arm 2.

ABT-450 Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
C <sub>max</sub> (ng/mL)	356 $\pm$ 406	466 $\pm$ 779
T <sub>max</sub> (h)	4.3 $\pm$ 1.2	3.9 $\pm$ 1.1
AUC <sub>24</sub> (ng•h/mL)	1600 $\pm$ 1320	2180 $\pm$ 3160
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	6.12 $\pm$ 2.60
C <sub>24</sub> (ng/mL)	7.62 $\pm$ 5.04	7.54 $\pm$ 6.34

- a. Harmonic mean  $\pm$  pseudo-standard deviation.  
b. t<sub>1/2</sub> calculated following the Study Day 22 dose only.

### Ritonavir

Table 7 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 2.

Ritonavir Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
C <sub>max</sub> (ng/mL)	1090 $\pm$ 445	1560 $\pm$ 578
T <sub>max</sub> (h)	4.5 $\pm$ 1.1	4.0 $\pm$ 1.0
AUC <sub>24</sub> (ng•h/mL)	7120 $\pm$ 2840	10400 $\pm$ 3250
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	5.83 $\pm$ 2.21
C <sub>24</sub> (ng/mL)	50.7 $\pm$ 29.2	65.8 $\pm$ 24.4

- a. Harmonic mean  $\pm$  pseudo-standard deviation.  
b. t<sub>1/2</sub> calculated following the Study Day 22 dose only.

### ABT-267

Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 in Arm 2.

ABT-267 Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
$C_{max}$ (ng/mL)	94.6 ± 29.3	97.0 ± 36.2
$T_{max}$ (h)	4.8 ± 0.6	4.9 ± 0.3
$AUC_{24}$ (ng•h/mL)	900 ± 302	1150 ± 429
$t_{1/2}^{a,b}$ (h)	--	28.9 ± 9.50
$C_{24}$ (ng/mL)	13.2 ± 5.47	24.2 ± 8.64

a. Harmonic mean ± pseudo-standard deviation.

b.  $t_{1/2}$  calculated following the Study Day 22 dose only.

## Methadone

Fig 1 shows the mean R-methadone plasma concentration-time profiles

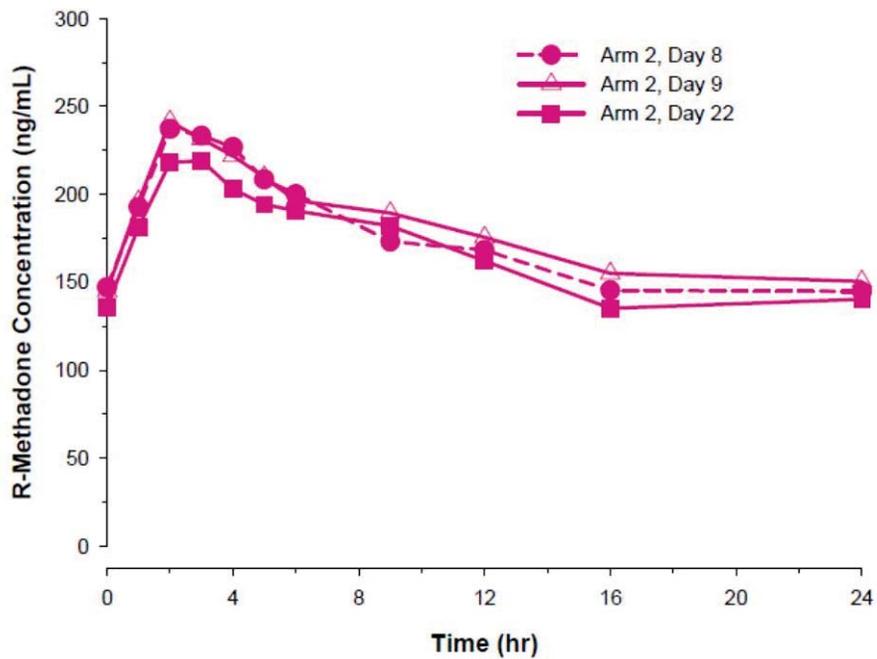


Fig 2 shows the mean S-methadone plasma concentration-time profiles.

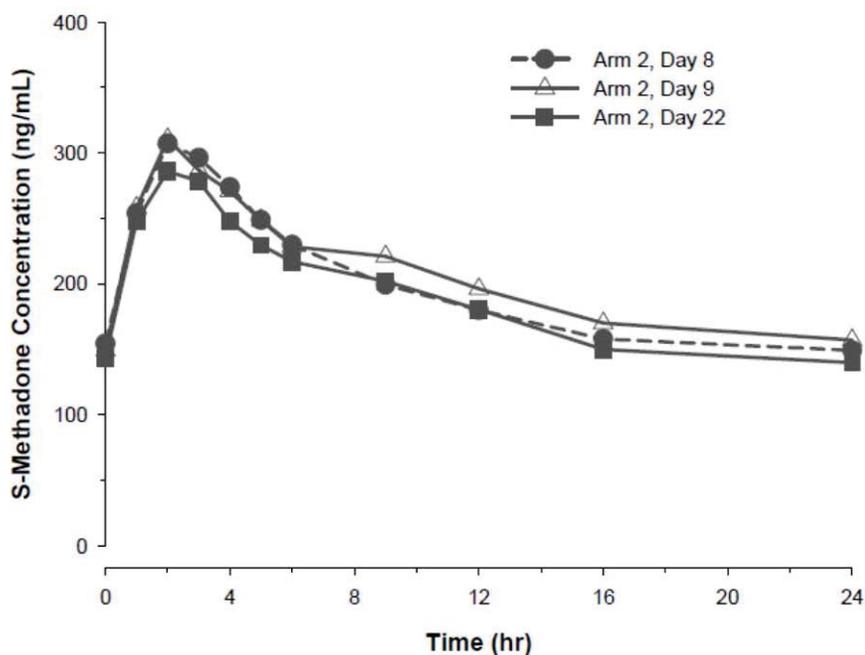


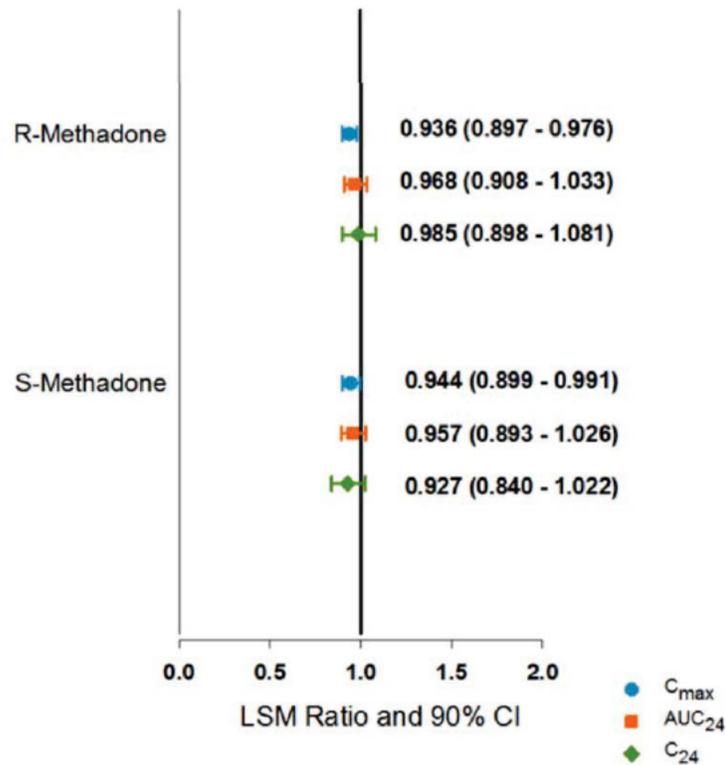
Table 9 shows the pharmacokinetic parameters (Mean  $\pm$ SD) of R-Methadone and S-Methadone.

Methadone Pharmacokinetic Parameter (Unit)	Day 8 Methadone QD (N = 12)	Day 9	Day 22
		ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
<b>R-Methadone</b>			
$C_{max}$ (ng/mL)	244 $\pm$ 102	256 $\pm$ 85.4	226 $\pm$ 94.0
$C_{max}/Dose$ (ng/mL/mg)	3.69 $\pm$ 0.83	4.29 $\pm$ 1.82	3.42 $\pm$ 0.56
$T_{max}$ (h)	2.7 $\pm$ 0.8	3.0 $\pm$ 2.0	3.2 $\pm$ 2.8
$AUC_{24}$ (ng•h/mL)	4130 $\pm$ 1760	4230 $\pm$ 1680	3950 $\pm$ 1640
$AUC_{24}/Dose$ (ng•h/mL/mg)	62.6 $\pm$ 15.4	65.5 $\pm$ 12.6	59.7 $\pm$ 10.3
$C_{24}$ (ng/mL)	145 $\pm$ 63.7	151 $\pm$ 66.2	140 $\pm$ 61.7
<b>S-Methadone</b>			
$C_{max}$ (ng/mL)	312 $\pm$ 102	331 $\pm$ 72.6	294 $\pm$ 100
$C_{max}/Dose$ (ng/mL/mg)	4.96 $\pm$ 1.53	5.93 $\pm$ 3.36	4.70 $\pm$ 1.54
$T_{max}$ (h)	2.4 $\pm$ 0.5	2.8 $\pm$ 2.0	2.3 $\pm$ 0.5
$AUC_{24}$ (ng•h/mL)	4690 $\pm$ 1510	4860 $\pm$ 1300	4500 $\pm$ 1580
$AUC_{24}/Dose$ (ng•h/mL/mg)	75.9 $\pm$ 27.9	80.9 $\pm$ 26.6	73.8 $\pm$ 31.7
$C_{24}$ (ng/mL)	149 $\pm$ 53.0	157 $\pm$ 56.2	140 $\pm$ 59.8

Note: methadone dose (mg), mean  $\pm$  SD: 67.1  $\pm$  30.0.

## Statistical Evaluation of the Effect of 2-DAA on R-Methadone and S-Methadone (Arm 2)

Fig 5 shows the least squares mean ratio and 90 % confidence intervals for R-methadone and S-methadone dose normalized  $C_{max}$  and  $AUC_{24}$ .



Arm 2 was administered as separate formulations of ABT-450 (b) (4) ritonavir (capsule) and ABT-267 (b) (4).

### Effect of Methadone on the Individual Components of the 2-DAA regimen

Table 10 shows the ABT-450  $C_{max}$  and AUC during co-administration of the 3-DAA and the 2-DAA regimen with methadone relative to exposures in other studies (ABT-450 (b) (4) tablets).

Study	3 DAA ABT-450/r + ABT-267 + ABT-333		2 DAA ABT-450/r + ABT-267	
	C <sub>max</sub> (ng/mL)	AUC (ng•h/mL)	C <sub>max</sub> (ng/mL)	AUC (ng•h/mL)
M13-783	1890	7390	518	2720
M13-506 <sup>c</sup>	681	4300	443	2550
M13-506 <sup>a,c</sup>	359	2360	-	-
M13-103	1140	6970	701	4430
M12-221	633	3100	NA	NA
M13-491 <sup>c</sup>	649	3570	263	1810
M13-492 <sup>c</sup>	854	5080	204	1500
M13-492 <sup>a,c</sup>	--	--	530	2900
Current Study <sup>b</sup>	125	722	218	1300

NA = Not Applicable

a. Arm 4.

b. Arms 1 and 2.

c. Preliminary data.

Notes: Geometric mean values are reported.

AUC = AUC<sub>24</sub> at steady-state.

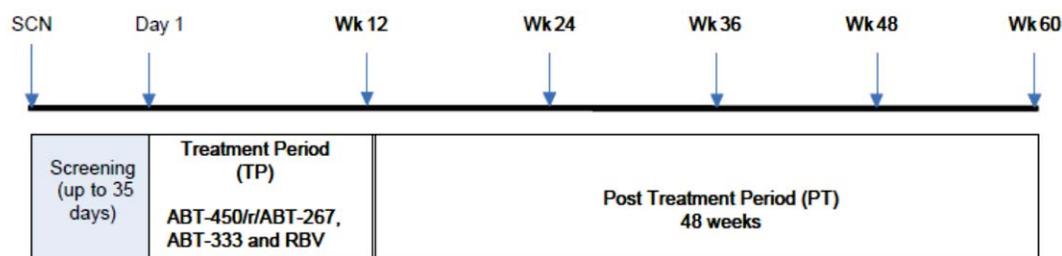
Based on cross study comparison, co-administration of the 2-DAA regimen (ABT-450 (b) (4) tablet) with methadone resulted in comparable to 70% lower ABT-450 C<sub>max</sub> and 14% – 70% lower AUC relative to exposures in subjects when the 2-DAA regimen was administered alone.

In order to further assess the clinical relevance of decrease in ABT-450 exposures in the presence of methadone (based on cross trial comparison), the sponsor assessed the efficacy and safety and the 3-DAA regimen in patients stabilized on methadone or buprenorphine/naloxone therapy in trial M14-103.

Summary of Trial **M14-103** (Safety, pharmacokinetics, and antiviral activity of 12 weeks of 3-DAA regimen +RBV in HCV genotype 1 infected subjects on chronic opioid replacement therapy).

Trial M14-103, an open label, single arm trial, evaluated the safety, pharmacokinetics, and antiviral activity of 12 weeks of 3-DAA regimen+RBV in HCV genotype 1 infected patients on chronic opioid replacement therapy. 38 subjects were enrolled in the trial; 19 subjects were on stable methadone maintenance therapy and 19 subjects were on buprenorphine (with or without naloxone). All subjects were on a stable opioid replacement therapy for at least 6 months prior to screening.

Fig 9 shows the trial design:



ABT-450/r/ABT-267 (coformulated product) was administered orally once daily and ABT-333 and RBV were administered twice daily. Plasma samples were collected on day 1 prior to dosing; intensive PK assessments (samples collected up to 24 hours) were conducted on or after 2 weeks of beginning of 3-DAA treatment. Intensive PK data was available from 22/38 subjects (12 subjects on stable opioid replacement therapy of buprenorphine ± naloxone and 10 subjects on stable methadone therapy).

Table 11 shows the virologic response (SVR<sub>12</sub>, ITT population) observed in the trial.

Virologic Finding	3-DAA + RBV N = 38 n/N (%)
	37/38 (97.4%)
<b>SVR<sub>12</sub></b>	<b>95% CI<sup>a</sup>: 92.3%, 100.0%</b>
Reasons for nonresponse	
On-treatment virologic failure	0
Rebound	0
Fail to suppress	0
Relapse by Post-Treatment Week 12	0/37
Premature study drug discontinuation	1/38 (2.6%)
Missing SVR <sub>12</sub> data	0
Other	0

CI = confidence interval; DAA = direct-acting antiviral agent; ITT = intent-to-treat; RBV = ribavirin; SVR<sub>12</sub> = sustained virologic response 12 weeks postdosing

a. Calculated using the normal approximation to the binomial distribution.

Table 12 shows the comparison of the pharmacokinetic parameters of all the components of the DAA regimen (and ABT-333 M1) observed in trial M14-103 and in Phase 1 trials conducted using the Phase 3 formulation.

	HCV Genotype 1-Infected Adults		Exposures from Phase 1 Studies with the Phase 3 Formulation (Range) N = 113
	Study M14-103		
	Buprenorphine ± Naloxone N = 12	Methadone N = 10	
ABT-450			
C <sub>max</sub> (ng/mL)	1,090	1,750	771 – 3,360
AUC <sub>t</sub> (ng•hr/mL)	10,800	19,400	3,819 – 18,600
Ritonavir			
C <sub>max</sub> (ng/mL)	1,070	815	1,289 – 2,240
AUC <sub>t</sub> (ng•hr/mL)	11,800	10,100	7,571 – 14,400
ABT-267			
C <sub>max</sub> (ng/mL)	98.8	90.6	83.8 – 130
AUC <sub>t</sub> (ng•hr/mL)	1,460	1,410	1,050 – 1,560
ABT-333			
C <sub>max</sub> (ng/mL)	725	602	826 – 1,460
AUC <sub>t</sub> (ng•hr/mL)	5,070	4,490	5,624 – 9,790
ABT-333 M1			
C <sub>max</sub> (ng/mL)	390	355	507 – 962
AUC <sub>t</sub> (ng•hr/mL)	2,550	2,310	2,929 – 6,200

AUC<sub>t</sub> = area under the concentration-time curve from time 0 to the last measureable concentration; C<sub>max</sub> = maximum plasma concentration; DAA = direct-acting antiviral; HCV = hepatitis C virus

a. The ABT-450/r coformulated tablet was administered. This formulation has comparable exposures to the ABT-450/r/ABT-267 coformulated tablet (Study M13-391<sup>6</sup>).

Notes: Preliminary geometric mean values for C<sub>max</sub> and AUC were obtained from the 3-DAA treatment arms (ABT-450/r/ABT-267 coformulated tablet) from Studies M12-202, M12-204, M13-394<sup>3</sup> and M14-013.

Final geometric mean values for C<sub>max</sub> and AUC were obtained from the 3-DAA treatment arms (ABT-450/r/ABT-267 coformulated tablet) from Studies M12-199<sup>7</sup> and M13-782<sup>8</sup>.

AUC<sub>t</sub> is AUC<sub>24</sub> for ABT-450, ritonavir, and ABT-267 and is AUC<sub>12</sub> for ABT-333 and ABT-333 M1.

Exposure values were obtained from Study M13-100.<sup>5</sup>

The exposures achieved for all the components of the DAA regimen (and ABT-333 M1) and RBV in HCV genotype 1 subjects on methadone or buprenorphine/naloxone were comparable to- or slightly lower than the exposures in the Phase 1 studies with the same formulations.

It should be noted that although trial M14-103 was conducted using the 3-DAA regimen, the results can be extrapolated to the 2-DAA regimen because trial M14-103 used the ABT-450/r/ABT-267 coformulated (to-be-marketed) product and a decrease in ABT-450 exposures were not observed.

## Results

Co-administration of ABT-450/r/ABT-267 with methadone did not significantly alter the pharmacokinetic parameters of R-methadone and S-methadone or the individual components of the 2-DAA regimen.

## Conclusion

ABT-450/ritonavir/ABT-267 can be co-administered with methadone without any dose adjustments.

## **Drug-Drug Interaction Trial with Buprenorphine/Naloxone**

### **M13-100**

#### **Title**

**An Open Label, Phase 1 Study to Assess the Effect of the Combination of ABT-450 plus ritonavir (ABT-450/r) with ABT-267 and/or ABT-333 on the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Buprenorphine/Naloxone in Subjects in Stable Maintenance Therapy**

#### **Trial Period**

August 17, 2012 to August 30, 2013  
Final report date: March 25, 2014.

*Reviewer's Note: As the proposed labeling recommendations in NDA 207931 are based on 2 DAAs (ABT-450/ritonavir/ABT-267), the results section in this review focuses only on the results observed with the 2-DAAs (Arm 3). For results with the 3-DAAs, please refer to the review of NDA 206619.*

#### **Trial Design**

Phase 1, single-center, open-label, sequential, multiple-dose study to evaluate the coadministration of buprenorphine/naloxone with DAAs. Arm 3 included the coadministration of the 2-DAA regimen of ABT-450/r/ABT-267 with buprenorphine/naloxone. In Arm 3, the DAAs and buprenorphine/naloxone were administered at the same time.

#### **BUP/NAL Dosing:**

The dose of BUP and NAL did not differ throughout the study for a given subject; however, the timing of BUP and NAL doses in Arm 3 was determined based on available results of the preceding arms. For Arms 1 and 3, BUP and NAL doses were administered at the same as the DAAs (30 minutes after the start of a standardized breakfast).

#### **DAA Dosing:**

DAAs were administered approximately 30 minutes after the start of a standardized breakfast.

Table 1 shows the various sequence groups in the trial:

	Subject Numbers	Regimens	
		Study Days 1 through 8 and 23 through 25	Study Days 9 through 22
Arm 1	1001, 1002, 1003 <sup>c</sup> , 1004, 1005, 1006, 1007, 1008 <sup>a</sup> , 1009 <sup>c</sup> , 1010, 1011 <sup>c</sup> and 1012 <sup>b</sup>	A	B
Arm 2	2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008 <sup>d</sup> , 2009 <sup>e</sup> , 2010, 2011 <sup>f</sup> , 2012 and 2013	A	C
Arm 3	3001, 3002, 3003, 3004, 3005, 3006, 3007, 3008, 3009, 3010 and 3011	A	D

- a. Subject 1008 was discontinued from study drugs on Study Day 21.
- b. Subject 1012 was discontinued from study drugs on Study Day 15.
- c. Subjects 1003, 1009, and 1011 were discontinued on Study Day 24; the subjects completed all DAA dosing.
- d. Subject 2008 was discontinued from study drugs on Study Day 9 and was not dosed with the DAAs.
- e. Subject 2009 was discontinued from the study on Study Day 5 and was not dosed with the DAAs.
- f. Subject 2011 was discontinued from study drugs on Study Day 17.

In all the arms, the study drug was administered on study day 1 as shown in table 2 below.

<b>Regimen A<sup>a</sup></b>	Buprenorphine/naloxone QD was administered (as per prescribing physician's instructions) on Study Days 1 through 8 and Study Days 23 through 25.
<b>Regimen B</b>	On Study Days 9 through 22, buprenorphine/naloxone QD + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID were administered under non-fasting conditions for 14 days.
<b>Regimen C<sup>b</sup></b>	On Study Days 9 through 22, ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 400 mg BID were administered under non-fasting conditions in the morning, 30 minutes after the start of a standardized breakfast (AM dose) and 30 minutes after the evening snack (PM dose, ABT-333 only). Buprenorphine/naloxone QD was administered under non-fasting conditions 30 minutes after the start of a standardized lunch, approximately 4 hours after the DAA AM dose.
<b>Regimen D<sup>b</sup></b>	On Study Days 9 through 22, buprenorphine/naloxone QD + ABT-450/r/ABT-267 150/100/25 mg QD were administered under non-fasting conditions in the morning, 30 minutes after the start of a standardized breakfast.

- a. In Arm 1, buprenorphine/naloxone was administered 30 minutes after the start of a standardized breakfast. In Arm 2, buprenorphine/naloxone was administered 30 minutes after the start of a standardized lunch, approximately 4 hours after the morning DAA administration. At the investigator's discretion, in Arm 2, the subject's time of buprenorphine/naloxone dose could have been gradually increased such that the subject could have taken buprenorphine/naloxone approximately 30 minutes after the start of lunch by Study Day 6. In these cases, subjects would have taken buprenorphine/naloxone without regard to meal times from Study Days 1 to 5. In Arm 3, buprenorphine/naloxone was dosed similarly to Arm 1.
- b. Based on a review of the pharmacokinetic, safety and tolerability results of the previous arm(s), a decision was made whether to conduct the next sequential arm. Doses in Arms 2 and 3 (Regimens C and D) could have been modified based on safety, tolerability, and pharmacokinetic results available from preceding arms. Doses in Arms 2 and 3 could have been as low as 0 mg and were not to exceed ABT-450/r/ABT-267 225/150/37.5 mg QD and ABT-333 800 mg BID. The dose of buprenorphine/naloxone did not differ throughout the study for a given subject. The timing of buprenorphine/naloxone dosing in Arm 3 was determined based on safety, tolerability, and pharmacokinetic results available from the preceding arms.

## Rationale for Conducting the Trial

BUP is a substrate of CYP3A4. CYP3A4 is involved in ABT-450 and ABT-267 disposition and CYP3A and CYP2C8 are involved in ABT-267 metabolism. Ritonavir inhibits CYP3A4 and to a lesser extent, CYP2D6. The overlapping enzymes involved in the drugs' metabolism and CYP450 inhibition by ritonavir can lead to drug-drug interactions of BUP with ABT-450, ritonavir and ABT-267.

## Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily) and ABT-267 (25 mg) were the doses that were determined to be safe and efficacious in Phase 3 trials. The dose of BUP was individualized for each subject who enrolled in the trial and ranged from 4 mg/day to 24 mg/day.

## Identity of Investigational Products

Table 3 shows the identity of the investigational products used in the trial.

	ABT-267	ABT-450	Ritonavir	ABT-333	ABT-450/r/ABT-267 Co-Formulation
Dosage Form	Film Coated (b) (4) Tablet	(b) (4) Tablet	Soft Gelatin Capsule (SGC)	Tablet	Tablet
Mode of Administration	Oral	Oral	Oral	Oral	Oral
Strength (mg)	25	50	100	400	75/50/12.5
Bulk Product Lot Number	11-002033	11-000781	11-005635/110262E	11-005348	12-006414
Potency (% of Label Claim)	101.3	100.5	100.8	100.7	101.6/100.3/102.3
Manufacturing Site	AbbVie, Ludwigshafen, Germany	(b) (4)	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL
Manufacturing Date	10 June 2011	09 December 2010	07 October 2011	06 January 2012	10 May 2012
Finishing Lot Number	12-004982	12-004984	12-004985	12-004983	12-007611
Expiration/Retest Date	(b) (4)				

## Sample Collection

### Pharmacokinetics

#### *Arm 1, 2, 3, Study Days 9 through 25-DAA/ritonavir Sampling*

Prior to dosing (0 hour) and at 1, 2, 3, 4, 6, 9, 12, and 16 hours after the morning dose on study days 9 and 22. A 24 hour sample was collected on study day 10 and 23; 48 and 72 hour samples were collected on study days 24 and 25 after the morning dose on study day 22. Trough samples were also collected before the morning dosing on study days 11, 13, 15, 17, and 21.

#### *Arms 1, 2, and 3 BUP, nor-BUP, and NAL Sampling*

Study days 1 through 8: Prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, and 16 hours (16 hour sample was collected only in Arm 1) after dosing on study day 8. Trough samples were collected prior to BUP/NAL dosing on study day 7.

Study days 9 through 25: Prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, and 16 hours hours after dosing on days 9 and 22. An additional trough sample was collected on 24 hours after dosing on study day 9 (on study day 10) and study day 22 (on study day 23). Trough samples were also collected prior to the morning dose on study days 11, 13, 15, 17, 21, 24, and 25.

## Pharmacodynamic Assessments

Short Opiate Withdrawal Scale (SOWS): The responses on the SOWS were linked to specific periods of time in relation to buprenorphine/naloxone drug administration (study days 8, 9 through 11, 13, 15, 17, 21 , and 21 through 25).

Desire for Drugs Questionnaire (DDQ) Heroin: The responses on DDQ heroin were linked to specified periods of time in relation to buprenorphine/naloxone drug administration (study days 8, 9 through 11, 13, 15, 17, 21 , and 21 through 25).

Pupillometry: Measurements to assess the pupillary size were lined to specified periods of time in relation to buprenorphine/naloxone drug administration (study days 8, 9 through 11, 13, 15, 17, 21 , and 21 through 25).

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, BUP, nor-BUP, and NAL were determined using non-compartmental methods.

## Results

### *Bioanalytical methods*

The concentrations of ABT-450, ritonavir, ABT-267, ABT-333, buprenorphine, norbuprenorphine, and naloxone were determined using HPLC with MS/MS detection. All samples were analyzed within the maximum validated storage stability.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.65-402	0.65	1.48, 24.7, 309	2.8 % to 7.3 %	0 % to 2.7 %
Ritonavir	5.39-3330	5.39	12.2, 203, 2540	3.7% to 4.6 %	-1.6 % to 0.5 %
ABT-267	0.492-304	0.49	1.09, 18.2, 228	1.8 % to 6 %	1.8 % to 3.5 %
BUP*	100-25000	100	300, 3000, 17,500	4 % to 5 %	-2.3 %-0.6 %
Nor-BUP*	100-25000	100	300, 3000, 17,500	3 % to 5.1 %	-2 % to -0.6 %
Naloxone*	20-5000	20	60,600,3500	4.6 % to 7.6 %	-3.8 % to -0.6 %

\*: Concentrations are in pg/mL

### *Subject Disposition and Demographics*

Table 4 below shows the demographic summary of all subjects enrolled in the trial. 24 subjects completed the trial.

	<b>Mean ± SD (N = 36)</b>	<b>Min – Max</b>
Age (years)	31.8 ± 8.3	20 – 55
Weight (kg)	74.4 ± 13.4	49.5 – 101
Height (cm)	174 ± 7.2	153 – 187
Sex	28 Males (77.8%) and 8 Females (22.2%)	
Race	36 White (100%)	

### *Pharmacokinetics*

#### Arm 3:

ABT-450

Table 5 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 3.

<b>ABT-450 Pharmacokinetic Parameter (Unit)</b>	<b>Day 9</b>	<b>Day 22</b>
	<b>ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)</b>	<b>ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)</b>
C <sub>max</sub> (ng/mL)	577 ± 562	1250 ± 1530
T <sub>max</sub> (h)	4.4 ± 0.92	4.4 ± 0.92
AUC <sub>24</sub> (ng·h/mL)	2430 ± 2000	4590 ± 5020
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	6.38 ± 2.81
C <sub>24</sub> (ng/mL)	12.2 ± 7.44	14.6 ± 17.0

Formulation: ABT-450/r/ABT-267 co-formulated tablet.

Arm 3: Day 9: First day of dosing ABT-450/r/ABT-267 with daily dosing of buprenorphine/naloxone at steady state.

Arm 3: Day 22: Steady-state dosing of ABT-450/r/ABT-267 and buprenorphine/naloxone.

a. Harmonic mean ± pseudo-standard deviation.

b. t<sub>1/2</sub> calculated following the Study Day 22 dose only.

The higher ABT-450 exposures on Day 22 compared to Day 9 represents ABT-450 accumulation following multiple doses.

Ritonavir

Table 6 shows the mean ± SD pharmacokinetic parameters of ritonavir in Arm 1.

Ritonavir Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)
C <sub>max</sub> (ng/mL)	1160 ± 634	1760 ± 475
T <sub>max</sub> (h)	4.6 ± 0.69	4.5 ± 0.93
AUC <sub>24</sub> (ng·h/mL)	6790 ± 4400	10400 ± 3250
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	6.17 ± 3.46
C <sub>24</sub> (ng/mL)	49.7 ± 37.2	65.6 ± 44.8

Formulation: ABT-450/r/ABT-267 co-formulated tablet.

Arm 3: Day 9: First day of dosing ABT-450/r/ABT-267 with daily dosing of buprenorphine/naloxone at steady state.

Arm 3: Day 22: Steady-state dosing of ABT-450/r/ABT-267 and buprenorphine/naloxone.

a. Harmonic mean ± pseudo-standard deviation.

b. t<sub>1/2</sub> calculated following the Study Day 22 dose only.

## ABT-267

Table 7 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 1.

ABT-267 Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)
C <sub>max</sub> (ng/mL)	96.6 ± 30.4	100 ± 25.1
T <sub>max</sub> (h)	5.1 ± 0.30	4.9 ± 0.30
AUC <sub>24</sub> (ng·h/mL)	819 ± 298	1050 ± 300
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	23.2 ± 3.80
C <sub>24</sub> (ng/mL)	14.6 ± 6.90	22.9 ± 10.6

Formulation: ABT-450/r/ABT-267 co-formulated tablet.

Arm 3: Day 9: First day of dosing ABT-450/r/ABT-267 with daily dosing of buprenorphine/naloxone at steady state.

Arm 3: Day 22: Steady-state dosing of ABT-450/r/ABT-267 and buprenorphine/naloxone.

a. Harmonic mean ± pseudo-standard deviation.

b. t<sub>1/2</sub> calculated following the Study Day 22 dose only.

ABT-267 C<sub>max</sub> and AUC values on day 22 were slightly higher compared to day 9, which is consistent with the minimal accumulation of ABT-267 with multiple dosing.

## BUP and nor-BUP (Arm 3)

Table 9 shows the mean ± SD pharmacokinetic parameters of BUP and nor-BUP in Arm 3.

Pharmacokinetic Parameter (Unit)	Day 8	Day 9	Day 22
	Buprenorphine/naloxone QD (N = 11)	ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)
<b>Buprenorphine</b>			
C <sub>max</sub> (pg/mL)	8210 ± 4650	10500 ± 4770	9670 ± 4730
C <sub>max</sub> /Dose (pg/mL/mg)	697 ± 299	878 ± 309	821 ± 309
T <sub>max</sub> (h)	1.9 ± 0.45	1.6 ± 0.39	2.0 ± 0.15
AUC <sub>24</sub> (pg•h/mL)	58800 ± 33100	86200 ± 47000	90100 ± 48400
AUC <sub>24</sub> /Dose (pg•h/mL/mg)	5030 ± 2300	7210 ± 3120	7430 ± 2850
C <sub>24</sub> (pg/mL)	1210 ± 801	1710 ± 1150	2030 ± 1180
C <sub>24</sub> /Dose (pg/mL/mg)	104 ± 60.2	141 ± 78.7	165 ± 78.1
<b>Norbuprenorphine</b>			
C <sub>max</sub> (pg/mL)	5900 ± 4120	7010 ± 3880	11300 ± 9650
C <sub>max</sub> /Dose (pg/mL/mg)	464 ± 220	564 ± 235	865 ± 530
T <sub>max</sub> (h)	1.9 ± 0.63	6.2 ± 3.6	5.2 ± 3.6
AUC <sub>24</sub> (pg•h/mL)	89600 ± 54500	131000 ± 72400	201000 ± 160000
AUC <sub>24</sub> /Dose (pg•h/mL/mg)	7200 ± 3220	10500 ± 4310	15600 ± 8720
C <sub>24</sub> (pg/mL)	3110 ± 1650	4290 ± 2400	6300 ± 4250
C <sub>24</sub> /Dose (pg/mL/mg)	252 ± 86.4	341 ± 134	498 ± 245

Formulation: ABT-450/r/ABT-267 co-formulated tablet.

Arm 3: Day 8: Daily dosing of buprenorphine/naloxone at steady state.

Arm 3: Day 9: First day of dosing ABT-450/r/ABT-267 with daily dosing of buprenorphine/naloxone at steady state.

Arm 3: Day 22: Steady-state dosing of ABT-450/r/ABT-267 and buprenorphine/naloxone.

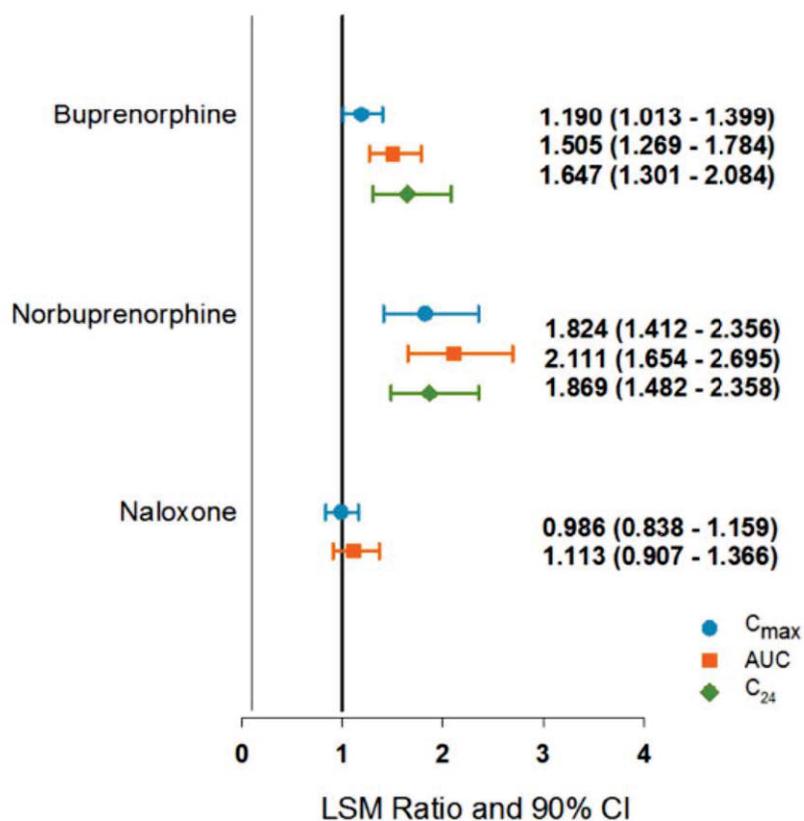
Buprenorphine dose in Arm 3, median (min – max): 12 (4 – 16) mg.

Norbuprenorphine was dose-normalized using buprenorphine dose.

## Statistical Evaluation of the Pharmacokinetic Parameters

### Buprenorphine

Fig 1 shows the dose normalized C<sub>max</sub>, AUC, and C<sub>24</sub> of central values and 90 % CIs for the comparisons (study days 22 versus 8) for buprenorphine, norbuprenorphine (normalized using buprenorphine dose), and naloxone).



Arm 3: Phase 3 formulation of ABT-450/r/ABT-267 co-formulated tablet

AUC<sub>24</sub>: Buprenorphine and norbuprenorphine; AUC<sub>t</sub>: naloxone

### Pharmacodynamic Assessments

Overall, there were no changes in the pupil response, SOWS response, and the DDQ response after administration of the 2-DAA regimen with buprenorphine/naloxone.

### Safety

No death, serious adverse events, or other significant adverse events were reported in the trial.

### Results

Co-administration of ABT-450/r/ABT-267 and buprenorphine/naloxone (Arm 3):

- Increased the mean  $C_{max}$  and AUC of buprenorphine by 19 % and 50 %, respectively.
- Increased the mean  $C_{max}$  and AUC of norbuprenorphine by 82 % and 111 %, respectively.

- Cross study comparison of ABT-450, ritonavir and ABT-267 exposures suggested no impact of BUP/NAL on the pharmacokinetics of ABT-450, ritonavir, and ABT-267.

### **Proposed Clinical Recommendation**

“No dose adjustment of BUP/NAL is required upon co-administration with the 2-DAA regimen. Patients should be closely monitored for sedation and cognitive effects”.

The recommendation outlined above is identical to the approved clinical recommendation related to co-administration of VIEKIRA PAK™ (3-DAA regimen) with buprenorphine/naloxone. Although the magnitude of increase in buprenorphine exposures, when buprenorphine/naloxone is co-administered with the 2-DAA regimen (~50 %) is smaller than the increase in buprenorphine exposures when buprenorphine/naloxone is co-administered with the 3-DAA regimen (~106 %), the magnitude of increase in norbuprenorphine exposures with the 2-DAA regimen (111 %) is higher as compared to the 3-DAA regimen (83 %). Increased buprenorphine exposures have been associated with increased sedation and cognitive effects. Further, the approved prescribing information of Stribild also provides a similar recommendation with buprenorphine/naloxone, despite a lower magnitude of increase in buprenorphine exposures. Hence, to be conservative and consistent across antiviral labels, the recommendation outlined above is proposed.

## Drug-Drug Interaction Trial with Raltegravir

### M13-392

#### Title

**A Phase 1, Open Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-administration of Raltegravir and ABT-450 with ritonavir (ABT-450/r) with ABT-333 and/or ABT-267 in Healthy Adult Subjects**

#### Trial Period

March 19, 2012 to November 8, 2012

Final report date: February 20, 2014

*Reviewer's Note: As the proposed labeling recommendations in NDA 207931 are based on 2 DAAs (ABT-450/ritonavir/ABT-267), the results section in this review focuses only on the results observed with the 2-DAAs (Arm 3 of trial M13-392). For results with the 3-DAAs, please refer to the review of NDA 206619.*

#### Trial Objectives

- To determine the pharmacokinetics, safety, and tolerability of the combination of ABT-450 plus ritonavir plus ABT-267 when dosed with raltegravir in healthy subjects.
- To determine the pharmacokinetics, safety, and tolerability of raltegravir when coadministered with a combination of ABT-450 plus ritoanavir plus ABT-267 in healthy subjects.

#### Trial Design

This was a Phase 1, multiple-dose, sequential, non-fasting, open-label study. **An optional Arm 4 was not conducted.**

Having met the selection criteria, 36 subjects were enrolled to the following arms:

Arm 1: Regimen A in period 1 and regimen B in period 2.

Arm 2: Regimen A in period 1 and regimen C in period 2.

Arm 3: Regimen A in period 1 and regimen D in period 2.

Table 1 shows the various regimens used in the trial.

<b>Regimen A</b>	Raltegravir 400 mg BID on Study Days 1 to 3
<b>Regimen B</b>	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + raltegravir 400 mg BID from Study Days 4 to 17
<b>Regimen C<sup>a</sup></b>	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + raltegravir 400 mg BID from Study Days 4 to 17
<b>Regimen D<sup>a</sup></b>	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + raltegravir 400 mg BID from Study Days 4 to 17

- a. Based on a review of the tolerability, safety, and pharmacokinetic results of the previous arm(s), a decision was made whether to conduct the next sequential arm (Arms 2 or 3). Doses in Arms 2 and 3 (Regimens C and D) could have been modified based on safety, tolerability, and pharmacokinetic results from previous arms. Doses in Arms 2 and 3 (Regimens C and D) could have been as low as 0 mg and did not exceed ABT-450/r 250/100 mg QD, ABT-333 800 mg BID, ABT-267 100 mg QD, and raltegravir 800 mg BID.

The study drug was taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast for all morning doses. The meal content was identical on pharmacokinetic sampling days.

### Rationale for Conducting the Trial

The trial was conducted to provide quantitative drug-drug interaction information for the use of raltegravir with the 3-DAA combination. The DAAs are metabolized by CYP3A (ABT-450 and ABT-267) and CYP2C8 (ABT-267[minor extent]). Raltegravir does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A in vitro. Further, raltegravir does not induce CYP1A2, CYP2B6, or CYP3A4 and does not inhibit P-gp mediated transport. Hence, raltegravir was not expected to alter the pharmacokinetics of the DAAs.

### Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily) and ABT-267 (25 mg) were the doses evaluated in Phase 3 trials. The dose of raltegravir (400 mg twice daily) is the clinically recommended dose.

### Identity of Investigational Products

Table 2 shows the identity of investigational products used in the trial

	ABT-267	ABT-450	Ritonavir	ABT-333	Raltegravir
Dosage Form	Film Coated (b) (4) ablet	(b) (4) Tablet	Soft Gelatin Capsule	Tablet	Film-Coated Tablet
Mode of Administration	Oral	Oral	Oral	Oral	Oral
Strength (mg)	25	50	100	400	400
Bulk Product Lot Number	11-002033	11-000781	11-005635	11-002720	12-000975 and 12-001865
Potency (% of Label Claim)	101.3	100.5	100.8	99.6	Unknown
Manufacturing Site	AbbVie, Ludwigshafen	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL	(b) (4)
Manufacturing Date	10 June 2011	09 December 2010	07 October 2011	19 July 2011	Unknown
Finishing Lot Number	12-000734	12-000735	12-000737 and 12-003904	12-000736	12-001023 and 12-001626
Expiration/Retest Date	(b) (4)				

## Sample Collection

Period 1 (study day 3): Blood samples for raltegravir were collected prior to dosing (0 hour) and up to 12 hours after the morning dose.

Period 2 (study days 4 through 16): Blood samples for raltegravir, ABT-450, ritonavir, and ABT-267 were collected prior to dosing and up to 16 hours after the morning dose on day 4. Trough samples were collected on study day 5, 6, 7, 9, 11, 13, 15, and 16.

Period 2 (study days 17 through 20): Blood samples for raltegravir, ABT-450, ritonavir, and ABT-267 were collected prior to dosing and up to 72 hours after the morning dose on day 17.

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ABT-267 and raltegravir were calculated using non-compartmental methods.

## Results

### *Bioanalytical methods*

Table 3 shows the bioanalytical assay parameters

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.595-428	0.595	1.72, 28.7, 259	3 % to 6.4 %	-1.2 % to 1.1 %
Ritonavir	4.93-3540	4.93	14,233,2920	3.3 %- 4.8 %	-1.3 % to 2.7 %
ABT-267	0.424-305	0.424	1.25, 20.8, 259	2.8 % to 3.6 %	-0.5 to 6.6 %
Raltegravir	10-10,000	10	30,75,300, 1200, and 7500	3.79 % to 7.76 %	1.86 % to 3.06 %

### *Subject Disposition and Demographics*

36 subjects (26 males and 10 females) were enrolled in the trial and 35 subjects (26 males and 9 females) completed the trial. Subject 1002 (43 year old white female) was discontinued from the study post AM dose in study day 2 of period 1 due to adverse events. The pharmacokinetic data from this subject was not included in any pharmacokinetic or statistical analysis.

Table 4 shows the shows the demographic summary of all subjects enrolled in the trial.

	Mean ± SD (N = 36)	Min – Max
Age (years)	40.1 ± 9.8	20 – 54
Weight (kg)	78.8 ± 12.0	59 – 101
Height (cm)	174.9 ± 11.0	155 – 194
Sex	26 Males (72.2%) and 10 Females (27.8%)	
Race	9 Black or African American (25.0%), 25 White (69.4%), and 2 Multi-race (5.6%)	

### Pharmacokinetics

#### ABT-450 (Arm 3)

Table 5 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 3.

Parameter (Unit)	Day 4	Day 17
	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
N	11 <sup>c</sup>	11 <sup>c</sup>
C <sub>max</sub> (ng/mL)	600 ± 356	865 ± 836
T <sub>max</sub> (h)	4.7 ± 0.90	4.9 ± 1.5
AUC <sub>24</sub> (ng•h/mL)	2920 ± 1380	4740 ± 4450
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	5.86 ± 0.80
C <sub>24</sub> (ng/mL)	17.6 ± 9.09	17.6 ± 19.5

a. Harmonic mean ± pseudo-standard deviation.

b. t<sub>1/2</sub> calculated following the Study Day 17 dose only.

c. Subject 1002 was discontinued from the study post AM dose on Study Day 2 of Period 1 due to adverse events.

The higher exposure of ABT-450 on day 17 as compared to day 4 may reflect the accumulation of ABT-450 upon multiple dosing.

#### Ritonavir (Arm 3)

Table 6 shows the mean ± SD pharmacokinetic parameters of ritonavir in Arm 3.

Parameter (Unit)	Day 4	Day 17
	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
N	11 <sup>c</sup>	11 <sup>c</sup>
C <sub>max</sub> (ng/mL)	1190 ± 368	1520 ± 323
T <sub>max</sub> (h)	4.6 ± 0.69	5.2 ± 2.4
AUC <sub>24</sub> (ng•h/mL)	7540 ± 2390	9480 ± 1950
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	4.88 ± 1.03
C <sub>24</sub> (ng/mL)	42.5 ± 30.9	46.7 ± 25.1

- a. Harmonic mean ± pseudo-standard deviation.  
b. t<sub>1/2</sub> calculated following the Study Day 17 dose only.  
c. Subject 1002 was discontinued from the study post AM dose on Study Day 2 of Period 1 due to adverse events.

The higher exposure of ritonavir on day 17 as compared to day 4 may reflect the accumulation of ritonavir upon multiple dosing.

### ABT-267 (Arm 3)

Table 7 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 3.

Parameter (Unit)	Day 4	Day 17
	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
N	11 <sup>c</sup>	11 <sup>c</sup>
C <sub>max</sub> (ng/mL)	110 ± 42.6	126 ± 43.8
T <sub>max</sub> (h)	5.0 ± 0	5.1 ± 0.30
AUC <sub>24</sub> (ng•h/mL)	956 ± 355	1330 ± 424
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	32.5 ± 9.11
C <sub>24</sub> (ng/mL)	14.5 ± 6.09	27.1 ± 9.69

- a. Harmonic mean ± pseudo-standard deviation.  
b. t<sub>1/2</sub> calculated following the Study Day 17 dose only.  
c. Subject 1002 was discontinued from the study post AM dose on Study Day 2 of Period 1 due to adverse events.

The higher exposure of ABT-267 on day 17 as compared to day 4 may reflect the accumulation of ABT-267 upon multiple dosing.

### Raltegravir (Arm 3)

Table 8 shows the mean ± SD pharmacokinetic parameters of raltegravir in Arm 3.

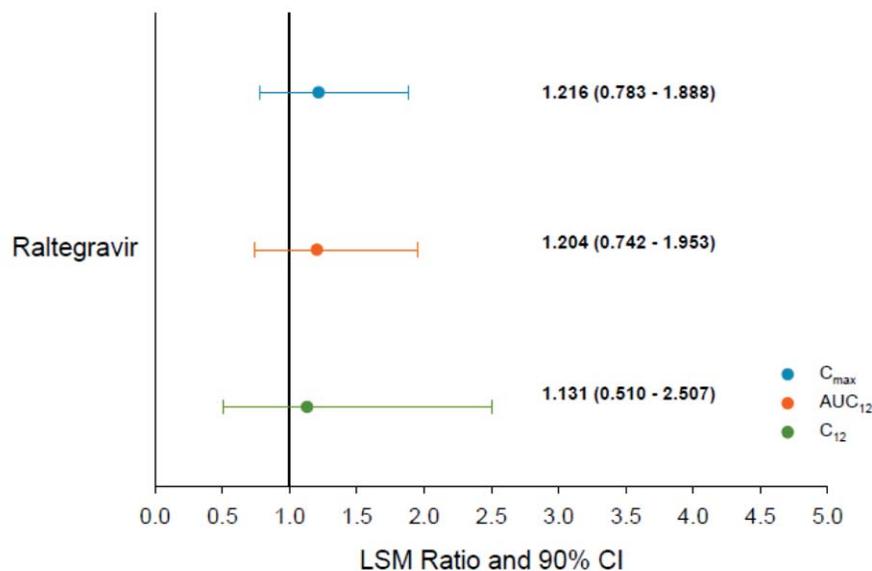
Parameter (Unit)	Day 3	Day 4	Day 17
	Raltegravir 400 mg BID	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
N	11 <sup>c</sup>	11 <sup>c</sup>	11 <sup>c</sup>
C <sub>max</sub> (ng/mL)	1100 ± 1220	2220 ± 1480	1400 ± 1140
T <sub>max</sub> (h)	4.8 ± 2.8	6.9 ± 4.2	5.9 ± 2.8
AUC <sub>12</sub> (ng•h/mL)	5200 ± 3870	10700 ± 6050	7580 ± 5230
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	--	14.8 ± 12.8 <sup>d</sup>
C <sub>12</sub> (ng/mL)	342 ± 518	1340 ± 1520	377 ± 371
C <sub>24</sub> (ng/mL)	207 ± 130	294 ± 233	150 ± 97.8

- a. Harmonic mean ± pseudo-standard deviation.  
b. t<sub>1/2</sub> calculated following the Study Day 17 dose only.  
c. Subject 1002 was discontinued from the study post AM dose on Study Day 2 of Period 1 due to adverse events.  
d. N = 7.

## Statistical Evaluation of the Pharmacokinetic Parameters

### Effect of DAAs on Raltegravir

Fig 1 shows the least squares mean ratios of C<sub>max</sub>, AUC<sub>12</sub>, and C<sub>12</sub>, and 90 % Confidence Intervals for Raltegravir (Study Day 17/Study Day 3)



Arm 3 DAAs: ABT-450/r + ABT-267

Co-administration of raltegravir with ABT-450/r + ABT-267 at steady state increased the mean RAL C<sub>max</sub>, AUC<sub>12</sub>, and C<sub>12</sub> by approximately 21 %, 20 %, and 13 % relative to the administration of raltegravir alone.

### Reviewer's Note Regarding Increase in RAL exposures

The increase in RAL exposure observed in this trial when RAL was co-administered with DAAs does not warrant a dose adjustment because the approved prescribing information of raltegravir indicates that the mean RAL  $C_{max}$  and  $AUC_{12}$  was increased by 315 % and 212 %, respectively when raltegravir was co-administered with omeprazole as compared with when raltegravir was administered alone. The approved prescribing information of raltegravir does not recommend any dose adjustments when raltegravir is co-administered with omeprazole.

### Effect of Raltegravir on DAAs

As the DAAs were always administered with raltegravir in the trial, the pharmacokinetic parameters of DAAs observed in the trial were compared with the pharmacokinetic parameters of DAAs observed in other trials where DAAs were administered alone.

Table 9 shows the cross study comparison of the pharmacokinetic parameters of the various DAAs.

DAA	Pharmacokinetic Parameter	Range of Geometric Mean Pharmacokinetic Parameter Across 4 Studies (Historic Data)	Geometric Mean Pharmacokinetic Parameter (Study M13-392)
ABT-450	$C_{max}$ (ng/mL)	359 – 1889	1301
	AUC (ng•h/mL)	2357 – 7395	6770
	$C_{trough}$ (ng/mL)	11.6 – 32.3	21.3
Ritonavir	$C_{max}$ (ng/mL)	1291 – 2166	1623
	AUC (ng•h/mL)	9045 – 11770	11086
	$C_{trough}$ (ng/mL)	34.7 – 62.1	42.7
ABT-267	$C_{max}$ (ng/mL)	82.0 – 141	151
	AUC (ng•h/mL)	1022 – 1581	1863
	$C_{trough}$ (ng/mL)	20.6 – 30.0	42.4
ABT-333	$C_{max}$ (ng/mL)	822 – 1083	1113
	AUC (ng•h/mL)	5556 – 7744	7798
	$C_{trough}$ (ng/mL)	203 – 289	308
ABT-333 M1	$C_{max}$ (ng/mL)	458 – 767	715
	AUC (ng•h/mL)	2679 – 4638	4576
	$C_{trough}$ (ng/mL)	85.0 – 148	157

A cross trial comparison of the pharmacokinetic parameters of individual DAAs observed in the trial compared with the pharmacokinetic parameters of DAAs observed in other trials suggest that raltegravir did not have a significant impact on the pharmacokinetics of the individual DAAs.

## **Safety**

No death, serious adverse events, or other significant adverse events were reported in the trial. All treatment emergent events were considered mild in severity.

## **Results**

Co-administration of ABT-450/r/ABT-267 with raltegravir:

- Increased the mean  $C_{\max}$  and  $AUC_{12}$  of RAL by 21 % and 20 %, respectively.
- Cross trial comparison of the systemic exposures of DAAs suggest that RAL did not have a significant impact on the pharmacokinetics of the individual DAAs.

## **Conclusion**

ABT-450/ritonavir/ABT-267 and raltegravir can be co-administered without any dose adjustments.

## **Drug-Drug Interaction Trial with Atazanavir**

### **M13-394**

#### **Title**

**A Phase 1, Open Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-administration of Atazanavir with ABT-450/ritonavir (ABT-450/r) and ABT-267 with or without ABT-333 in Healthy Adult Subjects**

#### **Trial Period**

November 13, 2012 to June 05, 2013

Final report date: March 14, 2014

*Reviewer's Note: As the proposed labeling recommendations in NDA 207931 are based on 2 DAAs (ABT-450/ritonavir/ABT-267), the results section in this review focuses only on the results observed with the 2-DAAs (Arm 2). For results with the 3-DAAs, please refer to the review of NDA 206619.*

#### **Trial Objectives**

The objectives of the trial were:

- to evaluate the pharmacokinetics, safety, and tolerability of the combination of ABT-450/ritonavir and ABT-267 with or without ABT-333 when co-administered with atazanavir at steady state in healthy subjects.
- to evaluate the pharmacokinetics, safety, and tolerability of atazanavir when co-administered with a combination of ABT-450/ritonavir and ABT-267 with or without ABT-333 at steady state in healthy subjects

#### **Trial Design**

Phase 1, single-center, randomized, multiple dose, non-fasting, open-label trial. Based on the results from Arm 1, Arm 3 was dosed prior to Arm 2. The trial was designed to enroll up to 72 subjects (24 subjects per arm assigned in a 1:1 ratio to Cohort 1 or Cohort 2 (12 subjects per cohort). Table 1 shows the trial design.

Arms 1 to 3	Cohort 1	Study Days 1 to 14	Study Days 15 to 28
		DAA	DAA + Atazanavir 300 mg
Cohort 2	Study Days 1 to 14	Study Days 15 to 28	
	Atazanavir 300 mg + ritonavir 100 mg	DAA + Atazanavir 300 mg	

All study drugs were administered under non-fasting conditions.

Arm 1 (3 DAAs): ABT-450/r + ABT-267 + ABT-333; Arm 2 (2 DAAs): ABT-450/r + ABT-267; Arm 3 (3 DAAs): ABT-450/r + ABT-267 + ABT-333.

DAA regimens: ABT-450/r 150/100 mg QD, ABT-267 25 mg QD, ABT-333 400 mg BID.

Atazanavir regimens: Atazanavir 300 mg QD administered in the morning (Arms 1 and 2) or evening (Arm 3).

Ritonavir regimens: Ritonavir 100 mg administered with atazanavir during Study Days 1 to 14 in Cohort 2 across Arms 1, 2 and 3 and with the evening dose of atazanavir during Study Days 15 to 28 in Arm 3.

DAA formulations: ABT-450/r 75/50 mg co-formulated tablet, ABT-267 25 mg tablet, ABT-333 400 mg tablet.

Atazanavir formulation: Atazanavir 300 mg capsule. Ritonavir formulation: Ritonavir 100 mg capsule.

Table 2 shows the various treatments administered in the trial.

	Cohort	Number of Subjects	Period 1 Dosing (Study Days 1 – 14)	Period 2 Dosing (Study Days 15 – 28)
Arm 1	1	12	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + atazanavir 300 mg QD in the morning + ABT-333 400 mg BID
	2	12	Atazanavir 300 mg QD co-administered with RTV 100 mg QD in the morning	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + atazanavir 300 mg QD in the morning + ABT-333 400 mg BID
Arm 2	1	12	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + atazanavir 300 mg QD in the morning
	2	12	Atazanavir 300 mg QD co-administered with RTV 100 mg QD in the morning	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + atazanavir 300 mg QD in the morning
Arm 3	1	12	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID + atazanavir 300 mg QD co-administered with RTV 100 mg QD in the evening
	2	12	Atazanavir 300 mg QD co-administered with RTV 100 mg QD in the evening	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID in the morning + atazanavir 300 mg QD co-administered with RTV 100 mg QD in the evening

## Rationale for Conducting the Trial

The trial was conducted to collect quantitative drug-drug interaction information for the safe and effective use of Atazanavir (combined with ritonavir administered separately or the ritonavir administered as part of the 2-DAA regimen) with the 2-DAA regimen in HIV/HCV co-infected population.

## Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), and ABT-267 (25 mg) were evaluated in the Phase 3 trials. The dose of atazanavir (300 mg in combination with 100 mg ritonavir) is the approved dose.

## Identity of Investigational Products

Table 3 shows the identity of the investigational products used in the trial.

Investigational Products	ABT-267	ABT-450/ Ritonavir	ABT-333	Ritonavir	Atazanavir
Mode of Administration	Oral	Oral	Oral	Oral	Oral
Dosage Form	Tablet	Tablet	Tablet	Capsule	Capsule
Strength (mg)	25	75/50	400	100	300
Bulk Product Lot Number	11-002033	12-002722	12-001228	11-005635, 11-005635/ 110262E	12-007210
Manufacturer	AbbVie Inc, Ludwigshafen, Germany	AbbVie Inc, Lake County, IL	AbbVie Inc, Lake County, IL	AbbVie Inc, Lake County, IL	(b) (4)
Finishing Lot Numbers <sup>a</sup>	12-007093, 12-007358	13-000503, 12-007092, 12-007356	12-007096, 12-007357	12-007091, 12-007359	12-007095
Expiration/Retest Date	(b) (4)				

## Sample Collection

PK samples for ABT-450, ritonavir, ABT-267, and atazanavir were collected at steady state on study days 14, 15, and 28.

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, and ABT-267 were computed using non-compartmental methods.

## Results

### *Bioanalytical methods*

Table 4 provides the summary of the bioanalytical assay parameters.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.595-406	0.595	1.57, 26.2, 328	3.8 % to 9.6 %	-10.7 % to -9.1 %
Ritonavir	4.91-3340	4.91	12.4, 207, 2580	4.9 % to 5.6 %	-5.8 % to -3.2 %
ABT-267	0.46-314	0.46	1.18, 20.1, 251	2.7 % to 6.1 %	-8.4 % to -6.6 %
Atazanavir	10-10,000	10	30, 75, 300, 1200, 7500	4.19 % to 5.40 %	0.984 % to 2.98 %

### *Subject Disposition and Demographics*

Table 5 below shows the overall demographic summary of all subjects enrolled in the trial.

Characteristic	Treatment Group						
	Arm 1/Cohort 1	Arm 1/Cohort 2	Arm 2/Cohort 1	Arm 2/Cohort 2	Arm 3/Cohort 1	Arm 3/Cohort 2	Overall/Total
Sex, n (%)	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12	N = 72
Female	5 (41.7)	4 (33.3)	2 (16.7)	2 (16.7)	4 (33.3)	3 (25.0)	20 (27.8)
Male	7 (58.3)	8 (66.7)	10 (83.3)	10 (83.3)	8 (66.7)	9 (75.0)	52 (72.2)
Race, n (%)	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12	N = 72
White	5 (41.7)	5 (41.7)	11 (91.7)	10 (83.3)	9 (75.0)	8 (66.7)	48 (66.7)
Black or African American	6 (50.0)	7 (58.3)	1 (8.3)	2 (16.7)	3 (25.0)	3 (25.0)	22 (30.6)
Asian	1 (8.3)	0	0	0	0	1 (8.3)	2 (2.8)
Age, years	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12	N = 72
Mean ± SD	37.2 ± 9.69	33.6 ± 6.80	33.2 ± 8.30	35.4 ± 6.89	33.9 ± 8.06	33.8 ± 8.53	34.5 ± 7.94
Median	34.0	31.5	32.5	34.5	32.0	32.5	33.0
Min - Max	24 - 54	22 - 46	20 - 48	25 - 46	20 - 48	22 - 51	20 - 54
Weight, kg	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12	N = 72
Mean ± SD	77.2 ± 6.99	76.1 ± 13.85	76.1 ± 7.60	78.3 ± 12.55	79.0 ± 12.56	75.6 ± 13.65	77.0 ± 11.20
Median	77.9	76.3	78.3	77.1	76.0	73.2	76.9
Min - Max	67.9 - 90.3	52.4 - 95.0	59.5 - 88.1	57.6 - 101.3	63.1 - 104.2	57.1 - 96.4	52.4 - 104.2
Height, cm	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12	N = 72
Mean ± SD	167.3 ± 3.84	173.3 ± 11.50	171.7 ± 5.72	175.7 ± 9.73	171.0 ± 10.80	171.3 ± 9.13	171.7 ± 8.95
Median	166.9	170.5	171.2	175.8	169.0	172.0	170.2
Min - Max	160.0 - 173.0	158.0 - 191.6	161.7 - 181.0	155.0 - 191.5	158.3 - 198.3	160.0 - 183.4	155.0 - 198.3

SD = Standard deviation, Max = Maximum, Min = Minimum

## Pharmacokinetics

Note: Only the results from Arm 2 are presented in this review.

### Arm 2

#### ABT-450

Table 6 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 2.

ABT-450 Pharmacokinetic Parameters (Unit)	Cohort 1		
	Regimen D (N = 12)	Regimen E (N = 12)	Regimen E (N = 10)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	2460 ± 1560	5170 ± 2380	4660 ± 2170
T <sub>max</sub> (h)	4.8 ± 1.0	4.0 ± 1.1	3.9 ± 1.2
C <sub>24</sub> (ng/mL)	45.0 ± 34.9	161 ± 169	114 ± 53.3
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	4.9 ± 1.3
AUC <sub>24</sub> (ng•h/mL)	14600 ± 9930	35000 ± 20800	27800 ± 9340
ABT-450 Pharmacokinetic Parameters (Unit)	Cohort 2		
	Regimen F (N = 11)	Regimen E (N = 11)	Regimen E (N = 11)
	Study Day 14 Atazanavir 300 mg QD + Ritonavir 100 mg QD	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	--	1550 ± 984	4450 ± 2080
T <sub>max</sub> (h)	--	3.6 ± 0.5	3.8 ± 0.9
C <sub>24</sub> (ng/mL)	--	39.0 ± 22.5	115 ± 72.7
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	4.8 ± 1.4
AUC <sub>24</sub> (ng•h/mL)	--	7960 ± 3400	28000 ± 11200

a. Harmonic mean ± pseudo-standard deviation.

## Ritonavir

Table 7 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 2.

Ritonavir Pharmacokinetic Parameters (Unit)	Cohort 1		
	Regimen D (N = 12)	Regimen E (N = 12)	Regimen E (N = 10)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD
$C_{max}$ (ng/mL)	1780 $\pm$ 307	2200 $\pm$ 505	1520 $\pm$ 409
$T_{max}$ (h)	4.3 $\pm$ 0.8	4.2 $\pm$ 0.6	4.2 $\pm$ 0.6
$C_{24}$ (ng/mL)	32.8 $\pm$ 14.0	52.3 $\pm$ 27.4	44.5 $\pm$ 22.6
$t_{1/2}^a$ (h)	--	--	4.9 $\pm$ 0.7
$AUC_{24}$ (ng•h/mL)	11000 $\pm$ 2750	13700 $\pm$ 2920	9940 $\pm$ 1830
Ritonavir Pharmacokinetic Parameters (Unit)	Cohort 2		
	Regimen F (N = 11)	Regimen E (N = 11)	Regimen E (N = 11)
	Study Day 14 Atazanavir 300 mg QD + Ritonavir 100 mg QD	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD
$C_{max}$ (ng/mL)	2310 $\pm$ 489	2340 $\pm$ 951	1990 $\pm$ 883
$T_{max}$ (h)	3.9 $\pm$ 0.3	3.9 $\pm$ 0.3	4.4 $\pm$ 0.8
$C_{24}$ (ng/mL)	73.5 $\pm$ 46.0	74.0 $\pm$ 49.4	72.8 $\pm$ 46.4
$t_{1/2}^a$ (h)	--	--	4.8 $\pm$ 0.9
$AUC_{24}$ (ng•h/mL)	14500 $\pm$ 4140	14700 $\pm$ 5520	13900 $\pm$ 5710

a. Harmonic mean  $\pm$  pseudo-standard deviation.

## ABT-267

Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 in Arm 2.

ABT-267 Pharmacokinetic Parameters (Unit)	Cohort 1		
	Regimen D (N = 12)	Regimen E (N = 12)	Regimen E (N = 10)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD
$C_{max}$ (ng/mL)	111 $\pm$ 26.0	107 $\pm$ 25.1	89.3 $\pm$ 26.8
$T_{max}$ (h)	5.3 $\pm$ 1.1	5.1 $\pm$ 1.2	5.3 $\pm$ 1.2
$C_{24}$ (ng/mL)	27.3 $\pm$ 9.71	26.8 $\pm$ 8.63	24.8 $\pm$ 8.24
$t_{1/2}^a$ (h)	--	--	29.9 $\pm$ 7.3
$AUC_{24}$ (ng•h/mL)	1330 $\pm$ 356	1290 $\pm$ 304	1160 $\pm$ 330
ABT-267 Pharmacokinetic Parameters (Unit)	Cohort 2		
	Regimen F (N = 11)	Regimen E (N = 11)	Regimen E (N = 11)
	Study Day 14 Atazanavir 300 mg QD + Ritonavir 100 mg QD	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD
$C_{max}$ (ng/mL)	--	79.1 $\pm$ 21.0	91.7 $\pm$ 18.1
$T_{max}$ (h)	--	4.5 $\pm$ 1.0	5.3 $\pm$ 1.0
$C_{24}$ (ng/mL)	--	12.0 $\pm$ 2.38	25.4 $\pm$ 7.39
$t_{1/2}^a$ (h)	--	--	28.0 $\pm$ 6.3
$AUC_{24}$ (ng•h/mL)	--	780 $\pm$ 191	1180 $\pm$ 257

a. Harmonic mean  $\pm$  pseudo-standard deviation.

# Atazanavir

Table 9 shows the mean ± SD pharmacokinetic parameters of atazanavir in Arm 2.

Atazanavir Pharmacokinetic Parameters (Unit)	Cohort 1		
	Regimen D (N = 12)	Regimen E (N = 12)	Regimen E (N = 10)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	--	4750 ± 815	5620 ± 1120
T <sub>max</sub> (h)	--	3.2 ± 1.2	3.7 ± 1.2
C <sub>24</sub> (ng/mL)	--	650 ± 298	993 ± 407
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	7.2 ± 1.8
AUC <sub>24</sub> (ng•h/mL)	--	39800 ± 8500	57000 ± 9340

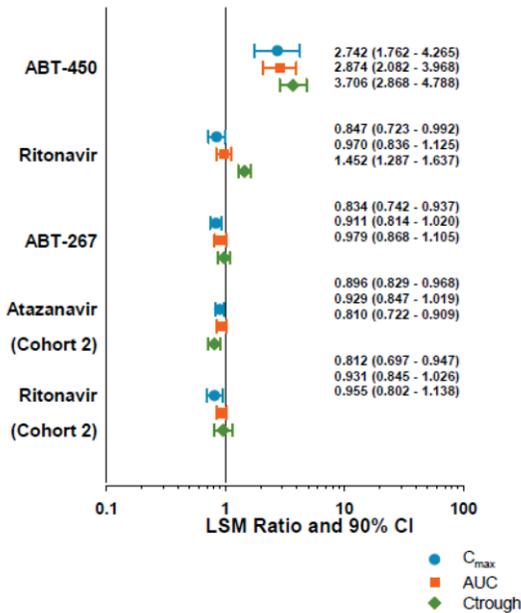
  

Atazanavir Pharmacokinetic Parameters (Unit)	Cohort 2		
	Regimen F (N = 11)	Regimen E (N = 11)	Regimen E (N = 11)
	Study Day 14 Atazanavir 300 mg QD + Ritonavir 100 mg QD	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	6930 ± 1630	6990 ± 1590	6220 ± 1460
T <sub>max</sub> (h)	2.7 ± 0.8	2.5 ± 0.7	3.1 ± 1.3
C <sub>24</sub> (ng/mL)	1350 ± 659	1340 ± 701	1100 ± 503
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	6.5 ± 1.8
AUC <sub>24</sub> (ng•h/mL)	68700 ± 19700	69500 ± 19900	63700 ± 17200

b. Harmonic mean ± pseudo-standard deviation.

Statistical Comparison of the Pharmacokinetic Parameters:

Fig 1 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, and atazanavir in Arm 2.



AUC<sub>24</sub> and C<sub>24</sub>: ABT-450, ritonavir, ABT-267 and atazanavir

## Safety

No deaths, serious adverse events, or other significant adverse events were reported during the study. Five subjects discontinued from the study due to the occurrence of at least one adverse event.

## Results

- Co-administration of ABT-450/r, ABT-267 with atazanavir (Arm 2)
  - Increased the mean  $C_{\max}$ , AUC, and  $C_{24}$  of ABT-450 by 174 %, 187 %, and 270 %, respectively.
  - Decreased the mean  $C_{\max}$  and AUC of ritonavir by 15 % and 3 %, respectively and increased the mean  $C_{\text{trough}}$  of ritonavir by 45 %.
  - Decreased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of ABT-267 by 17 %, 9 %, and 2 %, respectively.
  - Decreased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of atazanavir by 10 %, 7 %, and 19 %, respectively.
  - Decreased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of ritonavir by 19 %, 7 %, and 4%, respectively.

## Applicant's Proposed Clinical Recommendation

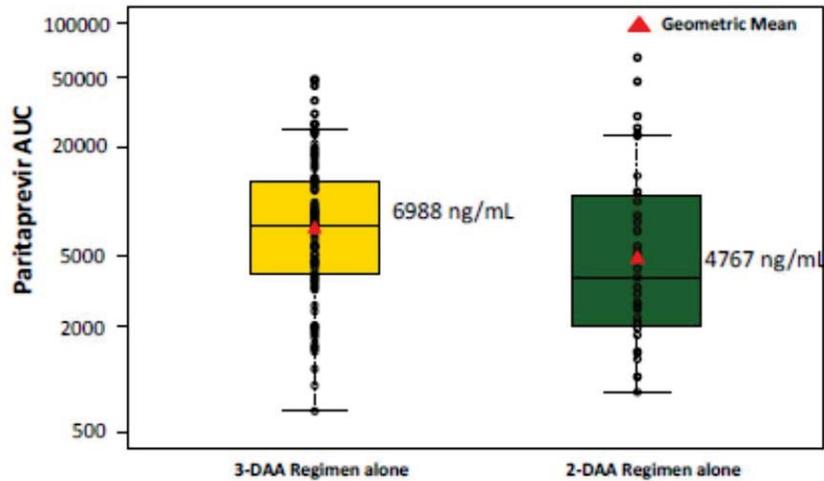
In the prescribing information of VIEKIRA PAK™, the following clinical recommendation is included for atazanavir (administered in the morning without ritonavir) “When co-administered with VIEKIRA PAK™, atazanavir should only be given in the morning”. The applicant has proposed (b) (4)

[REDACTED]

[REDACTED] (b) (4)

The mean exposures of paritaprevir are lower after administration of the 2-DAA regimen as compared with VIEKIRA PAK™ as shown in figure 2 below.

**Figure 2: Paritaprevir exposures (Cmax and AUC) following administration of the 3-DAA regimen and the 2-DAA regimen**



Source: eCTD sequence number 701, letter date 05/27/2015

Hence, if the lower mean exposures of paritaprevir after the 2-DAA regimen are taken into account, the mean paritaprevir exposures when 2-DAA regimen is co-administered with atazanavir are expected to be approximately 58 % higher as compared with mean paritaprevir exposures after administration of VIEKIRA PAK™ alone as shown in 10 below.

**Table 10:** Changes in paritaprevir exposures with various regimens relative to paritaprevir exposures after administration of VIEKIRA PAK™ alone

Paritaprevir AUC with 3D Regimen Alone	Change in Paritaprevir AUC Relative to the Values Achieved with the 3D Regimen Alone (1×)		
	Paritaprevir AUC with 3D Regimen + Atazanavir	Paritaprevir AUC with 2D Regimen Alone	Paritaprevir AUC with 2D Regimen + Atazanavir
1×	1 × 1.94-fold (or 94% ↑) = 1.94×	1 × 0.55-fold (or 45% ↓) = 0.55×	1 × 0.55-fold × 2.87-fold (or 187% ↑) = 1.58×

Source: Page 23 of White Paper on DDIs, IND 103526 SDN 679, Date of Submission March 13, 2015

The expected 58 % higher mean paritaprevir exposures (after administration of 2-DAA +atazanavir) are lower than the 94 % higher mean paritaprevir exposures observed after administration of atazanavir with VIEKIRA PAK™. It should be noted that atazanavir can be co-administered with VIEKIRA PAK™ without any need for dose adjustments. Hence, per the applicant, atazanavir can be co-administered with the 2-DAA regimen without any need for dose adjustments.

Further, per the applicant, dasabuvir is an inhibitor of BCRP and P-gp in vitro, therefore, the higher paritaprevir exposures for the 3-DAA regimen (presence of dasabuvir) compared to the 2-DAA regimen (absence of dasabuvir) could likely be due to the inhibition of these efflux transporters.

The applicant's proposed recommendation is not acceptable based on the following discussion:



Overall, the applicant's proposed recommendation is not acceptable and the following recommendation is proposed:

"Co-administration of ABT-450/r/ABT-267 with atazanavir (administered in the morning without additional ritonavir) is not recommended due to significant increase in ABT-450 exposures".

## **Drug-Drug Interaction Trial with Darunavir/ritonavir**

### **M13-506**

#### **Title**

**A Phase 1, Open Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-administration of Darunavir with ABT-450/ritonavir (ABT-450/r) and ABT-267 and/or ABT-333 in Healthy Adult Subjects**

#### **Trial Period**

Feb 9, 2012 to December 21, 2012

Final report date: September 25, 2013

*Reviewer's Note: As the proposed labeling recommendations in NDA 207931 are based on 2 DAAs (ABT-450/ritonavir/ABT-267), the results section in this review focuses only on the results observed with the 2-DAAs (Arm 2). For results with the 3-DAAs, please refer to the review of NDA 206619.*

#### **Trial Objectives**

The objectives of the trial were:

- to evaluate the pharmacokinetics, safety, and tolerability of the combination of ABT-450/ritonavir with ABT-267 and/or ABT-333 when co-administered with darunavir at steady state in healthy subjects.
- to evaluate the pharmacokinetics, safety, and tolerability of darunavir when co-administered with a combination of ABT-450/ritonavir and ABT-267 and/or ABT-333 at steady state in healthy subjects

#### **Trial Design**

Phase 1, single-center, randomized, multiple dose, non-fasting, open-label trial.

Table 1 shows the dosing sequences

Arm	Cohort	Subject Numbers	N	Regimens	
				Period 1	Period 2
1	1	601, 603, 604, 608, 611, 612, 614, 615, 616	9	A	B
	2	602 <sup>a</sup> , 605, 606, 607, 609, 610, 613, 617, 618	9	C	B
2	1	654, 655, 656, 657, 660, 662, 663, 664, 665	9	D	E
	2	651 <sup>a</sup> , 652, 653, 658, 659, 661, 666, 667 <sup>a</sup> , 668	9	F	E
3	1	702, 703, 704, 708, 711, 712, 713, 715, 717	9	G	H
	2	701, 705, 706 <sup>a</sup> , 707, 709, 710, 714, 716, 718	9	I	H
4	1	752 <sup>b</sup> , 753, 756, 757, 759, 760, 763, 764, 767 <sup>b</sup>	9	J	K
	2	751 <sup>a</sup> , 754, 755, 758, 761, 762, 765, 766, 768 <sup>a</sup>	9	L	K

a. Subject discontinued from the study due to adverse event(s).

b. Subject withdrew consent from the study due to family emergency.

Table 2 shows the various treatments administered in the trial.

<b>Regimen A</b>	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD administered under non-fasting conditions
<b>Regimen B</b>	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + darunavir 800 mg QD administered under non-fasting conditions
<b>Regimen C</b>	Darunavir 800 mg QD + ritonavir (RTV) 100 mg QD administered under non-fasting conditions
<b>Regimen D</b>	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions
<b>Regimen E</b>	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 800 mg QD administered under non-fasting conditions
<b>Regimen F</b>	Darunavir 800 mg QD + RTV 100 mg QD administered under non-fasting conditions
<b>Regimen G*</b>	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions
<b>Regimen H*</b>	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 800 mg QD administered under non-fasting conditions
<b>Regimen I*</b>	Darunavir 800 mg QD + RTV 100 mg QD administered under non-fasting conditions
<b>Regimen J*</b>	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions
<b>Regimen K*</b>	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 600 mg BID + RTV 100 mg every evening (QPM) administered under non-fasting conditions
<b>Regimen L*</b>	Darunavir 600 mg BID + RTV 100 mg BID administered under non-fasting conditions

\* Based on a review of the pharmacokinetic, safety and tolerability results of the previous Arm(s), a decision was made to conduct the next sequential arm (Arms 2, 3 and 4). Doses in Arm 3, and Arm 4 (Regimens G, H, I, J, K and L) could have been modified based on pharmacokinetic, safety and tolerability results of the previous arm(s). Doses in Arm 3 and Arm 4 could have been as low as 0 mg and were not to exceed ABT-450/r 250/100 mg, ABT-333 800 mg BID, RTV 200 mg daily, ABT-267 100 mg QD and darunavir 1200 mg BID. Based on the interactions observed with darunavir in Arm 1 and Arm 2, the darunavir doses in Arms 3 and 4 could have differed from those in previous arm(s) and could have been different between periods. In Arm 4, darunavir was administered 600 mg BID, and an additional RTV 100 mg dose was administered with the 2<sup>nd</sup> daily darunavir dose.

## Rationale for Conducting the Trial

The trial was conducted to collect quantitative drug-drug interaction information for the safe and effective use of darunavir with the 3-DAA regimen in HIV/HCV co-infected population.

## Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), and ABT-267 (25 mg) were the doses that were evaluated in the Phase 3 trials. The dose of darunavir /ritonavir 800/100 mg once daily is the approved dose.

## Identity of Investigational Products

Table 3 shows the identity of the investigational products used in the trial.

	ABT-450	ABT-333	ABT-267
Dosage Form	Tablet	Tablet	Tablet
Strength (mg)	50 mg	400 mg	25 mg
Bulk Product Lot Number	11-000781	11-000511	11-002033
Manufacturing Site	AbbVie North Chicago, IL	AbbVie North Chicago, IL	AbbVie Ludwigshafen, Germany
Finishing Lot Number	12-000251, 12-003949, 12-006199	12-000254	12-000252
Retest Date	(b) (4)		
	Norvir® (ritonavir)	Prezista® (darunavir)	Prezista® (darunavir)
Dosage Form	Soft Gelatin Capsule	Tablet	Tablet
Strength (mg)	100 mg	400 mg	600 mg
Vendor Lot Number	110262E	1MG370	1NG434
Manufacturing Site	AbbVie North Chicago, IL	(b) (4)	
Finishing Lot Number	12-000255, 12-003950, 12-006198	12-000404	12-000690
Expiration Date	07 October 2013	31 October 2013	31 October 2013

## Sample Collection

PK samples for ABT-450, ritonavir, ABT-267, and darunavir were collected on the following days:

- Prior to morning dosing and at 1, 2, 3, 4, 6, 9, 12, and 16 hours after morning dosing on Study Day 14.
- Prior to morning dosing and at 1, 2, 3, 4, 6, 9, 12, 16 and 24 (Study Day 16) hours after morning dosing on Study Day 15.
- Prior to morning dosing and at 1, 2, 3, 4, 6, 9, 12, 16, 24 (Study Day 29), 48 (Study Day 30), and 72 (Study Day 31) hours after morning dosing on Study Day 28 or upon subject discontinuation due to an adverse event

In addition, blood samples for measurement of trough concentrations were collected immediately prior to the morning dose on the following Study Days: 8, 11, 13, 20, 25 and 27.

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 and darunavir were computed using non-compartmental methods.

## Results

### *Bioanalytical methods*

Table 4 provides the summary of the bioanalytical assay parameters.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.595-428	0.595	1.53, 26.1, 325	3.5 % to 7.8 %	-0.4 % to 2 %
Ritonavir	4.93-3540	4.93	13.5, 229, 2850	3.5 % to 4.8 %	0.4 % to 4.4 %
ABT-267	0.424-305	0.424	1.18, 20.1, 251	3.4 % to 7 %	2 % to 4.2 %
Darunavir	25-12,500	25	75, 6250, 9750	2.8 % to 4.8 %	0.2 % to 1.3 %

### *Subject Disposition and Demographics*

Seventy two subjects were enrolled in the trial. 6 subjects prematurely discontinued the trial and 2 subjects withdrew consent from the trial.

- Subject 602, a 31-year-old Black male, discontinued from the study due to erythema, skin swelling, skin sensitization and urticaria on Study Day 26 while receiving Regimen B (ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + darunavir 800 mg QD) in Period 2 of Arm 1/Cohort 2. The last dosing of study drugs occurred on the evening of Study Day 26.
- Subject 651, a 26-year-old Black male, discontinued from the study due to vomiting on Study Day 15 while receiving Regimen E (ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 800 mg QD) in Period 2 of Arm 2/Cohort 2. The last dosing of study drugs occurred on the morning of Study Day 16.
- Subject 667, a 40-year-old White female, discontinued from the study due to vomiting on Study Day 15 while receiving Regimen E (ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 800 mg QD) in Period 2 of Arm 2/Cohort 2. The last dosing of study drugs occurred on the morning of Study Day 15.
- Subject 706, a 47-year-old White male, discontinued from the study due to maculopapular rash on Study Day 11 while receiving Regimen I (darunavir 800 mg QD + RTV 100 mg QD) in Period 1 of Arm 3/Cohort 2. The last dosing of study drugs occurred on Study Day 8. The subject developed pruritus and skin irritation to the chest, upper back, arms, neck and face.
- Subject 751, a 54-year-old White male, discontinued from the study due to maculopapular rash on Study Day 9 while receiving Regimen L (darunavir 600 mg BID + RTV 100 mg BID) in Period 1 of Arm 4/Cohort 2. The last dosing of study drugs occurred on Study Day 9.
- Subject 768, a 27-year-old White male, discontinued from the study due to maculopapular rash on Study Day 10 while receiving Regimen L (darunavir

600 mg BID + RTV 100 mg BID) in Period 1 of Arm 4/Cohort 2. The last dosing of study drugs occurred on Study Day 10.

- Subject 752, a 43-year-old White male, withdrew consent from the study due to a family emergency while receiving Regimen K (ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 600 mg BID + RTV 100 mg QPM) in Period 2 of Arm 4/Cohort 1. The last dosing of study drugs occurred on Study Day 22.
- Subject 767, a 47-year-old Black male, withdrew consent from the study due to a family emergency while receiving Regimen J (ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD) in Period 1 of Arm 4/Cohort 1. The last dosing of study drugs occurred on Study Day 12.

Table 5 below shows the overall demographic summary of all subjects enrolled in the trial.

	Mean ± SD (N = 72)	Min – Max
Age (years)	34.8 ± 9.5	20 – 54
Weight (kg)	79.3 ± 11.8	52 – 100
Height (cm)	175 ± 8.6	153 – 195
Sex	66 Males (92%), 6 Females (8%)	
Race	40 White (56%), 31 Black (43%), 1 Native Hawaiian or Other Pacific Islander (1%)	

### *Pharmacokinetics*

*Note: Only the results from Arm 2 (Regimens E, F, and G) are presented in this review.*

#### Arm 2

ABT-450

Table 6 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 2

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 2/Cohort 1		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 28
		N	9	9
$C_{max}$	(ng/mL)	1200 ± 1720	977 ± 1170	1870 ± 2200
$T_{max}$	(h)	4.3 ± 1.0	4.2 ± 1.1	3.7 ± 0.5
$AUC_{24}$	(ng•h/mL)	4750 ± 6040	5580 ± 6510	8680 ± 10000
$t_{1/2}^a$	(h)	--	--	6.0 ± 1.0
$C_{24}$	(ng/mL)	12.9 ± 9.8	22.5 ± 21.1	26.6 ± 25.7

Pharmacokinetic Parameters	(Units)	Arm 2/Cohort 2		
		Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
		N	--	7
$C_{max}$	(ng/mL)	--	310 ± 184	968 ± 473
$T_{max}$	(h)	--	4.6 ± 2.0	3.7 ± 0.5
$AUC_{24}$	(ng•h/mL)	--	1620 ± 659	4530 ± 1570
$t_{1/2}^a$	(h)	--	--	6.2 ± 1.1
$C_{24}$	(ng/mL)	--	9.1 ± 5.0	16.1 ± 3.6

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 800 mg QD administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen F: Darunavir 800 mg QD + RTV 100 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

## Ritonavir

Table 7 shows the mean ± SD pharmacokinetic parameters of ritonavir in Arm 2

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 2/Cohort 1		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 28
N		9	9	9
C <sub>max</sub>	(ng/mL)	1980 ± 838	1660 ± 667	1630 ± 725
T <sub>max</sub>	(h)	4.1 ± 0.8	4.1 ± 0.8	3.9 ± 0.3
AUC <sub>24</sub>	(ng•h/mL)	10800 ± 4700	9930 ± 3880	8530 ± 3540
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.7 ± 0.7
C <sub>24</sub>	(ng/mL)	43.7 ± 28.6	50.1 ± 29.4	40.7 ± 26.2

Pharmacokinetic Parameters	(Units)	Arm 2/Cohort 2		
		Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
N		9	7	7
C <sub>max</sub>	(ng/mL)	806 ± 350	1370 ± 646	1400 ± 481
T <sub>max</sub>	(h)	5.2 ± 2.2	4.6 ± 2.0	4.3 ± 0.8
AUC <sub>24</sub>	(ng•h/mL)	5530 ± 1540	7870 ± 2520	7760 ± 1970
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.6 ± 0.5
C <sub>24</sub>	(ng/mL)	52.2 ± 26.9	38.3 ± 17.0	29.2 ± 11.2

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 800 mg QD administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen F: Darunavir 800 mg QD + RTV 100 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

## ABT-267

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 2

Pharmacokinetic Parameters	(Units)	ABT-267 Arm 2/Cohort 1		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 28
N		9	9	9
C <sub>max</sub>	(ng/mL)	83.9 ± 14.5	88.3 ± 15.5	85.4 ± 19.2
T <sub>max</sub>	(h)	4.6 ± 1.1	5.0 ± 1.2	5.1 ± 1.1
AUC <sub>24</sub>	(ng•h/mL)	1010 ± 187	1030 ± 205	1010 ± 207
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	22.1 ± 6.5
C <sub>24</sub>	(ng/mL)	18.8 ± 3.7	20.8 ± 4.9	19.9 ± 4.2

		Arm 2/Cohort 2		
		Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
N		--	7	7
C <sub>max</sub>	(ng/mL)	--	70.2 ± 31.4	95.6 ± 35.9
T <sub>max</sub>	(h)	--	6.3 ± 2.7	5.3 ± 1.3
AUC <sub>24</sub>	(ng•h/mL)	--	688 ± 232	1150 ± 479
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	26.6 ± 8.8
C <sub>24</sub>	(ng/mL)	--	10.7 ± 3.9	22.3 ± 10.1

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 800 mg QD administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen F: Darunavir 800 mg QD + RTV 100 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

## Darunavir

Table 9 shows the mean ± SD pharmacokinetic parameters of darunavir in Arm 2

Pharmacokinetic Parameters	(Units)	Darunavir Arm 2/Cohort 1		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 28
N		--	9	9
C <sub>max</sub>	(ng/mL)	--	7160 ± 1930	7080 ± 1720
T <sub>max</sub>	(h)	--	3.1 ± 0.9	3.1 ± 0.8
AUC <sub>24</sub>	(ng•h/mL)	--	74100 ± 18300	76700 ± 18900
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	7.8 ± 1.5
C <sub>24</sub>	(ng/mL)	--	1870 ± 439	1870 ± 722

Pharmacokinetic Parameters	(Units)	Arm 2/Cohort 2		
		Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
N		9	7	7
C <sub>max</sub>	(ng/mL)	7150 ± 864	7820 ± 1050	7180 ± 990
T <sub>max</sub>	(h)	3.2 ± 1.3	4.1 ± 2.3	3.0 ± 0.6
AUC <sub>24</sub>	(ng•h/mL)	79200 ± 19500	85100 ± 21500	71400 ± 11000
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	8.7 ± 2.0
C <sub>24</sub>	(ng/mL)	2300 ± 685	1990 ± 497	1760 ± 490

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

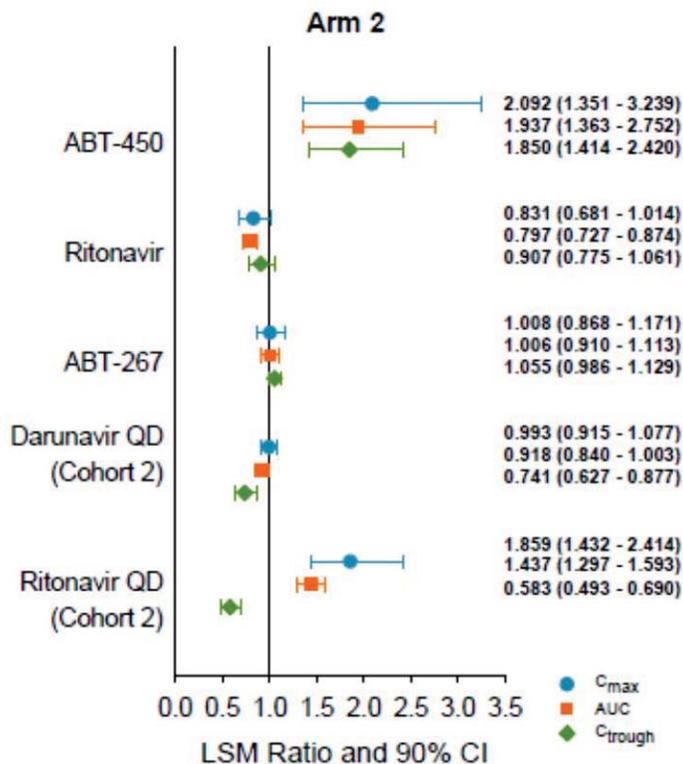
Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + darunavir 800 mg QD administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen F: Darunavir 800 mg QD + RTV 100 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

Statistical Comparison of the Pharmacokinetic Parameters:

Fig 1 shows the least squares mean (LSM) ratios of C<sub>max</sub>, AUC, and C<sub>trough</sub> and 90 % Confidence Intervals (CIs) for the DAAs and darunavir



Arm 2 (2 DAAs): ABT-450/r + ABT-267 + darunavir QD  
AUC<sub>24</sub> and C<sub>24</sub>: ABT-450, ABT-267, darunavir and ritonavir

## Results

- Co-administration of ABT-450/r, ABT-267 and darunavir once daily (administered in the morning with the 2-DAA regimen) [Arm 2]
  - Increased the mean C<sub>max</sub>, AUC, and C<sub>trough</sub> of ABT-450 by 109 %, 93 %, and 85 %, respectively.
  - Decreased the mean C<sub>max</sub>, AUC, and C<sub>trough</sub> of ritonavir by 17 %, 20 %, and 9 %, respectively
  - Decreased the mean AUC and C<sub>trough</sub> of darunavir by 9 % and 25 %, respectively (no significant change in the mean C<sub>max</sub>)
    - Increased ritonavir (using ritonavir given as part of DRV/rtv 800/100 mg as reference) mean C<sub>max</sub> and AUC by 85 % and 43 %, respectively and decreased mean C<sub>trough</sub> by 42 %.

## Conclusion

- 2-DAA regimen with Darunavir/ritonavir (800 mg/100 mg once daily; darunavir given in the morning with the DAA regimen) can be co-administered.
- There is no pharmacokinetic data available to support co-administration of the 2-DAA regimen with other regimens of darunavir (800/100 once daily administered in the evening or 600/100 mg twice daily).

## **Drug-Drug Interaction Trial with Emtricitabine and Tenofovir Disoproxil Fumarate**

**M13-783**

### **Title**

**A Phase 1, Open Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-Administration of Emtricitabine (Emtriva<sup>®</sup>) and Tenofovir Disoproxil Fumarate (Viread<sup>®</sup>) with ABT-450 plus Ritonavir (ABT-450/r) and ABT-267 With and Without ABT-333 in Healthy Adult Subjects.**

### **Trial Period**

July 13, 2012 to November 17, 2012

Final report date: June 7, 2013

*Reviewer's Note: As the proposed labeling recommendations in NDA 207931 are based on 2 DAAs (ABT-450/ritonavir/ABT-267), the results section in this review focuses only on the results observed with the 2-DAAs. For results with the 3-DAAs, please refer to the review of NDA 206619.*

### **Trial Objectives**

The objective of the trial were to:

- Evaluate the pharmacokinetics, safety and tolerability of the combination of ABT-450/r/ABT-267 with and without ABT-333 when co-administered with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) at steady state in healthy subjects.
- Evaluate the pharmacokinetics, safety and tolerability of emtricitabine and tenofovir disoproxil fumarate when co-administered with a combination of ABT-450/r/ABT-267 with and without ABT-333 at steady state in healthy subjects.

### **Trial Design**

Phase 1, single-center, randomized, multiple dose, sequential, non-fasting, open-label study. Adult male and female subjects (N = 36) were selected to participate in the study. 18 subjects in each of the arms 1 and 2 were randomly assigned in equal numbers (9 subjects per cohort) to one of two treatment sequences as shown in table 1 below:

	Cohort	Subject Numbers	N	Regimens	
				Period 1	Period 2
Arm 1	1	101, 105, 106, 108, 109, 112, 114, 115, 118	9	A	B
	2	102, 103, 104, 107, 110, 111, 113, 116, 117	9	C	B
Arm 2	1	202, 203, 204, 209, 210, 212, 213, 214, 217	9	D	E
	2	201, <sup>a</sup> 205, 206, 207, 208, 211, 215, 216, 218	9	F	E
Arm 3 <sup>b</sup> (Optional)	1	No subjects enrolled.	9	G	H
	2	No subjects enrolled.	9	I	H

- a. Subject 201, 24 year-old White male, withdrew consent from the study after receiving a single dose of emtricitabine 200 mg and tenofovir 300 mg on Study Day 1 of Period 1 in Cohort 2 of Arm 2.
- b. Optional Arm 3 was not conducted; Regimens G, H and I were not administered.

The study drugs were administered as shown in table 2 below.

<b>Regimen A</b> (Cohort 1, Study Days 1 – 14)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions
<b>Regimen B</b> (Cohort 1, Study Days 15 – 21) (Cohort 2, Study Days 8 – 21)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions
<b>Regimen C</b> (Cohort 2, Study Days 1 – 7)	Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions
<b>Regimen D<sup>a</sup></b> (Cohort 1, Study Days 1 – 14)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions
<b>Regimen E<sup>a</sup></b> (Cohort 1, Study Days 15 – 21) (Cohort 2, Study Days 8 – 21)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions
<b>Regimen F<sup>a</sup></b> (Cohort 2, Study Days 1 – 7)	Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions
<b>Regimen G<sup>a</sup></b> (Cohort 1, Study Days 1 – 14)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions
<b>Regimen H<sup>a</sup></b> (Cohort 1, Study Days 15 – 21) (Cohort 2, Study Days 8 – 21)	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions
<b>Regimen I<sup>a</sup></b> (Cohort 2, Study Days 1 – 7)	Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions

\* Based on review of the pharmacokinetic, safety and tolerability results of the previous Arm(s), a decision was made whether to conduct the next sequential arm (Arms 2 or 3). Doses in Arm 2 and Arm 3 (Regimens D, E, F, G, H and I) could have been modified based on pharmacokinetic, safety and tolerability results from the previous arm(s). Doses in Arm 2 and Arm 3 could have been as low as 0 mg and were not to exceed ABT-450/r 250/100 mg QD, ABT-267 100 mg QD, ABT-333 800 mg BID, emtricitabine 200 mg BID, and tenofovir disoproxil fumarate 600 mg QD.

- a. Optional Arm 3 was not conducted; Regimens G, H and I were not administered.

All doses of study drug were taken orally with approximately 240 mL of water approximately 30 minutes after starting a standardized breakfast for all morning doses. The meal content was identical on the intensive pharmacokinetic sampling days for subjects within each arm/cohort. Subjects received a standardized diet, providing approximately 40 % of the daily calories from fat and up to 45 % of daily calories from carbohydrates, for each meal during confinement. The total daily calories were approximately 1900 calories/day. Starting with lunch on Study Day –1 until after the 96-hour blood collection on Study Day 25, the subjects consumed only the scheduled meals provided.

## Rationale for Conducting the Trial

The trial was conducted to determine if the combination of ABT-267/ABT-450/r and FTC/TDF can be used in HCV and HIV-1 co-infected patients.

## Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), and ABT-267 (25 mg) were the doses evaluated in the Phase 3 trials. The dose of FTC/TDF is the approved dose used in the HIV-1 infected population.

## Identity of Investigational Products

Table 3 shows the identity of the investigational products used in the trial.

	ABT-450	Ritonavir	ABT-267
Dosage Form	Tablet	Soft Gelatin Capsule	Tablet
Strength (mg)	50 mg	100 mg	25 mg
Bulk Product Lot Number	11-000781	11-005635	11-000867
Manufacturing Site	Abbott Abbott Park, IL	Abbott Abbott Park, IL	Abbott Abbott Park, IL
Finishing Lot Number	12-004026	12-004029	12-004027
Expiration Date	30 Jun 2013	30 Sep 2013	31 Jan 2013
	ABT-333	Entriva* (emtricitabine)	Viread* (tenofovir disoproxil fumarate)
Dosage Form	Tablet	Capsule	Tablet
Strength (mg)	400 mg	200 mg	300 mg
Bulk Product Lot Number	11-002720	12-004534	12-004537
Manufacturing Site	Abbott Abbott Park, IL		(b) (4)
Finishing Lot Number	12-004028	12-004282	12-004165
Expiration Date	31 Jul 2014	31 Dec 2014	30 Nov 2016

## Sample Collection

### Arms 1 and 2 (Cohort 1)

In Cohort 1 of each arm, blood samples for the assay of ABT-450, ritonavir, ABT-267, FTC, and tenofovir were collected on the following days:

#### DAA only (3-mL collection)

- Study day 14: Prior to dosing and up to 16 hours after dosing on study day 14.
- Trough samples: Prior to morning dose on study days 9, 10, and 12.

#### DAA, FTC, Tenofovir (6 mL collection)

- Study day 15: Prior to morning dosing and up to 16 hours after dosing on study day 15.

- Study day 21: Prior to morning dosing and up to 96 hours after dosing on study day 21 or upon subject discontinuation due to adverse event.
- Trough samples: Prior to morning dose on study days 16, 18, 19, and 20.

#### Arms 1 and 2 (Cohort 2)

In Cohort 2 of each arm, blood samples for the assay of ABT-450, ritonavir, ABT-267, FTC, and tenofovir were collected on the following days:

#### FTC and Tenofovir (3-mL collection)

- Study day 7: Prior to dosing and at 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours after dosing on study day 7.
- Trough samples: Prior to morning dose on study days 4 and 6.

#### DAAs, FTC, Tenofovir (6 mL collection)

- Study day 8: Prior to dosing and up to 16 hours after dosing on study day 8.
- Study day 21: Prior to morning dosing and up to 96 hours after dosing on study day 21 or upon subject discontinuation due to adverse event.
- Trough samples: Prior to morning dose on study days 9, 10, 12, 14, 16, 18, 19, and 20.

### Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, FTC, and Tenofovir were computed using non-compartmental methods.

### Results

#### *Bioanalytical methods*

Table 4 provides the summary of the bioanalytical assay parameters.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.595-406	0.595	1.53, 26.1, 325	4.1 % to 8.2 %	0.3 % to 2 %
Ritonavir	4.91-3340	4.91	13.5, 229, 2850	2.9 % to 5.6 %	0.7 % to 1.5 %.
ABT-267	0.46-314	0.46	1.18, 20.1, and 251	4.1 % to 7.5 %	1.6 % to 6.8 %
FTC	20-4000	20	40,100, 300, 800, and 3000	2.9 % to 3.59 %	-0.6 % to 2.8 %
Tenofovir	5-1000	5	10, 25, 75, 200 and 750	4.05 % to 4.82 %	-3.47 % to 0.6 %

### Subject Disposition and Demographics

Adult male and female subjects (N = 36) were enrolled in the study and 35 subjects (31 males and 4 females) completed the study. 1 subject withdrew consent after receiving a single dose of FTC and TDF on day 1 of period 1 in cohort 2 of arm 2.

Table 5 below shows the demographic summary of all subjects enrolled in the trial.

	Mean ± SD (N = 36)	Min – Max
Age (years)	33.7 ± 10.3	19 – 56
Weight (kg)	78.5 ± 8.4	56 – 92
Height (cm)	175 ± 6.9	159 – 188
Sex	32 Males (89%), 4 Females (11%)	
Race	15 White (42%), 19 Black (53%), 1 Asian (3%), 1 Multi-race (3%)	

### Pharmacokinetics

ABT-450/ritonavir, ABT-267, ABT-333, FTC, Tenofovir (Arm 2)

ABT-450

Table 6 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 2.

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 2/Cohort 2 (N = 9)		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 21
C <sub>max</sub>	(ng/mL)	804 ± 1060	535 ± 694	704 ± 612
T <sub>max</sub>	(h)	4.7 ± 0.7	4.8 ± 0.7	4.6 ± 0.7
AUC <sub>24</sub>	(ng•h/mL)	3810 ± 4320	2840 ± 2540	3490 ± 2580
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.7 ± 1.2
C <sub>24</sub>	(ng/mL)	12.6 ± 7.5	13.9 ± 7.9	13.8 ± 6.8

Pharmacokinetic Parameters	(Units)	Arm 2/Cohort 2 (N = 8)		
		Regimen F: Day 7	Regimen E: Day 8	Regimen E: Day 21
C <sub>max</sub>	(ng/mL)	--	590 ± 600	1060 ± 928
T <sub>max</sub>	(h)	--	5.4 ± 1.5	4.6 ± 1.2
AUC <sub>24</sub>	(ng•h/mL)	--	2770 ± 1960	5490 ± 4140
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.6 ± 0.6
C <sub>24</sub>	(ng/mL)	--	19.7 ± 9.5	21.6 ± 11.2

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen F: Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 1 to 7 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation; evaluations of t<sub>1/2</sub> were based on statistical tests for β.

Ritonavir

Table 7 shows the mean ± SD pharmacokinetic parameters of ritonavir in Arm 2.

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 2/Cohort 1 (N = 9)		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 21
		$C_{max}$	(ng/mL)	1410 ± 512
$T_{max}$	(h)	4.7 ± 0.5	4.9 ± 3.1	5.1 ± 4.4
$AUC_{24}$	(ng•h/mL)	9110 ± 2940	8460 ± 3390	8740 ± 3070
$t_{1/2}^a$	(h)	--	--	5.1 ± 1.0 <sup>b</sup>
$C_{24}$	(ng/mL)	49.4 ± 18.9	62.6 ± 27.4	46.0 ± 22.7

Pharmacokinetic Parameters	(Units)	Arm 2/Cohort 2 (N = 8)		
		Regimen F: Day 7	Regimen E: Day 8	Regimen E: Day 21
		$C_{max}$	(ng/mL)	--
$T_{max}$	(h)	--	4.6 ± 0.7	5.1 ± 4.7
$AUC_{24}$	(ng•h/mL)	--	6810 ± 4010	11000 ± 7280
$t_{1/2}^a$	(h)	--	--	4.8 ± 1.6 <sup>c</sup>
$C_{24}$	(ng/mL)	--	50.2 ± 46.8	67.2 ± 60.3

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen F: Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 1 to 7 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation; evaluations of  $t_{1/2}$  were based on statistical tests for  $\beta$ .

b. N = 8.

c. N = 7.

## ABT-267 (Arm 2)

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 2.

Pharmacokinetic Parameters	(Units)	ABT-267 Arm 2/Cohort 1 (N = 9)		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 21
		$C_{max}$	(ng/mL)	128 ± 54.9
$T_{max}$	(h)	4.4 ± 0.9	4.7 ± 0.9	4.9 ± 0.9
$AUC_{24}$	(ng•h/mL)	1480 ± 810	1530 ± 853	1480 ± 822
$t_{1/2}^a$	(h)	--	--	31.9 ± 11.4
$C_{24}$	(ng/mL)	31.4 ± 23.5	31.4 ± 22.9	31.8 ± 23.0

Pharmacokinetic Parameters	(Units)	Arm 2/Cohort 2 (N = 8)		
		Regimen F: Day 7	Regimen E: Day 8	Regimen E: Day 21
		$C_{max}$	(ng/mL)	--
$T_{max}$	(h)	--	5.3 ± 0.5	5.1 ± 1.0
$AUC_{24}$	(ng•h/mL)	--	1120 ± 332	1330 ± 469
$t_{1/2}^a$	(h)	--	--	30.9 ± 15.6
$C_{24}$	(ng/mL)	--	17.4 ± 6.5	30.5 ± 14.3

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen F: Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 1 to 7 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation; evaluations of  $t_{1/2}$  were based on statistical tests for  $\beta$ .

## Emtricitabine (Arm 2)

Table 9 shows the mean  $\pm$  SD pharmacokinetic parameters of emtricitabine in Arm 2

Pharmacokinetic Parameters	(Units)	Emtricitabine Arm 2/Cohort 1 (N = 9)		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 21
C <sub>max</sub>	(ng/mL)	--	1320 $\pm$ 412	1500 $\pm$ 371
T <sub>max</sub>	(h)	--	3.2 $\pm$ 1.0	2.9 $\pm$ 0.6
AUC <sub>24</sub>	(ng•h/mL)	--	8840 $\pm$ 1560	10400 $\pm$ 1680
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	16.2 $\pm$ 5.5
C <sub>24</sub>	(ng/mL)	--	49.3 $\pm$ 6.8	81.1 $\pm$ 17.4

Pharmacokinetic Parameters	(Units)	Arm 2/Cohort 2 (N = 8)		
		Regimen F: Day 7	Regimen E: Day 8	Regimen E: Day 21
C <sub>max</sub>	(ng/mL)	1670 $\pm$ 133	1680 $\pm$ 184	1590 $\pm$ 249
T <sub>max</sub>	(h)	2.3 $\pm$ 1.0	2.1 $\pm$ 0.6	2.6 $\pm$ 0.9
AUC <sub>24</sub>	(ng•h/mL)	10800 $\pm$ 1450	11300 $\pm$ 1260	11500 $\pm$ 1310
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	25.4 $\pm$ 10.5
C <sub>24</sub>	(ng/mL)	78.2 $\pm$ 19.1	88.3 $\pm$ 25.7	97.7 $\pm$ 22.0

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen F: Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 1 to 7 (Cohort 2).

a. Harmonic mean  $\pm$  pseudo-standard deviation; evaluations of t<sub>1/2</sub> were based on statistical tests for  $\beta$ .

## Tenofovir (Arm 2)

Table 10 shows the mean  $\pm$  SD pharmacokinetic parameters of tenofovir in Arm 2

Pharmacokinetic Parameters	(Units)	Tenofovir Arm 2/Cohort 1 (N = 9)		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 21
C <sub>max</sub>	(ng/mL)	--	236 $\pm$ 75.1	275 $\pm$ 75.5
T <sub>max</sub>	(h)	--	1.3 $\pm$ 0.7	1.8 $\pm$ 0.8
AUC <sub>24</sub>	(ng•h/mL)	--	1910 $\pm$ 561	3380 $\pm$ 919
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	18.7 $\pm$ 2.6
C <sub>24</sub>	(ng/mL)	--	39.1 $\pm$ 9.9	73.6 $\pm$ 23.5

Pharmacokinetic Parameters	(Units)	Arm 2/Cohort 2 (N = 8)		
		Regimen F: Day 7	Regimen E: Day 8	Regimen E: Day 21
C <sub>max</sub>	(ng/mL)	324 $\pm$ 66.6	285 $\pm$ 44.3	258 $\pm$ 40.3
T <sub>max</sub>	(h)	1.4 $\pm$ 0.7	1.5 $\pm$ 0.5	1.9 $\pm$ 1.1
AUC <sub>24</sub>	(ng•h/mL)	3130 $\pm$ 591	3040 $\pm$ 601	3180 $\pm$ 701
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	21.8 $\pm$ 3.3
C <sub>24</sub>	(ng/mL)	58.6 $\pm$ 10.0	65.9 $\pm$ 12.6	66.6 $\pm$ 14.0

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

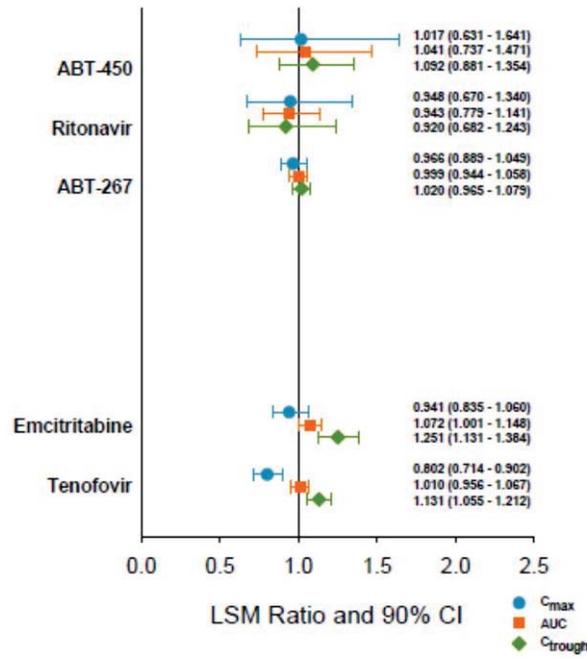
Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen F: Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 1 to 7 (Cohort 2).

a. Harmonic mean  $\pm$  pseudo-standard deviation; evaluations of t<sub>1/2</sub> were based on statistical tests for  $\beta$ .

## Statistical Evaluation of the Pharmacokinetic Parameters

Fig 1 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, FTC, and tenofovir in Arm 2.



AUC<sub>24</sub> and C<sub>24</sub>: ABT-450, ritonavir, ABT-267, emtricitabine and tenofovir

## Safety

No deaths or other serious adverse events were reported in this study.

## Results

Co-administration of ABT-450/r/ABT-267 with FTC and TDF:

- Increased the mean C<sub>max</sub>, AUC<sub>24</sub>, and C<sub>24</sub> of ABT-450 by 2 %, 4 %, and 9 % respectively.
- Decreased the mean C<sub>max</sub>, AUC<sub>24</sub>, and C<sub>24</sub> of ritonavir by 5 %, 6 %, and 8 %, respectively.
- Decreased the mean C<sub>max</sub>, AUC<sub>24</sub>, and C<sub>24</sub> of ABT-267 by 3 %, 0.1 %, and 2 %, respectively.
- Decreased the mean C<sub>max</sub> of FTC by 6 % and increased the mean AUC<sub>24</sub> and C<sub>24</sub> of FTC by 7 %, and 25 %, respectively.
- Decreased the mean C<sub>max</sub> of tenofovir by 20 % and increased the mean AUC<sub>24</sub> and C<sub>24</sub> of tenofovir by 1 % and 13 %, respectively.

## Conclusion

ABT-450/ritonavir/ABT-267 can be co-administered with emtricitabine/tenofovir without any dose adjustments.

## **Trial to Determine Absolute Bioavailability of ABT-450/ritonavir/ABT-267 coformulated tablet**

### **M12-229**

#### **Title**

**A Phase 1, open label, single center study designed to determine the absolute bioavailability of ABT-450 (150 mg) and ABT-267 (25 mg) when administered as an oral co-formulated product with ritonavir (100 mg), ABT-450/r/ABT-267 to healthy adult subjects**

#### **Trial Period**

January 14, 2014 to February 13, 2014

Final report date: July 2, 2014

#### **Trial Objectives**

The primary objectives of the study were:

- To determine the absolute bioavailability of ABT-450 (150 mg) when administered as an oral co-formulated product with ABT-267 (25 mg) and ritonavir (100 mg)
- To determine the absolute bioavailability of ABT-267 (25 mg) when administered as an oral co-formulated product with ABT-450 (150 mg) and ritonavir (100 mg)

The secondary objectives of the study were:

- To describe the intravenous (IV) pharmacokinetics (PK) of ABT-450 when administered as a “piggy-back” IV dose on top of an oral dose of ABT-450 (150 mg), ABT-267 (25 mg) and ritonavir (100 mg) as a co-formulated drug product.
- To describe the IV PK of ABT-267 when administered as a “piggy-back” IV dose on top of an oral dose of ABT-450 (150 mg), ABT-267 (25 mg) and ritonavir (100 mg) as a co-formulated drug product
- To provide additional information of the safety and tolerability of ABT-450, ABT-267 and ritonavir

#### **Trial Design**

Single center, open label, non-randomized, single dose study in healthy adult subjects. Subjects were assigned to 1 of 2 independent groups, Group 1 or Group 2, so that 8 subjects were enrolled in each group to ensure data in 6 evaluable subjects.

Each subject received one of the following regimens depending on whether they were assigned to group 1 or group 2:

Group 1 (Regimen A): ABT-450/ritonavir/ABT-267 co-formulated tablets in a dose containing 150 mg ABT-450, 25 mg ABT-267, and 100 mg ritonavir followed by a 15 minutes intravenous infusion of 100 µg [<sup>14</sup>C] ABT-450 (containing not more than 1 µCi [37 kBq <sup>14</sup>C] ending at the median T<sub>max</sub> for the oral dose of ABT-450 (5 h post-dose).

Group 2 (Regimen B): ABT-450/ritonavir/ABT-267 co-formulated tablets in a dose containing 150 mg ABT-450, 25 mg ABT-267, and 100 mg ritonavir followed by a 15 minutes intravenous infusion of 25 µg <sup>14</sup>C ABT-267 (containing not more than 1 µCi [37 kBq <sup>14</sup>C] ending at the median T<sub>max</sub> for the oral dose of ABT-267 (5 h post-dose).

### **Rationale for Dose Selection**

The doses of ABT-450, ritonavir, and ABT-267 used in the trial are identical to the doses of ABT-450, ritonavir, and ABT-267 used in the Phase 3 trials.

### **Drug Administration**

Subjects were admitted to the clinical unit at approximately 8 AM on the day before dosing (day -1) and commenced dosing with the oral dose administration in the morning of day 1 following a moderate fat breakfast. Subjects remained on site until 72 hours post-oral dose.

### **Identity of Investigational Products**

The sponsor provided ABT-450/r/ABT-267 75/50/12.5 mg as pink, oblong and biconvex tablets for oral dosing in Regimens A and B (lot ID: 12-008149). The tablets were packaged in (b) (4) and were stored at 15°C to 25°C (59°F to 77°F).

AbbVie Inc. provided <sup>14</sup>C-labelled ABT-450 and ABT-267 drug substances (batch numbers: 34133ZW00 and 35160ZW00, respectively) as white powders in (b) (4) for pharmaceutical development and clinical trial manufacture. (b) (4) was responsible for manufacturing the IV solution formulations of [<sup>14</sup>C]-ABT-450 (20 µg/mL; batch number: 116253/C/02) and [<sup>14</sup>C]-ABT-267 (5 µg/mL; batch number: 116253/C/01) as clear and colourless solutions. The solutions were stored at 2 to 8°C.

### **Sample Collection**

Blood samples for determining of plasma concentrations of ABT-450, ritonavir, and ABT-267 were taken at the following times:

After oral administration: Pre-dose, 1, 2, 3, 4, 4:30, 5, 5:30, 6, 7, 8, 9, 10, 12, 15, 18, 24, 30, 36, 48, 60, and 72 hours.

After intravenous administration: Pre-dose, 5 minutes and 10 minutes before the start of the infusion, immediately upon completing the infusion, and then at 5, 15, 30 minutes, and 1, 2, 3, 4, 5, 7, 10, 13, 19, 25, 31, 43, 55, and 67 hours after completion of the infusion (from 30 minutes post-completion of the infusion onwards, the intravenous blood sampling was similar to the oral blood sampling).

## **Pharmacokinetic Analysis**

The pharmacokinetic parameters of ABT-450 (oral dose for regimen A and regimen B), ABT-267 (oral doses for regimen A and regimen B), ritonavir (oral dose for regimen A and regimen B), [<sup>14</sup>C]-ABT-450 ([<sup>14</sup>C]-ABT-450 intravenous infusion; for regimen A only), and [<sup>14</sup>C]-ABT-267 ([<sup>14</sup>C]-ABT-267 intravenous infusion; for regimen B only) were determined using non-compartmental methods.

Formal statistical analysis was performed on the PK parameters AUC(0-inf) and AUC(0-last) to assess absolute bioavailability of both ABT-450 (Group I: Regimen A) and ABT-267 (Group II: Regimen B). The analysis was performed using mixed effect modelling, with separate analyses for Regimen A and Regimen B. The model included terms for dose (ie oral or IV) fitted as a fixed effect and subject fitted as a random effect. Dose normalised AUC (using the actual dose for the IV dose and the nominal dose for the oral dose) was used in the analyses and a natural logarithmic transformation was applied.

Point estimates and 90% confidence intervals (CIs) for the comparisons between the oral and IV doses were constructed. The point and interval estimates were back-transformed (ie exponentiated) to give model adjusted geometric mean ratios (GMRs) and 90% CIs. The ratios (%) were defined as  $100 \times (\text{dose normalised AUC for oral dose})/(\text{dose normalised AUC for IV dose})$  for each regimen. P-values for the GMRs are also presented.

## **Results**

### ***Subject Disposition and Demographics***

A total of 16 subjects were enrolled in the study, with 8 subjects assigned to each regimen (ie Regimen A and Regimen B). All 16 subjects were dosed and completed the study.

Table 1 shows the demographics of all subjects enrolled in the trial.

		Regimen A (N = 8)	Regimen B (N = 8)
Age (years)	Mean (SD)	49.6 (14.0)	45.0 (16.0)
Height (cm)	Mean (SD)	167.1 (5.8)	169.3 (7.6)
Weight (kg)	Mean (SD)	75.23 (11.02)	74.43 (15.20)
BMI (kg/m <sup>2</sup> )	Mean (SD)	26.86 (2.90)	25.80 (3.88)
Race	White (%)	8 (100)	7 (87.5)
	Other <sup>a</sup> (%)	0	1 (12.5)
Sex	Male (%)	6 (75.0)	4 (50.0)
	Female (%)	2 (25.0)	4 (50.0)

<sup>a</sup> Other: mixed race

Regimen A: ABT-450/r/ABT-267 co-formulated tablets in a dose containing 150 mg ABT-450, 25 mg ABT-267 and 100 mg ritonavir followed by an IV infusion of 100 µg [<sup>14</sup>C]-ABT-450

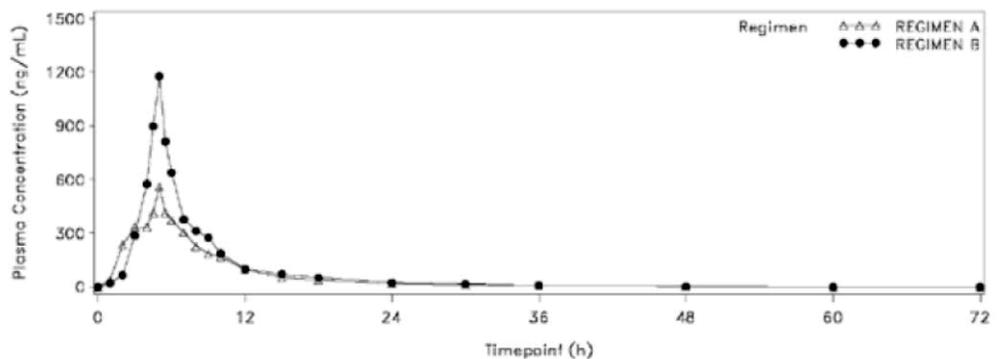
Regimen B: ABT-450/r/ABT-267 co-formulated tablets in a dose containing 150 mg ABT-450, 25 mg ABT-267 and 100 mg ritonavir followed by an IV infusion of 25 µg [<sup>14</sup>C]-ABT-267

Source: Table 14.1.3

## Pharmacokinetics

### ABT-450

Fig 1 shows the mean ABT-450 plasma concentration vs time profiles following oral dosing (regimens A and B)



Note: Data in the above graph are presented in table 14.2.1.1

All subjects received a single oral dose of co-formulated tablet containing 150 mg ABT-450, 25 mg ABT-267 and 100 mg ritonavir

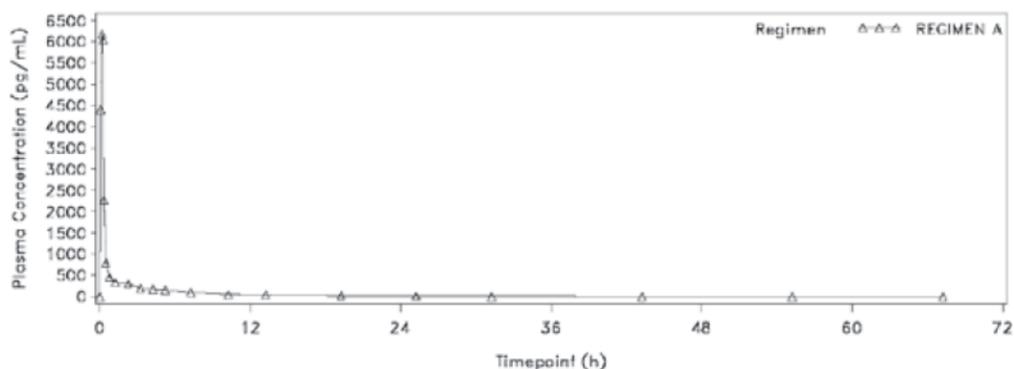
Regimen A: received a 100 µg IV dose of [<sup>14</sup>C]-ABT-450 after tablet

Regimen B: received a 25 µg IV dose of [<sup>14</sup>C]-ABT-267 after tablet

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Fig 2 shows the mean [<sup>14</sup>C]-ABT-450 plasma concentration vs time profiles following intravenous dosing (regimen A)



Note: Data in the above graph are presented in table 14.2.1.4  
 All subjects received a single oral dose of co-formulated tablet containing 150 mg ABT-450, 25 mg ABT-267 and 100 mg ritonavir  
 Regimen A: received a 100 ug IV dose of [<sup>14</sup>C]-ABT-450 after tablet  
 Regimen B: received a 25 ug IV dose of [<sup>14</sup>C]-ABT-267 after tablet  
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Table 2 shows the geometric mean (geometric CV %) values of the key plasma pharmacokinetic parameters following oral administration of ABT-450/ritonavir/ABT-267 and intravenous administration of [<sup>14</sup>C]-ABT-450 in regimen A: Pharmacokinetic population.

Analyte Route Dose	ABT-450 Oral 150 mg (N = 8)	ABT-267 Oral 25 mg (N = 8)	Ritonavir Oral 100 mg (N = 8)	[ <sup>14</sup> C]-ABT-450 IV 100 µg (N = 8)
Tmax (h) <sup>a</sup>	5.00 (3.00–5.00)	5.25 (3.98–6.00)	4.50 (2.00–5.00)	0.17 (0.17–0.25)
Cmax (ng/mL) <sup>b</sup>	535 (68.2)	114 (20.0)	1070 (40.5)	6300 (18.3)
AUC(0-last) (ng.h/mL) <sup>c</sup>	3030 (63.2)	1370 (30.5)	6370 (54.0)	3810 (35.3)
AUC(0-inf) (ng.h/mL) <sup>c</sup>	3040 (63.1)	1560 (32.1)	6440 (53.0)	3890 (34.4)
AUC%extrap (%)	0.40 (62.4)	11.32 (38.0)	0.89 (74.7)	1.85 (56.6)
T1/2 (h) <sup>d</sup>	6.18 (18.1)	29.42 (34.3)	5.68 (11.4)	8.71 (19.7)
MRT (h)	9.31 (21.6)	30.07 (21.5)	NC	3.96 (28.8)
CL (L/h)	25.9 (34.5)	NC	NC	25.9 (34.5)
Vd <sub>beta</sub> (L)	236 (38.2)	NC	NC	331 (48.4)
Vd <sub>ss</sub> (L)	NC	NC	NC	103 (45.3)
Fabs (%) <sup>e</sup>	52.6 (36.9)	NC	NC	NC

NC: not calculated

<sup>a</sup> Median (range)

<sup>b</sup> pg/mL for [<sup>14</sup>C]-ABT-450

<sup>c</sup> pg.h/mL for [<sup>14</sup>C]-ABT-450

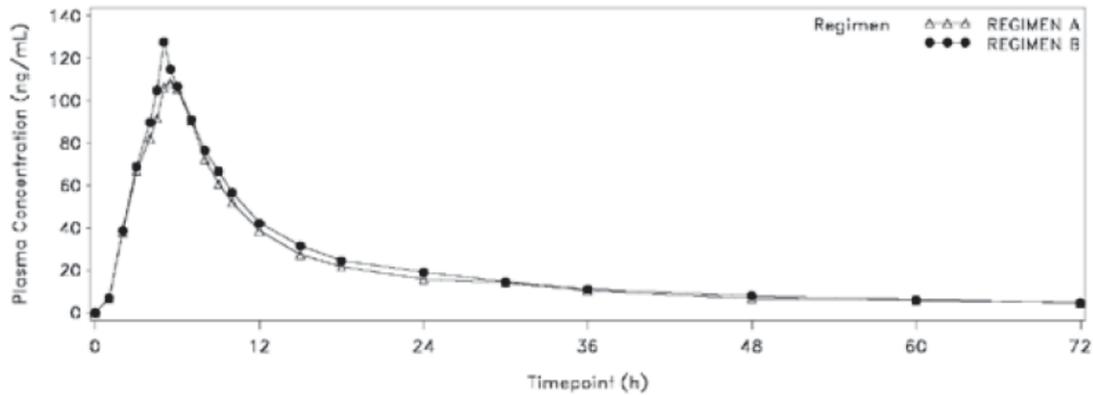
<sup>d</sup> Harmonic mean (pseudo CV%)

<sup>e</sup> Calculated using AUC(0-inf)

Regimen A: ABT-450/r/ABT-267 co-formulated tablets in a dose containing 150 mg ABT-450, 25 mg ABT-267 and 100 mg ritonavir followed by an IV infusion of 100 µg [<sup>14</sup>C]-ABT-450

### ABT-267

Fig 3 shows the mean ABT-267 plasma concentration vs time profiles following oral dosing (regimens A and B)



Note: Data in the above graph are presented in table 14.2.1.2

All subjects received a single oral dose of co-formulated tablet containing 150 mg ABT-450,

25 mg ABT-267 and 100 mg ritonavir

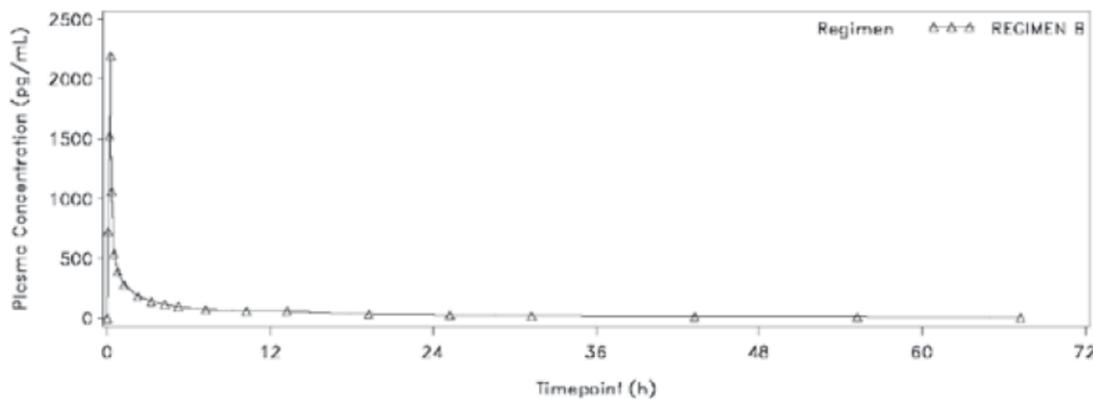
Regimen A: received a 100 ug IV dose of [<sup>14</sup>C]-ABT-450 after tablet

Regimen B: received a 25 ug IV dose of [<sup>14</sup>C]-ABT-267 after tablet

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Fig 4 shows the mean [<sup>14</sup>C]-ABT-267 plasma concentration vs time profiles following intravenous dosing (regimen B)



Note: Data in the above graph are presented in table 14.2.1.5

All subjects received a single oral dose of co-formulated tablet containing 150 mg ABT-450,

25 mg ABT-267 and 100 mg ritonavir

Regimen A: received a 100 ug IV dose of [<sup>14</sup>C]-ABT-450 after tablet

Regimen B: received a 25 ug IV dose of [<sup>14</sup>C]-ABT-267 after tablet

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Table 3 shows the geometric mean (geometric CV %) values of the key plasma pharmacokinetic parameters following oral administration of ABT-450/ritonavir/ABT-267 and intravenous administration of [<sup>14</sup>C]-ABT-267 in regimen B: Pharmacokinetic population

Analyte Route Dose	ABT-450 Oral 150 mg (N = 8)	ABT-267 Oral 25 mg (N = 8)	Ritonavir Oral 100 mg (N = 8)	[ <sup>14</sup> C]-ABT-267 IV 25 µg (N = 8)
Tmax (h) <sup>a</sup>	5.00 (4.00–7.00)	5.26 (4.50–7.00)	4.50 (4.00–6.00)	0.25 (0.17–0.27)
Cmax (ng/mL) <sup>b</sup>	716 (143.9)	120 (35.2)	1340 (41.7)	2110 (35.9)
AUC(0-last) (ng.h/mL) <sup>c</sup>	3740 (98.0)	1440 (43.3)	8420 (56.4)	2970 (34.3)
AUC(0-inf) (ng.h/mL) <sup>c</sup>	3760 (97.4)	1600 (46.3)	8490 (55.9)	3330 (37.3)
AUC%extrap (%)	0.33 (153.8)	9.48 (26.7)	0.71 (62.5)	10.03 (37.2)
T1/2 (h) <sup>d</sup>	7.12 (25.4)	25.89 (19.2)	5.62 (29.4)	28.49 (17.5)
MRT (h)	10.05 (27.2)	27.26 (13.7)	NC	23.07 (23.8)
CL (L/h)	NC	7.51 (37.9)	NC	7.51 (37.9)
Vd <sub>beta</sub> (L)	NC	303 (33.2)	NC	313 (29.7)
Vd <sub>ss</sub> (L)	NC	NC	NC	173 (27.1)
Fabs (%) <sup>e</sup>	NC	48.1 (17.1)	NC	NC

NC: not calculated

<sup>a</sup> Median (range)

<sup>b</sup> pg/mL for [<sup>14</sup>C]-ABT-267

<sup>c</sup> pg.h/mL for [<sup>14</sup>C]-ABT-267

<sup>d</sup> Harmonic mean (pseudo CV%)

<sup>e</sup> Calculated using AUC(0-inf)

Regimen B: ABT-450/r/ABT-267 co-formulated tablets in a dose containing 150 mg ABT-450, 25 mg ABT-267 and 100 mg ritonavir followed by an IV infusion of 25 µg [<sup>14</sup>C]-ABT-267

### Assessment of Absolute Bioavailability

Table 4 shows the assessment of absolute bioavailability, calculated using the dose normalized pharmacokinetic parameters and AUCs.

Parameter	Test/Reference	Oral Dose		IV Dose		Ratio <sup>a</sup>	P-value <sup>b</sup>	90% CI <sup>c</sup>
		N	Adjusted Geometric Mean	N	Adjusted Geometric Mean			
Dose Normalised AUC(0-last) (ng.h/mL/mg)	Regimen A: ABT-450/[ <sup>14</sup> C]-ABT-450	8	20.2	8	37.8	53.42	0.002	(42.04, 67.90)
	Regimen B: ABT-267/[ <sup>14</sup> C]-ABT-267	8	57.7	8	117	49.40	<0.001	(44.22, 55.20)
Dose Normalised AUC(0-inf) (ng.h/mL/mg)	Regimen A: ABT-450/[ <sup>14</sup> C]-ABT-450	8	20.3	8	38.6	52.56	0.001	(41.37, 66.79)
	Regimen B: ABT-267/[ <sup>14</sup> C]-ABT-267	8	64.0	8	133	48.06	<0.001	(42.91, 53.84)

Results obtained from mixed effect modelling techniques for natural log transformed PK parameters including terms for dose (ie oral or IV) fitted as a fixed effect and subject fitted as a random effect

<sup>a</sup> Ratio of (adjusted geometric means for oral dose/IV dose) × 100

<sup>b</sup> p-value for ratio of adjusted geometric means

<sup>c</sup> 90% CI for ratio of adjusted geometric means

Regimen A: ABT-450/r/ABT-267 co-formulated tablets in a dose containing 150 mg ABT-450, 25 mg ABT-267 and 100 mg ritonavir followed by an IV infusion of 100 µg [<sup>14</sup>C]-ABT-450

Regimen B: ABT-450/r/ABT-267 co-formulated tablets in a dose containing 150 mg ABT-450, 25 mg ABT-267 and 100 mg ritonavir followed by an IV infusion of 25 µg [<sup>14</sup>C]-ABT-267

### Safety

There were no deaths or other SAEs reported for any subject during the study and no subject was withdrawn as a result of an AE.

### Results

- Following single dose administration of ABT-450 as an oral co-formulated product with ABT-267 and ritonavir under non-fasting conditions with an IV dose of <sup>14</sup>C-radiolabelled ABT-450, the geometric mean absolute bioavailability of ABT-450 was 52.6%.

- Following single dose administration of ABT-267 as an oral co-formulated product with ABT-450 and ritonavir under non-fasting conditions with an IV dose of  $^{14}\text{C}$ -radiolabelled ABT-267, the geometric mean absolute bioavailability of ABT-267 was 48.1%.
- Following IV administration of 100  $\mu\text{g}$  [ $^{14}\text{C}$ ]-ABT-450, the harmonic mean  $T_{1/2}$  was 8.71 h. The geometric mean CL was 25.9 L/h and the geometric mean values for  $V_{\text{d}\beta}$  and  $V_{\text{dss}}$  were 331 L and 103 L, respectively.
- Following IV administration of 25  $\mu\text{g}$  [ $^{14}\text{C}$ ]-ABT-267, the harmonic mean  $T_{1/2}$  was 28.49 h. The geometric mean CL was 7.51 L/h and the geometric mean values for  $V_{\text{d}\beta}$  and  $V_{\text{dss}}$  were 313 L and 173 L, respectively.

## Conclusion

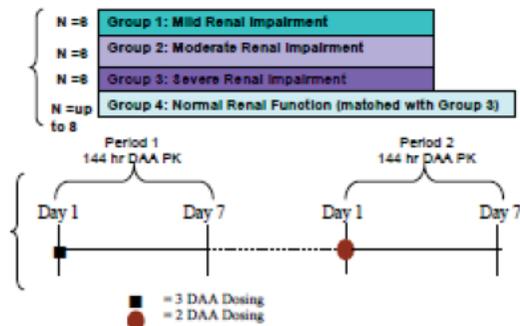
Following single dose administration of ABT-450 as an oral co-formulated product with ABT-267 and ritonavir under non-fasting conditions, the geometric mean absolute bioavailability of ABT-450 and ABT-267 is 52.6% and 48.1 %, respectively.

## RENAL IMPAIRMENT STUDY REVIEW

<b>Study #</b>	Protocol M12-193	<b>Study Period</b>	12/14/2012 -10/04/2013
<b>Title</b>	Evaluation of the Pharmacokinetics and Safety of Co-administered ABT-450/ritonavir (ABT-450/r) and ABT-267 With and Without ABT-333 as a Single Dose in Subjects with Either Normal Renal Function or Subjects with Mild, Moderate and Severe Renal Impairment		

### STUDY DESIGN

A Phase 1, multicenter, single-dose, non-fasting, open-label, two periods study:



Treatments	1. ABT-450/ritonavir: 75mg/50mg tablet. 2. ABT-267: 25 mg tablet.												
Dose Selection Rationale	ABT-450, ritonavir, and ABT-267 doses are the label recommended daily doses of 150 mg QD, 100 mg QD, and 25 mg QD, respectively.												
Administration	<input type="checkbox"/> Fasted <input checked="" type="checkbox"/> Fed Subjects received a standardized diet (approximately 2,100 calories/day) for all meals during confinement.												
Formulation	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 20%;">Drug</th> <th style="width: 40%;">ABT-450/r</th> <th style="width: 40%;">ABT-267</th> </tr> </thead> <tbody> <tr> <td>Dosage Form/ Strength</td> <td>Tablet (75/50 mg)</td> <td>Table (25 mg)</td> </tr> <tr> <td>Bulk Product Lot Number</td> <td>12-002722</td> <td>11-002033</td> </tr> <tr> <td>Finishing Lot Number</td> <td>12-007176</td> <td>12-004915</td> </tr> </tbody> </table>	Drug	ABT-450/r	ABT-267	Dosage Form/ Strength	Tablet (75/50 mg)	Table (25 mg)	Bulk Product Lot Number	12-002722	11-002033	Finishing Lot Number	12-007176	12-004915
Drug	ABT-450/r	ABT-267											
Dosage Form/ Strength	Tablet (75/50 mg)	Table (25 mg)											
Bulk Product Lot Number	12-002722	11-002033											
Finishing Lot Number	12-007176	12-004915											
Interfering Substances Excluded	Grapefruit, star fruit, Seville oranges, or products containing any of these Alcohol Caffeine												
Groups matching	Subjects with normal renal function were matched to the subjects with severe renal impairment in terms of age, weight, sex, smoking status and race. Subjects with mild and moderate renal impairment were also similar to the subjects with normal renal function in terms of these covariates, though not matched.												
Renal Function Assessment	The Cockcroft-Gault equation was used to estimate CL <sub>Cr</sub> to categorize the degree of renal impairment for assignment of subjects into groups as follows: mild (CL <sub>Cr</sub> = 60 – 89 mL/min), moderate (CL <sub>Cr</sub> = 30 – 59 mL/min), severe (CL <sub>Cr</sub> = 15 – 29 mL/min), and normal (CL <sub>Cr</sub> ≥ 90 mL/min).												
Sampling Times	PK: Pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 72, 96, and 144 hours post-dose. Protein binding: Pre-dose in all subjects.												
PK Parameters	AUC, AUC <sub>τ</sub> , C <sub>max</sub> , T <sub>max</sub> , t <sub>1/2</sub> , CL/F, V <sub>β</sub> /F.												
PK Analysis	Non-Compartmental PK analysis.												
Statistical Analysis	An analysis of covariance (ANCOVA) was performed on the logarithms PK parameters when applicable. Body weight, sex, age and other variables were considered as possible covariates.												
Is the study design acceptable? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No													

**STUDY CONDUCT****Bioanalytical Method:**

Method Type	LC-MS/MS	Matrix-Plasma
Analytes	ABT-450	ABT-267
Range	0.6 - 431	0.4 - 299

Validation	<ul style="list-style-type: none"> <li>▪ Method validated prior to use</li> <li>▪ Method validation acceptable</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA
Study Samples Analysis	<ul style="list-style-type: none"> <li>▪ Samples analyzed within the established stability period</li> <li>▪ Quality control samples range acceptable</li> <li>▪ Chromatograms provided</li> <li>▪ Accuracy and precision of the calibration curve acceptable</li> <li>▪ Accuracy and precision of the quality control samples acceptable</li> <li>▪ Incurred samples analysis is acceptable</li> <li>▪ Overall performance acceptable</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Inspection	<ul style="list-style-type: none"> <li>▪ Will the bioanalytical site be inspected</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

**Protocol Deviations**

- Are there any protocol deviations listed in the study report?  Yes  No
- Do any of the listed deviations affect the integrity of the study?  Yes  No  NA

There was one protocol deviation reported. Subject 203, received excluded concomitant treatment with omeprazole. Omeprazole does not affect the PK of the DAAs and hence the deviation should not affect the integrity of the trial.

**STUDY RESULTS****Study Population (all subjects)**

Randomized	24
Treated	24
Completed	24
Discontinued Due to AE	0
PK Population/Safety Population	24/24
Age [Mean (range)]	62.7 [47-71]
Male/Female	21/3
Race (Caucasian/Black/Asian/Other)	20/4/0/0

**Notes:**

1. One subject in the severe group had very low weigh (~ 55 Kg) and a healthy match could not be found. The selected match was 90 Kg.
2. There were 3 females among the subjects with mild renal impairment and none among the subjects with moderate or severe renal impairment or normal renal function.

**Pharmacokinetics:** AUC and  $C_{max}$  LS means ratio and 90 % CI for the renal impairment groups relative to the control group in part 2 of the study (2-DAAs) are displayed in the table below:

Pharmacokinetic Parameter (unit)	Ratio (90% CI): Renal-Impaired Group vs. Normal Renal Function Group		
	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
<b>ABT-450</b>			
C <sub>max</sub> (ng/mL)	0.892 (0.556 – 1.431)	0.827 (0.376 – 1.818)	0.781 (0.281 – 2.175)
AUC <sub>∞</sub> (ng•h/mL)	1.107 (0.765 – 1.602)	1.185 (0.640 – 2.194)	1.247 (0.560 – 2.777)
<b>Ritonavir</b>			
C <sub>max</sub> (ng/mL)	1.282 (1.030 – 1.597)	1.514 (1.050 – 2.183)	1.714 (1.065 – 2.758)
AUC <sub>∞</sub> (ng•h/mL)	1.404 (1.127 – 1.748)	1.759 (1.221 – 2.536)	2.084 (1.296 – 3.353)
<b>ABT-267</b>			
C <sub>max</sub> (ng/mL)	0.913 (0.818 – 1.019)	0.859 (0.715 – 1.032)	0.820 (0.646 – 1.041)
AUC <sub>∞</sub> (ng•h/mL)	1.010 (0.891 – 1.145)	1.017 (0.825 – 1.254)	1.022 (0.779 – 1.342)
<ul style="list-style-type: none"> <li>▪ Were there any outliers or excluded data from analysis? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA</li> <li>▪ Are the study results acceptable? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</li> </ul>			
<b>Safety</b>			
Was there any death or serious adverse events? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
<b>CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS</b>			
<b>CONCLUSIONS</b>			
No dose adjustment is necessary in subjects with mild and moderate renal impairment.			

## In Vitro Assessments

The applicant submitted in vitro reports which characterize the substrate properties of ABT-450 and ABT-267 towards OCT1 transporter, potential for ABT-450 and ABT-267 to inhibit various UGT enzymes, potential for time dependent inhibition of various enzymes and the lack of interaction with the OCT2 transporter.

Based on the information provided by the applicant:

### ABT-450:

- Did not inhibit UGT1A9 and 2B7 at concentrations up to 50  $\mu\text{M}$  ( $\text{IC}_{50} > 50 \mu\text{M}$ ).
- Is an inhibitor of UGT1A4 and 1A6 with  $\text{IC}_{50}$  values of 6.81 and 46.7  $\mu\text{M}$ , respectively.
- Is not expected to show clinically meaningful inhibition of UGT1A4, 1A6, 1A9 and 2B7.
- Is not a substrate of OCT1.
- Does not interact with OCT2 (< 10 % inhibition at 30  $\mu\text{M}$ ) using pyrimethamine as a positive control.
- Does not show time dependent inhibition of CYP2B6 and CYP2D6 following an extended pre-incubation period. Given that the clinical DDI studies with 3-DAA's have addressed DDI via inhibition of CYP3A4, 2C8, 2C9, 2C19 and 1A2, no further in vitro TDI studies with ABT-450 were conducted.

### ABT-267:

- Did not inhibit UGT1A4, 1A6, 1A9 and 2B7 at concentration up to 50  $\mu\text{M}$  ( $\text{IC}_{50} > 50 \mu\text{M}$ ).
- Is not a substrate of OCT1
- Is a substrate for P-gp but not BCRP in vitro
- Lack of uptake transporter involvement in the hepatic disposition
- Lack of interaction with OCT2 (< 10% inhibition at 30  $\mu\text{M}$ ), using pyrimethamine as a positive control

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VIKRAM ARYA  
06/29/2015

ISLAM R YOUNIS  
06/29/2015

# CLINICAL PHARMACOLOGY FILING FORM

## Application Information

<b>NDA/BLA Number</b>	207931	<b>SDN</b>	000
<b>Applicant</b>	Abbvie Inc.	<b>Submission Date</b>	February 25, 2015
<b>Generic Name</b>	Ombitasvir/Paritaprevir/Ritonavir	<b>Brand Name</b>	Technivie
<b>Drug Class</b>	NS5A Inhibitor (Ombitasvir), NS3A Protease Inhibitor (Paritaprevir), HIV-1 Protease Inhibitor (Ritonavir)		
<b>Indication</b>	Indicated, in combination with ribavirin, for the treatment of patients with Genotype 4 Chronic Hepatitis C Virus (HCV) Infection		
<b>Dosage Regimen</b>	Two 12.5 mg/75 mg/50 mg co-formulated tablets once daily (in the morning) with a meal without regard to fat or calorie content		
<b>Dosage Form</b>	Co-formulated tablets	<b>Route of Administration</b>	Oral
<b>OCP Division</b>	DCPIV	<b>OND Division</b>	DAVP
<b>OCP Review Team</b>	<b>Primary Reviewer(s)</b>	<b>Secondary Reviewer/ Team Leader</b>	
<b>Division</b>	DCPIV	DCPIV	
<b>Pharmacometrics</b>	N/A	N/A	
<b>Genomics</b>	N/A	N/A	
<b>Review Classification</b>	<input type="checkbox"/> Standard <input type="checkbox"/> Priority <input checked="" type="checkbox"/> Expedited		
<b>Filing Date</b>	4/26/2015	<b>74-Day Letter Date</b>	5/10/2015
<b>Review Due Date</b>	6/30/2015	<b>PDUFA Action Date</b>	7/24/2015

## Application Fileability

**Is the Clinical Pharmacology section of the application fileable?**

- Yes  
 No

**Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?**

- Yes  
 No

**Is there a need for clinical trial(s) inspection?**

- Yes  
 No

## Clinical Pharmacology Package

Tabular Listing of All Human Studies  Yes  No      Clinical Pharmacology Summary  Yes  No  
 Bioanalytical and Analytical Methods  Yes  No      Labeling  Yes  No

### Clinical Pharmacology Studies

Study Type	Count	Comment(s)
<b>In Vitro Studies</b>		
<input checked="" type="checkbox"/> Metabolism Characterization	8	
<input checked="" type="checkbox"/> Transporter Characterization	13	
<input type="checkbox"/> Distribution		
<input type="checkbox"/> Drug-Drug Interaction		
<b>In Vivo Studies</b>		

<b>Biopharmaceutics</b>			
<input checked="" type="checkbox"/> Absolute Bioavailability	1		
<input type="checkbox"/> Relative Bioavailability			
<input type="checkbox"/> Bioequivalence			
<input type="checkbox"/> Food Effect			
<input type="checkbox"/> Other			
<b>Human Pharmacokinetics</b>			
Healthy Subjects	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
<b>Intrinsic Factors</b>			
<input checked="" type="checkbox"/> Race	1		
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input checked="" type="checkbox"/> Renal Impairment	1		
<input type="checkbox"/> Genetics			
<b>Extrinsic Factors</b>			
<input checked="" type="checkbox"/> Effects on Primary Drug	6		
<input checked="" type="checkbox"/> Effects of Primary Drug	3		
<b>Pharmacodynamics</b>			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<b>Pharmacokinetics/Pharmacodynamics</b>			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<input type="checkbox"/> QT			
<b>Pharmacometrics</b>			
<input type="checkbox"/> Population Pharmacokinetics			
<input type="checkbox"/> Exposure-Efficacy			
<input type="checkbox"/> Exposure-Safety			
<b>Total Number of Studies</b>		<b>In Vitro</b>	<b>In Vivo</b>
<b>Total Number of Studies to be Reviewed</b>		21	12
		21	12

<b>Criteria for Refusal to File (RTF)</b>		
<b>RTF Parameter</b>	<b>Assessment</b>	<b>Comments</b>
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	The data from trial M13-391 was reviewed by the Biopharm group during review of NDA 206619.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
<b>Complete Application</b> 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

a justification that was previously agreed to before the NDA submission?		
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist</b>		
<b>Data</b>		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
<b>Studies and Analysis</b>		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
<b>General</b>		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

### Filing Memo

Please see the attached slide set for additional information.

# NDA 207931

Ombitasvir [ABT-267], Paritaprevir [ABT-450]  
and ritonavir co-formulated tablets

Review Team: Vikram Arya, Ph.D. FCP, Islam Younis, Ph.D.

1

## To-Be-Marketed Formulation

Drug	Class	Total Daily Dose (mg)	Frequency	How Supplied
Ombitasvir	NS5A Inhibitor	25	Once Daily (morning)	12.5/75/50 mg co-formulated tablets
Paritaprevir	NS3A Protease Inhibitor	150	Once Daily (morning)	
Ritonavir	HIV-1 Protease Inhibitor	100	Once Daily (morning)	

Note: Ombitasvir/Paritaprevir/ritonavir co-formulated tablets were also used in Phase III trials in HCV-genotype 1 subjects (NDA 206619)



## Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR<sub>12</sub>): GT4

Assessment	HCV GT4 Group			
	12 Wks 2-DAA	12 Wks 2-DAA + RBV		
	Group 1 T-Naive N = 44	Group 4 T-Naive N = 42	Group 6 T-Exp-All N = 49	Groups 4 + 6 N = 91
SVR <sub>12</sub> <sup>a</sup> , n/N (%)	40/44 (90.9)	42/42 (100.0)	49/49 (100.0)	91/91 (100.0)
95% CI <sup>b</sup>	78.3, 97.5	91.6, 100.0	92.7, 100.0	96.0, 100.0
Nonresponse <sup>c</sup> , n/N (%)	4/44 (9.1)	0/42	0/49	0/91
Reason for nonresponse, n/N (%)				
On-treatment virologic failure	1/44 (2.3)	0/42	0/49	0/91
Rebound <sup>d</sup>	1/44 (2.3)	0/42	0/49	0/91
Fail to suppress <sup>e</sup>	0/44	0/42	0/49	0/91
Relapse <sub>12</sub> <sup>f</sup>	2/42 (4.8)	0/42	0/49	0/91
Premature study drug discontinuation <sup>g</sup>	1/44 (2.3)	0/42	0/49	0/91

- 2-DAA = ABT-450 150 mg + ritonavir 100 mg + ABT-267 25 mg; CI = confidence interval; DAA = direct-acting antiviral agent; GT = genotype; ITT = intent-to-treat; LLOQ = lower limit of quantification; RBV = ribavirin; SVR = sustained virologic response; T-Exp-All = all treatment-experienced with pegylated-interferon/RBV (includes partial and null responders and relapsers); T-Naive = treatment-naive; Wks = weeks
- SVR<sub>12</sub> = HCV RNA < LLOQ in the SVR<sub>12</sub> window (12 weeks after last actual dose of study drug) without any confirmed quantifiable post-treatment value before or during that SVR window.
  - Confidence interval constructed using the Clopper-Pearson exact method.
  - Nonresponse = did not achieve SVR<sub>12</sub>.
  - Rebound = confirmed HCV RNA ≥ LLOQ (after < LLOQ during treatment), or confirmed increase from nadir (2 consecutive HCV RNA measurements > 1 log<sub>10</sub> IU/mL above nadir) at any time point during treatment.
  - Fail to suppress = never achieved HCV RNA < LLOQ during at least 6 weeks of treatment (study drug duration ≥ 36 days).
  - Relapse<sub>12</sub> = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR<sub>12</sub> assessment time point) for a subject with HCV RNA < LLOQ at final treatment visit who completes treatment (defined as study drug duration ≥ 77 days for subjects in Substudy 1 and ≥ 154 days for subjects in Substudy 2).
  - Prematurely discontinued study drug with no on-treatment virologic failure.

5

## Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR<sub>12</sub>): GT1b

Assessment	HCV GT1b Group					
	Noncirrhotic (12 Wks 2-DAA)			Cirrhotic (24 Wks 2-DAA)		
	Group 2 T-Naive N = 42	Group 3 T-Exp-Null N = 40	Groups 2 + 3 N = 82	Group 7 T-Naive N = 47	Group 8 T-Exp-All N = 52	Groups 7 + 8 N = 99
SVR <sub>12</sub> <sup>a</sup> , n/N (%)	40/42 (95.2)	36/40 (90.0)	76/82 (92.7)	46/47 (97.9)	50/52 (96.2)	96/99 (97.0)
95% CI <sup>b</sup>	83.8, 99.4	76.3, 97.2	84.8, 97.3	88.7, 99.9	86.8, 99.5	91.4, 99.4
Nonresponse <sup>c</sup> , n/N (%)	2/42 (4.8)	4/40 (10.0)	6/82 (7.3)	1/47 (2.1)	2/52 (3.8)	3/99 (3.0)
Reason for nonresponse, n/N (%)						
On-treatment virologic failure	0/42	1/40 (2.5)	1/82 (1.2)	0/47	0/52	0/99
Rebound <sup>d</sup>	0/42	1/40 (2.5)	1/82 (1.2)	0/47	0/52	0/99
Fail to suppress <sup>e</sup>	0/42	0/40	0/82	0/47	0/52	0/99
Relapse <sub>12</sub> <sup>f</sup>	0/42	3/39 (7.7)	3/79 (3.8)	0/44	1/52 (1.9)	1/96 (1.0)
Premature study drug discontinuation <sup>g</sup>	1/42 (2.4)	0/40	1/82 (1.2)	1/47 (2.1)	0/52	1/99 (1.0)
Missing SVR <sub>12</sub> data	1/42 (2.4)	0/40	1/82 (1.2)	0/47	1/52 (1.9)	1/99 (1.0)

- 2-DAA = ABT-450 150 mg + ritonavir 100 mg + ABT-267 25 mg; DAA = direct-acting antiviral agent; GT = genotype; ITT = intent-to-treat; LLOQ = lower limit of quantification; RBV = ribavirin; SVR = sustained virologic response; T-Exp-All = all treatment-experienced with pegylated-interferon/RBV (includes partial and null responders and relapsers); T-Exp-Null = treatment-experienced with pegylated-interferon/RBV-null responders only; T-Naive = treatment-naive; Wks = weeks
- SVR<sub>12</sub> = HCV RNA < LLOQ in the SVR<sub>12</sub> window (12 weeks after last actual dose of study drug) without any confirmed quantifiable post-treatment value before or during that SVR window.
  - Confidence interval constructed using the Clopper-Pearson exact method.
  - Nonresponse = did not achieve SVR<sub>12</sub>.
  - Rebound = confirmed HCV RNA ≥ LLOQ (after < LLOQ during treatment), or confirmed increase from nadir (2 consecutive HCV RNA measurements > 1 log<sub>10</sub> IU/mL above nadir) at any time point during treatment.
  - Fail to suppress = never achieved HCV RNA < LLOQ during at least 6 weeks of treatment.
  - Relapse<sub>12</sub> = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR<sub>12</sub> assessment time point) for a subject with HCV RNA < LLOQ at final treatment visit who completes treatment (defined as study drug duration ≥ 77 days for subjects in Substudy 1 and ≥ 154 days for subjects in Substudy 2).
  - Prematurely discontinued study drug with no on-treatment virologic failure.

6

## SVR<sub>12</sub>-Subgroup Analysis

Subgroup	Groups 4 + 6 GT4 Noncirrhotic 12 Wks 2-DAA + RBV		Groups 2 + 3 GT1b Noncirrhotic 12 Wks 2-DAA		Groups 7 + 8 GT1b Cirrhotic 24 Wks 2-DAA	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
<b>Sex</b>						
Male	64/64 (100.0)	94.4, 100.0	36/40 (90.0)	76.3, 97.2	54/56 (96.4)	87.7, 99.6
Female	27/27 (100.0)	87.2, 100.0	40/42 (95.2)	83.8, 99.4	42/43 (97.7)	87.7, 99.9
<b>Age</b>						
< 55 years	66/66 (100.0)	94.6, 100.0	27/30 (90.0)	73.5, 97.9	29/30 (96.7)	82.8, 99.9
≥ 55 years	25/25 (100.0)	86.3, 100.0	49/52 (94.2)	84.1, 98.8	67/69 (97.1)	89.9, 99.6
< 65 years	88/89 (100.0)	95.9, 100.0	72/78 (92.3)	84.0, 97.1	80/82 (97.6)	91.5, 99.7
≥ 65 years	2/2 (100.0)	15.8, 100.0	4/4 (100.0)	39.8, 100.0	16/17 (94.1)	71.3, 99.9
<b>Race</b>						
Black	6/6 (100.0)	54.1, 100.0	12/12 (100.0)	73.5, 100.0	0/0	NA
Non-Black	85/85 (100.0)	95.8, 100.0	64/70 (91.4)	82.3, 96.8	96/99 (97.0)	91.4, 99.4
<b>BMI</b>						
< 30	77/77 (100.0)	95.3, 100.0	58/62 (93.5)	84.3, 98.2	77/80 (96.3)	89.4, 99.2
≥ 30	14/14 (100.0)	76.8, 100.0	18/20 (90.0)	68.3, 98.8	19/19 (100.0)	82.4, 100.0
<b>Geographic Region</b>						
North America	13/13 (100.0)	75.3, 100.0	35/37 (94.6)	81.8, 99.3	6/7 (85.7)	42.1, 99.6
Europe	78/78 (100.0)	95.4, 100.0	41/45 (91.1)	78.8, 97.5	90/92 (97.8)	92.4, 99.7
<b>IL28B Genotype<sup>a</sup></b>						
CC	17/17 (100.0)	80.5, 100.0	14/15 (93.3)	68.1, 99.8	13/13 (100.0)	75.3, 100.0
Non-CC	74/74 (100.0)	95.1, 100.0	61/66 (92.4)	83.2, 97.5	83/86 (96.5)	90.1, 99.3
CT	58/58 (100.0)	93.8, 100.0	41/46 (89.1)	76.4, 96.4	64/67 (95.5)	87.5, 99.1
TT	16/16 (100.0)	79.4, 100.0	20/20 (100.0)	83.2, 100.0	19/19 (100.0)	82.4, 100.0
<b>HCV RNA Level, IU/mL</b>						
< 800,000	24/24 (100.0)	85.8, 100.0	11/12 (91.7)	61.5, 99.8	18/19 (94.7)	74.0, 99.9
≥ 800,000	67/67 (100.0)	94.6, 100.0	65/70 (92.9)	84.1, 97.6	78/80 (97.5)	91.3, 99.7
<b>IP-10, ng/L</b>						
< 600	71/71 (100.0)	94.9, 100.0	46/50 (92.0)	80.8, 97.8	51/52 (98.1)	89.7, 100.0
≥ 600	17/17 (100.0)	80.5, 100.0	26/26 (100.0)	86.8, 100.0	39/41 (95.1)	83.5, 99.4
Missing	3/3 (100.0)	29.1, 100.0	4/6 (66.7)	22.3, 95.7	6/6 (100.0)	54.1, 100.0

7

## Available PK Information from M13-393

- Samples to determine plasma concentration of ABT-267, ABT-450, ritonavir, and ribavirin collected after:
  - Single dose: one sample at 4 hour from all subjects/group
  - Steady state: one sample at each visit (starting week 2) from all subjects/group

8

### Formulation Used in M13-393 vs TBM Formulation

- Individual formulations of ABT-267 (b) (4) ABT-450 (b) (4) and ritonavir soft gelatin capsule [SGC]
  - Mean ABT-450  $C_{max}$  and AUC are 95 % and 63 % higher when given as ABT-267/ABT-450/ritonavir uncoated co-formulated product as compared to individually administered (b) (4) ABT-450 formulation (+RTV+ABT-267) [Trial M13-391; reviewed by Biopharm group]
  - ABT-267/ABT-450/ritonavir film coated tablet is the TBM formulation
- Differences in formulation not anticipated to be clinically relevant from efficacy and safety perspective
  - Safety has been demonstrated in GT1
  - Efficacy has been demonstrated at the lower ABT-450 exposures (using the ABT-450 (b) (4) formulation) in GT4

### Overview of Review- In Vivo Trials

- 1 Absolute BA trial for ABT-267/ABT-450/rtv
- 1 DDI trial between the three components
- 1 DDI trial between the three components in Han Chinese, Japanese, Caucasians [3-DAA portion reviewed during VIEKIRA PAK NDA review]
- 8 DDI trials (only the portion that pertains to evaluation of the 2-DAA regimen)
- 1 trial in renal impairment (only the portion that pertains to evaluation of the 2-DAA regimen)

**Total Number of Trials: 12**

10

## Overview of Review- In Vitro Trials

- ~20 in vitro reports
  - New Information
  - Additional Information

11

## No Filing Issues Identified...

- Applicant has provided all the information needed to review the application
- Hyperlinks are functional and information is searchable

12

## Some Review Related Questions...

- Are the label claims supported by the available information?
- Can DDI data generated using either the 3-DAA regimen or the 2-DAA regimen (ABT-450/ritonavir +ABT-333) applied to the 2-DAA (ABT-450/r +ABT-267) regimen?

13

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VIKRAM ARYA  
04/16/2015

ISLAM R YOUNIS  
04/16/2015